

KRETANJE OBOLEVANJA I UMIRANJA OD RAKA PANKREASA U CENTRALNOJ SRBIJI, U PERIODU OD 1999. DO 2019. GODINE

Belma Muratović, Aleksandra Nikolić¹, Sandra Šipetić Grujičić^{1*}

¹ Institut za epidemiologiju, Medicinski fakultet Univerziteta u Beogradu, Beograd, Republika Srbija

* Korespondencija: sandra.grujicic2014@gmail.com

SAŽETAK

Uvod/Cilj: Rak pankreasa je četrnaesti vodeći uzrok obolevanja i sedmi vodeći uzrok umiranja među svim malignim bolestima. Cilj istraživanja je bio da se analizira kretanje obolevanja i umiranja od raka pankreasa u centralnoj Srbiji za period 1999-2019. godine.

Metode: Podaci o obolelima i umrlima od malignih tumora, kao i o broju stanovnika, po polu i uzrastu, za period od 1999. do 2015. godine, preuzeti su iz registara za rak u Centralnoj Srbiji, a podaci za 2016., 2017., 2018. i 2019. dobijeni su od Instituta za javno zdravlje Srbije. Na osnovu dobijenih podataka izračunate su sirove, specifične i standardizovane stope incidencije i mortaliteta za rak pankreasa. Kretanje obolevanja i umiranja za šesnaestogodišnji period analiziran je korišćenjem *joinpoint* regresione analize.

Rezultati: U periodu 1999-2019. godine u centralnoj Srbiji prosečan godišnji broj obolelih je bio 378 muškaraca i 305 žena, a umrlih 406 muškaraca i 336 žena. Prosečna godišnja standardizovana stopa incidencije (na 100.000) je iznosila 7,7 za muškarce i 5,0 za žene, a standardizovana stopa mortaliteta (na 100.000) 7,9 za muškarce i 5,1 za žene. Kod muškaraca, najviša prosečna godišnja uzrasno specifična stopa incidencije zabeležena je u uzrastu 60-69 godina (39,7 na 100.000), a stopa mortaliteta u uzrastu 70 i više godina (42,4 na 100.000). Kod žena, najviše stope incidencije i mortaliteta su bile u najstarijem uzrastu (70 i više) i iznosile su 25,7 i 34,8 na 100.000. Tokom posmatranog perioda zabeležen je značajan porast standardizovanih stopa incidencije kod muškaraca od 2,9% i kod žena od 3,7% godišnje. Takođe, uočen je trend porasta standardizovanih stopa mortaliteta kod muškaraca (od 1,2%) i žena (od 0,6%), ali je značajnost postignuta samo kod muškaraca.

Zaključak: U periodu 1999-2019. godine u centralnoj Srbiji stope incidencije i mortaliteta su u porastu. Neophodna su istraživanja o faktorima rizika za nastanak ove bolesti u cilju preduzimanja preventivnih mera. Takođe, rano otkrivanje i pravovremena terapija treba da doprinesu redukciji umiranja od ovog malignoma.

Ključne reči: rak pankreasa, incidencija, mortalitet, trend, *joinpoint* regresiona analiza

Uvod

Rak pankreasa je četrnaesti vodeći uzrok obolevanja i sedmi vodeći uzrok umiranja među svim malignim bolestima (1). U 2020. godini u svetu je dijagnostikovano 495.773 slučajeva raka pankreasa, a kao posledica istog zabeleženo je 466.003 slučajeva smrti (1). Drugim rečima, rak pankreasa je, zbog svoje loše prognoze, odgovoran za sličan broj obolelih i smrtnih slučajeva. Na globalnom nivou u 2020. godini zabeležena je i značajna razlika u obolevanju među polovima. Kod muškaraca je veća stopa incidencije (5,7 na 100.000) nego kod žena (4,1 na 100.000) (1).

Slično je i sa stopama mortaliteta koje su veće kod muškaraca (5,3 na 100.000) nego kod žena (3,8 na 100.000). Starenjem se incidencija ove bolesti povećava kod oba pola. Skoro da ove bolesti i nema pre 55. godine života, a posle 70. godine zapaža se najveća incidencija (2). Takođe, mortalitet raste sa uzrastom, skoro 90% smrtnih slučajeva je kod osoba starosti 55 i više godina.

Kao faktori rizika za nastanak raka pankreasa navode se pozitivna porodična anamneza, pušenje cigareta, unošenje veće količine alkohola, ishrana, fizička neaktivnost i prisustvo dijabetes melitu-

TRENDS IN INCIDENCE AND MORTALITY FROM PANCREATIC CANCER IN CENTRAL SERBIA, IN THE PERIOD FROM 1999 TO 2019

Belma Muratovic, Aleksandra Nikolic¹, Sandra Grujicic¹

¹ Institute of Epidemiology, Faculty of Medicine, University of Belgrade, Belgrade, Republic of Serbia

* Correspondence: sandra.grujicic2014@gmail.com

SUMMARY

Introduction: Pancreatic cancer is the fourteenth leading cause of disease and the seventh leading cause of death among all malignant diseases. The aim of the research was to analyze the trends in the incidence and death of pancreatic cancer in central Serbia for the period 1999-2019. years.

Methods: The data about diseased and dead, as well as population by sex and age, in the period 1999-2015 were taken over from the Cancer registry of Central Serbia, and the data for 2016, 2017, 2018 and 2019 were obtained from the Institute of Public Health of Serbia. Based on obtained data, we counted crude, specific and standardized rates of incidence and mortality for pancreatic cancers, for all ages. Trends rate in incidence and mortality were counted using joinpoint regression analysis.

Results: In the period 1999-2019. In central Serbia, the average annual number of patients was 378 men and 305 women, and the average number of deaths was 406 men and 336 women. The average annual standardized incidence rate (per 100,000) was 7.7 for men and 5.0 for women, and the standardized mortality rate (per 100,000) was 7.9 for men and 5.1 for women. In men, the highest average annual age-specific incidence rate was recorded at the age of 60-69 (39.7 per 100,000), and the mortality rate at the age of 70 and over (42.4 per 100,000). Among women, the highest incidence and mortality rates were in the oldest age (70 and over) and were 25.7 and 34.8 per 100,000. During the observed period, there was a significant increase in standardized incidence rates for men of 2.9% and for women of 3.7% per year. Also, a trend of increasing standardized mortality rates was observed in men (of 1.2%) and women (of 0.6%), but significance was achieved only in men.

Conclusion: In the period 1999-2019. in central Serbia, incidence and mortality rates are on the rise. Research on risk factors for the development of this disease is necessary in order to take preventive measures. Also, early detection and timely therapy should contribute to the reduction of death from this malignancy.

Keywords: pancreatic cancer, incidence, mortality, trend, joinpoint regression analysis

Introduction

Pancreatic cancer is the fourteenth leading cause of disease and the seventh leading cause of death among all malignant diseases (1). In 2020, 495,773 cases of pancreatic cancer were diagnosed worldwide, while 466,003 cases of death were reported due to pancreatic cancer (1). In other words, pancreatic cancer is, due to its poor prognosis, responsible for the similar number of new cases and deaths. Globally, a significant difference between sexes was noted in 2020. In men, the incidence rate was higher (5.7 per 100,000) than in women (4.1 per 100,000) (1). Similarly, mortality

rates were higher in men (5.3 per 100,000) than in women (3.8 per 100,000). The incidence of this disease increases with age in both sexes. Pancreatic cancer is seldom diagnosed before 55 years of age, while the highest incidence is reported in people over 70 years (2). Also, mortality increases with age, and almost 90% of deaths were reported in people over 55 years of age.

Risk factors for the occurrence of pancreatic cancer are the following: positive family history, smoking, alcohol consumption, diet, physical inactivity, and diabetes mellitus (3-8). Pancreatic

sa (3–8). Rak pankreasa je jedan od najmalignijih tumora, i njegova prognoza je vrlo loša. Podaci pokazuju da je petogodišnje preživljavanje manje od 10%, a razlike u preživljavanju malo variraju između razvijenih i zemalja u razvoju (7,9). U prilog ovako visokom mortalitetu ide i podatak da se ovaj tumor otkriva u uznapređovalom stadijumu, zato što je u ranom stadijumu bez simptoma, a i kada ima simptome, oni su nespecifični. Kada se otkrije u uznapređovalom stadijumu, kod 80-90% pacijenata ga je nemoguće operisati (2).

Bolji uvid u epidemiološke trendove raka pankreasa doprineo bi i boljem razumevanju njegove etiologije i imao bi implikacije na preventivne mere i kliničku negu. Cilj istraživanja je bio da se analizira kretanje obolevanja i umiranja od raka pankreasa u centralnoj Srbiji, u periodu od 1999. do 2019. godine.

Metod

Podaci o obolelima i umrlima od raka pankreasa, kao i o broju stanovnika, po polu i uzrastu, za period od 1999. do 2015. godine, preuzeti su iz registara za rak u centralnoj Srbiji Instituta za javno zdravlje Srbije „Dr Milan Jovanović Batut“. Podaci za 2016., 2017., 2018. i 2019. dobijeni su na zahtev od Instituta za javno zdravlje Srbije „Dr Milan Jovanović Batut“, jer nisu publikovani u registrima. Na osnovu dobijenih podataka izračunate su sirove, specifične i standardizovane stope incidencije i mortaliteta za rak pankreasa, za sve uzraste. Direktnom metodom standardizacije izračunate su standardizovane stope incidencije i mortaliteta i to tako što je za standardnu populaciju korišćena standardna populacija sveta prema Segi-ju (1960) (10). Trendovi standardizovanih stopa incidencije i mortaliteta su izračunati korišćenjem *joinpoint* regresione analize (*Joinpoint Regression Program, Version 4.9.0.1. February, 2022; Statistical Methodology and Applications Branch, Surveillance Research Program, National Cancer Institute*), prema metodi Kim et al. (11). *Joinpoint* regresionom analizom određena je procentualna godišnja promena (engl. *Annual percent change-APC*), kao i tačke u kojima dolazi do značajnih promena u trendovima. Određena je i prosečna procentualna godišnja promena (engl. *Average annual percent change – AAPC*) za celokupan posmatrani period. Kao nezavisna varijabla postavljene su godine, dok je zavisna varijabla bila odgovarajuća uzrasno-specifična

ili standardizovana stopa. Minimalan broj podataka od početka serije bio je podešen na 2, dok je najmanji broj podataka između dva *joinpoint*-a bio 2. Maksimalan broj *joinpoint*-a bio je podešen na 3. Korišćen je *Grid Search* metod (12). *Permutation Test* je korišćen za selekciju najboljeg modela *joinpoint*-a sa uopštenim nivoom značajnosti od 0,05 i 4499 slučajno permutovanih setova. Pored toga, 95% intervali poverenja računati su za svaku procenu APC kako bi se utvrdilo da li je APC za svaki segment različit od 0. Korišćen je test uporedivosti (engl. *comparability test*) kako bi se uporedile dve segmentirane linije regresije, odnosno trendovi standardizovanih stopa po polu. Cilj je bio da se upoređi da li su trendovi bili paralelni.

Rezultati

U periodu od 1999-2019. godine u centralnoj Srbiji je prosečno godišnje od raka pankreasa obolevalo 378 muškaraca (tabela 1). Prosečna stopa incidencije za muškarce iznosila je 14,7 na 100.000, a standardizovana 7,7 na 100.000. U istom periodu prosečno je godišnje od raka pankreasa obolevalo 305 žena. Prosečna sirova stopa incidencije kod žena iznosila je 11,2 na 100.000, a standardizovana 5 na 100.000. Najviše obolelih registrovano je 2017. godine, i to 572 muškarca i 461 žena.

U periodu od 1999-2019. godine u centralnoj Srbiji je prosečno godišnje od raka pankreasa umiralo 406 muškaraca (tabela 2). Prosečna stopa mortaliteta za muškarce iznosila je 15,7 na 100.000, a standardizovana 7,9 na 100.000. U istom periodu prosečno je godišnje od raka pankreasa umiralo 336 žena. Prosečna sirova stopa incidencije kod žena iznosila je 12,3 na 100.000, a standardizovana 5,1 na 100.000. Najviše umrlih muškaraca registrovano je 2017. godine, i to 487, a 2016. najviše umrlih žena 414.

Najviše uzrasno-specifične stope incidencije za rak pankreasa kod muškaraca beleže se za uzrast 60-69 godina (39,7 na 100.000) (tabela 3). Značajan prosečan procentualni godišnji porast obolevanja bio je u uzrastima 50-59, 60-69 i 70+, a najveći značajan porast od 5,6% u uzrastu 70+. Kod žena je najviša uzrasno-specifična stopa incidencije zabeležena u uzrastu 70+ (25,7 na 100.000). Značajan godišnji porast zabeležen je u uzrasnim grupama 40-49, 50-59 i 60-69, a najviši u uzrastu 50-59 od 5,7% godišnje. Beleži se i značajan go-

cancer is one of the most malignant tumors, and its prognosis is very poor. Data show that five-year survival is less than 10%, and there is a slight difference between developed and developing countries (7,9). High mortality rates may be attributed to the fact that this tumor is diagnosed in an advanced stage, because at its early stages it has no symptoms, and when symptoms appear, they are non-specific. When it is detected at an advanced stage, in 80-90% of patients, it can no longer be operated.

A better insight into the epidemiological trends of pancreatic cancer would contribute to better understanding of its etiology and would have implications for preventive measures and clinical care. The aim of the research was to analyze the trends in pancreatic cancer incidence and mortality in central Serbia in the period 1999-2019.

Methods

The data about new cases and deaths caused by pancreatic cancer, as well as about population by sex and age for the period 1999-2015, were taken from the Cancer Registry of Central Serbia of the Institute of Public Health of Serbia "Dr Milan Jovanovic Batut". The data for 2016, 2017, 2018 and 2019 were requested and obtained from the Institute of Public Health "Dr Milan Jovanovic Batut" because they were not published in registries. The obtained data were used to calculate crude, specific and standardized incidence and mortality rates for all age groups. Standardized incidence and mortality rates were calculated using the method of direct standardization, where the population of the world by Segi was used as the standard population (1960) (10). The trends in standardized incidence and mortality rates were calculated with the help of joinpoint regression analysis (Joinpoint Regression Program, Version 4.9.0.1. February, 2022; Statistical Methodology and Applications Branch, Surveillance Research program, National Cancer Institute), according to the method by Kim et al. (11). Using the joinpoint regression analysis, the annual percentage change (APC) was estimated, as well as the time intervals of important trend changes. The average annual percentage change (AAPC) for the entire observed period was also determined. Age was set as an independent variable, while corresponding age-specific or standardized rate was a dependent

variable. Grid Search method was used (12). The minimum number of data from the beginning of the series was set to 2, while the minimum number of data between the two joinpoints was 2. The maximum number of joinpoints was set to 3. Permutation Test was used for the selection of the best model of joinpoint with the general significance level from 0.05 to 4499 of accidentally permuted sets. In addition, 95% confidence intervals were calculated for each APC and AAPC estimate to determine if the APC/AAPC for each segment was different from 0. Comparability test was used to compare two segmented line regression functions, that is, trends by gender. The aim was to compare whether the trends were parallel.

Results

In the period 1999-2019, in central Serbia the average annual number of cases was 378 men (Table 1). The average incidence rate for men was 14.7 per 100,000, while the standardized rate was 7.7 per 100,000. During the same period, the average annual number of cases was 305 women. The average crude incidence rate in women was 11.2 per 100,000, while the standardized rate was 5 per 100,000. The greatest number of new cases was registered in 2017, that is, 572 men and 461 women.

In the period 1999-2019 in central Serbia, the average annual number of deaths caused by pancreatic cancer was 406 men (Table 2). The average mortality rate for men was 15.7 per 100,000, while the standardized rate was 7.9 per 100,000. In the same period, the average annual number of deaths was 336 women. The average crude mortality rate was 12.3 per 100,000, while the standardized rate was 5.1 per 100,000. The highest number of deaths among men was registered in 2017, that is, 486 men, while the highest number of deaths among women was registered in 2016, that is, 414 women.

The highest age-specific incidence rates for pancreatic cancer were registered in the age group 60-69 years (39.7 per 100,000) (Table 3). A significant average incidence increase was in the age groups 50-59, 60-69 and 70+, while the highest significant increase of 5.6% was in the age group 70+. In women, the highest age-specific incidence rate was found in the group of people

dišnji porast standardizovanih stopa incidencije i kod muškaraca (2,9%) i kod žena (3,7%).

Najviše uzrasno-specifične stope mortaliteta od raka pankreasa bile su kod muškaraca u uzrastu 70+ (42,4 na 100.000) i 60-69 godina (41,4 na 100.000) (tabela 4). Značajan porast stopa mortaliteta kod muškaraca zabeležen je za uzraste 60-69 (od 1,7% godišnje) i 70+ (4,6% godišnje). Kod žena su najviše vrednosti stopa mortaliteta zabeležene za uzrast 70+ (34,8 na 100.000). Značajan je porast stopa mortaliteta u uzrastima 50-59, 60-69 i 70+, s najvišim porastom u uzrastu 70+ od 3,9% godišnje. Standardizovane stope mortaliteta rastu kod muškaraca (od 1,2%) i kod žena (0,6%) godišnje, ali značajnost je postignuta samo kod muškaraca.

Test paralelizma trendova stopa incidencije kod muškaraca i žena, kao i stopa mortaliteta kod muškaraca i žena pokazao je da su trendovi po polu bili paralelni $p > 0,05$ (grafikon 1).

Diskusija

U centralnoj Srbiji u periodu 1999-2019. godine prosečna standardizovana stopa incidencije (na 100.000) od raka pankreasa kod muškaraca bila je 7,7, a kod žena 5 (odnos stopa 1,5). U razvijenim i visoko razvijenim zemljama standardizovana stopa incidencije (na 100.000) za rak pankreasa kod muškaraca iznosila je 7,2, a u srednje i slabije razvijenim 1,6 (1). Kod žena u razvijenim zemljama stope incidencije (na 100.000) iznosile su 5,0, a u slabije razvijenim zemljama 1,0. Odnosno, stope su 4 do 5 puta više u razvijenim zemljama. Najviše stope incidencije (na 100.000) beleže se u Australiji (15,3 za muškarce i 10 za žene), Severnoj Americi (14,2 za muškarce i 10,0 za žene) i Evropi. Nisu u potpunosti jasne razlike u stopama incidencije između zemalja, ali je moguće da su posledica različitih sredinskih faktora, kao i izloženosti faktorima rizika, kao što su pušenje, faktori ishrane

Tabela 1. Broj obolelih, sirove i standardizovane* stope incidencije (na 100.000), centralna Srbija, 1999-2019. godine

Godine	Muškarci			Žene		
	Broj obolelih	Sirova stopa	Standardizovana stopa	Broj obolelih	Sirova stopa	Standardizovana stopa
1999	245	9,1	5,3	205	7,3	4,3
2000	245	9,2	5,4	187	6,6	3,2
2001	314	11,8	6,9	206	7,3	3,6
2002	332	12,5	7,2	238	8,5	4,2
2003	302	11,4	6,4	240	8,6	4,0
2004	342	12,9	7,3	251	9,0	4,3
2005	325	12,3	7,0	309	11,1	5,0
2006	266	10,1	5,7	208	7,5	3,6
2007	356	13,6	7,6	265	9,6	4,3
2008	356	13,6	7,3	234	8,5	3,7
2009	312	12,0	6,6	258	9,4	4,5
2010	312	12,0	6,6	270	9,9	4,4
2011	420	16,3	8,7	317	11,6	5,1
2012	322	12,5	6,4	272	10,0	4,4
2013	455	17,8	8,6	362	13,4	5,3
2014	473	18,6	8,9	365	13,6	5,4
2015	472	18,6	9,2	403	15,1	6,5
2016	463	18,4	8,5	451	17,0	6,6
2017	572	22,8	10,8	461	17,5	6,7
2018	525	21,1	10,2	456	17,4	7,6
2019	528	21,2	10,4	454	17,3	7,6
Prosek	378	14,7	7,7	305	11,2	5,0

*Standardizovane stope prema populaciji sveta

aged 70 and older (25.7 per 100,000). A significant annual increase was registered in the age groups 40-49, 50-59 and 60-69, while the highest increase of 5.7% annually was in the age group 50-59. A significant annual increase of standardized incidence rates was registered in men (2.9%) and women (3.7%).

The highest age-specific mortality rates of pancreatic cancer were in men aged 70+ (42.4 per 100,000) and 60-69 (41.4 per 100,000) (Table 4). A significant increase of mortality rates in men was registered in the age groups 60-69 (of .7% annually) and 70+ (4.6% annually). In women, the highest mortality rates were registered in the age group 70+ (34.8 per 100,000). A significant increase of mortality rates was found in the age groups 50-59, 60-69 and 70+, with the highest annual increase of 3.9% in the age group 70+. Standardized mortality rates increased in men (1.2%) and in women (0.6%) annually, but the significance was found only in men.

Comparability test of trends in incidence rates in men and women, as well as in mortality rates in men and women showed that trends regarding gender were parallel $p > 0.05$ (Figure 1).

Discussion

In central Serbia in the period 1999-2019, the average standardized incidence rate (per 100,000) of pancreatic cancer was 7.7 in men and 5 in women (rates ratio 1.5). In developed and highly developed countries, standardized incidence rate (per 100,000) for pancreatic cancer in men was 7.2, while in middle-income countries and less developed countries it was 1.6 (1). In developed countries, incidence rates (per 100,000) amounted to 5.0 in women, while in less developed countries, they amounted to 1.0. These rates were 4 to 5 times higher in developed countries. The highest incidence rates (per 100,000) were found in Australia (14.3 for men and 10 for women), North America (14.2 for men and 10.0 for women) and in

Table 1. The number of cases, crude and standardized* incidence rates (per 100,000), central Serbia, 1999-2019.

Year	Men			Women		
	Number of cases	Crude rate	Standardized rate	Number of cases	Crude rate	Standardized rate
1999	245	9.1	5.3	205	7.3	4.3
2000	245	9.2	5.4	187	6.6	3.2
2001	314	11.8	6.9	206	7.3	3.6
2002	332	12.5	7.2	238	8.5	4.2
2003	302	11.4	6.4	240	8.6	4.0
2004	342	12.9	7.3	251	9.0	4.3
2005	325	12.3	7.0	309	11.1	5.0
2006	266	10.1	5.7	208	7.5	3.6
2007	356	13.6	7.6	265	9.6	4.3
2008	356	13.6	7.3	234	8.5	3.7
2009	312	12.0	6.6	258	9.4	4.5
2010	312	12.0	6.6	270	9.9	4.4
2011	420	16.3	8.7	317	11.6	5.1
2012	322	12.5	6.4	272	10.0	4.4
2013	455	17.8	8.6	362	13.4	5.3
2014	473	18.6	8.9	365	13.6	5.4
2015	472	18.6	9.2	403	15.1	6.5
2016	463	18.4	8.5	451	17.0	6.6
2017	572	22.8	10.8	461	17.5	6.7
2018	525	21.1	10.2	456	17.4	7.6
2019	528	21.2	10.4	454	17.3	7.6
Average	378	14.7	7.7	305	11.2	5.0

*Standardized rates according to the world population

Tabela 2. Broj obolelih, sirove i standardizovane* stope mortaliteta (na 100.000), centralna Srbija, 1999-2019. godine

Godine	Muškarci			Žene		
	Broj obolelih	Sirova stopa	Standardizovana stopa	Broj obolelih	Sirova stopa	Standardizovana stopa
1999	338	12,6	7,3	248	9,2	5,2
2000	299	11,2	6,5	246	8,7	4,1
2001	326	12,2	6,8	240	8,5	3,6
2002	342	12,9	7,1	270	9,6	4,4
2003	355	13,4	7,4	277	9,9	4,4
2004	358	13,5	7,3	261	9,3	4,0
2005	389	14,7	8,1	348	12,5	5,2
2006	377	14,3	7,8	296	10,7	4,7
2007	365	13,9	7,3	355	12,8	5,3
2008	426	16,3	8,3	354	12,8	5,1
2009	402	15,4	8,1	358	13,0	5,2
2010	423	16,3	8,5	379	13,8	5,7
2011	449	17,4	8,9	349	12,8	5,4
2012	441	17,2	8,1	386	14,3	5,4
2013	462	18,1	8,7	359	13,3	5,1
2014	432	17	7,9	352	13,1	5,1
2015	474	18,7	8,7	392	14,7	5,8
2016	441	17,5	8,0	414	15,6	5,7
2017	487	19,4	8,8	387	14,6	5,4
2018	473	19,0	8,6	395	15,0	5,6
2019	473	19,0	8,6	400	15,2	5,7
Prosek	406	15,7	7,9	336	12,3	5,1

*Standardizovane stope prema populaciji sveta

Tabela 3. Prosečne uzrasno-specifične i standardizovane stope incidencije (na 100.000) za rak pankreasa, joinpoint analiza kretanja stopa, centralna Srbija, 1999-2019. godine

Uzrasne grupe	Muškarci			Žene		
	Stope incidencije	Period	APC/AAPC (95% IP)	Stope incidencije	Period	APC/AAPC (95% IP)
0-29	0	-	-	0	-	-
30-39	1,2	1999-2019	-2,7 (-6,1 – 0,9)	0,8	1999-2019	0,1 (-3,9 – 4,3)
40-49	5,9	1999-2019	0,9 (-1,1 – 3,0)	3,7	1999-2019	3,3* (0,6 – 6,0)
50-59	19,8	1999-2002	13,0 (-3,6 – 32,5)	24,9	1999-2008	0,1 (-3,3 – 3,7)
		2002-2014	-0,9 (-3,0 – 1,3)		2008-2019	6,4* (3,7 – 9,2)
		2014-2019	10,1* (2,5 – 18,2)		1999-2019	3,5* (1,5 – 5,6)
		1999-2019	3,8* (0,8 – 6,9)			
60-69	39,7	1999-2019	3,2* (2,0 – 4,5)	24,9	1999-2017	6,8* (5,0 – 8,7)
					2017-2019	-22,5 (-54,8 – 32,7)
					1999-2019	3,5 (-1,8 – 8,9)
70+	33,3	1999-2019	5,6* (4,0 – 7,2)	25,7	1999-2017	6,8* (5,0 – 8,7)
					2017-2019	-22,5 (-54,8 – 32,7)
					1999-2019	3,5 (-1,8 – 8,9)
Standardizovana stopa	7,7	1999-2019	2,9* (2,0 – 3,8)	5,0	1999-2010	1,2 (-0,9 – 3,4)
					2010-2019	6,8* (3,7 – 9,9)
					1999-2019	3,7* (2,0 – 5,4)

Standardizovane stope prema populaciji sveta; APC – *Annual Percent Change*; AAPC *Annual Percent Change* – prosečna procentualna godišnja promena; 95%IP - 95% interval poverenja; *APC/AAPC je značajno različit od 0 za alfa=0,05; joinpoint rezultati nisu prikazani za uzrast 0-29 jer je bilo manje od 5 slučajeva godišnje.

Table 2. The number of deaths, crude and standardized* mortality rates (per 100,000), central Serbia, 1999-2019.

Year	Men			Women		
	Number of deaths	Crude rate	Standardized rate	Number of deaths	Crude rate	Standardized rate
1999	338	12.6	7.3	248	9.2	5.2
2000	299	11.2	6.5	246	8.7	4.1
2001	326	12.2	6.8	240	8.5	3.6
2002	342	12.9	7.1	270	9.6	4.4
2003	355	13.4	7.4	277	9.9	4.4
2004	358	13.5	7.3	261	9.3	4.0
2005	389	14.7	8.1	348	12.5	5.2
2006	377	14.3	7.8	296	10.7	4.7
2007	365	13.9	7.3	355	12.8	5.3
2008	426	16.3	8.3	354	12.8	5.1
2009	402	15.4	8.1	358	13.0	5.2
2010	423	16.3	8.5	379	13.8	5.7
2011	449	17.4	8.9	349	12.8	5.4
2012	441	17.2	8.1	386	14.3	5.4
2013	462	18.1	8.7	359	13.3	5.1
2014	432	17.0	7.9	352	13.1	5.1
2015	474	18.7	8.7	392	14.7	5.8
2016	441	17.5	8.0	414	15.6	5.7
2017	487	19.4	8.8	387	14.6	5.4
2018	473	19.0	8.6	395	15.0	5.6
2019	473	19.0	8.6	400	15.2	5.7
Average	406	15.7	7.9	336	12.3	5.1

*Standardized rates according to the world population

Table 3. Average age-specific and standardized incidence rates (per 100,000) for pancreatic cancer, joinpoint analysis of trends, central Serbia, 1999-2019.

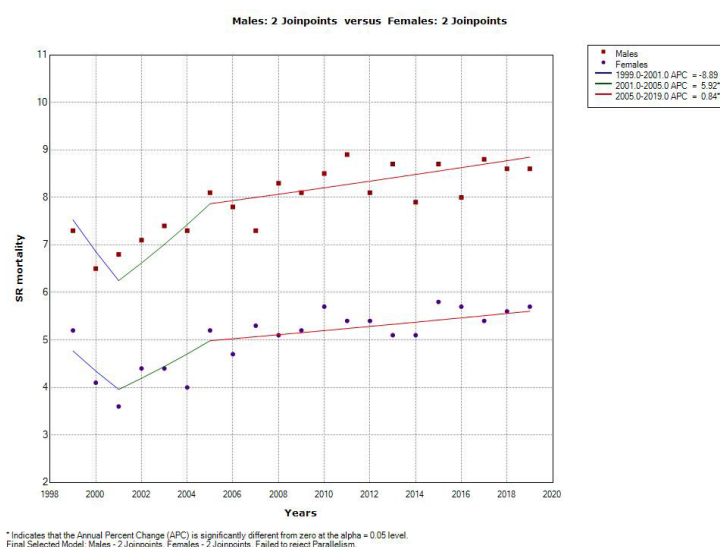
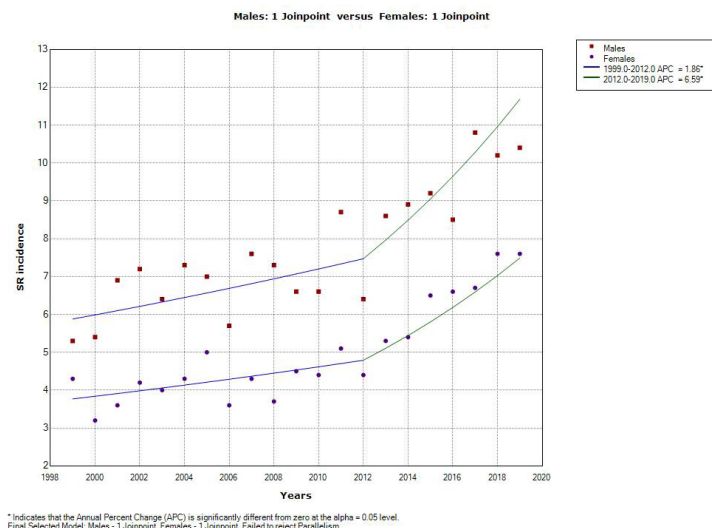
Age groups	Men			Women		
	Incidence rates	Period	APC/AAPC (95% CI)	Incidence rates	Period	APC/AAPC (95% CI)
0-29	0	-	-	0	-	-
30-39	1.2	1999-2019	-2.7 (-6.1 – 0.9)	0.8	1999-2019	0.1 (-3.9 – 4.3)
40-49	5.9	1999-2019	0.9 (-1.1 – 3.0)	3.7	1999-2019	3.3* (0.6 – 6.0)
50-59	19.8	1999-2002	13.0 (-3.6 – 32.5)	24.9	1999-2008	0.1 (-3.3 – 3.7)
		2002-2014	-0.9 (-3.0 – 1.3)		2008-2019	6.4* (3.7 – 9.2)
		2014-2019	10.1* (2.5 – 18.2)		1999-2019	3.5* (1.5 – 5.6)
		1999-2019	3.8* (0.8 – 6.9)			
60-69	39.7	1999-2019	3.2* (2.0 – 4.5)	24.9	1999-2017	6.8* (5.0 – 8.7)
					2017-2019	-22.5 (-54.8 – 32.7)
					1999-2019	3.5 (-1.8 – 8.9)
70+	33.3	1999-2019	5.6* (4.0 – 7.2)	25.7	1999-2017	6.8* (5.0 – 8.7)
					2017-2019	-22.5 (-54.8 – 32.7)
					1999-2019	3.5 (-1.8 – 8.9)
Standardized rate	7.7	1999-2019	2.9* (2.0 – 3.8)	5.0	1999-2010	1.2 (-0.9 – 3.4)
					2010-2019	6.8* (3.7 – 9.9)
					1999-2019	3.7* (2.0 – 5.4)

Standardized rates according to the world population; APC – Annual Percent Change; AAPC – Average Annual Percent Change; 95% CI-95% confidence interval; *AAPC is significantly different from 0 at the alpha=0.05 level; joinpoint results were not presented for age group 0-29 because there were less than 5 cases per year.

Tabela 4. Prosečne uzrasno-specifične i standardizovane stope mortaliteta (na 100.000) za rak pankreasa, joinpoint analiza kretanja stopa, centralna Srbija, 1999-2019. godine

Uzrasne grupe	Muškarci			Žene		
	Stope mortaliteta	Period	APC/AAPC (95% IP)	Stope mortaliteta	Period	APC/AAPC (95% IP)
0-29	0	-	-	0	-	-
30-39	0,8	1999-2019	-5,0 (-12,0 – 2,5)	0,5	1999-2019	-10,1 (-20,2 – 1,3)
40-49	4,5	1999-2019	-1,0 (-2,6 – 0,6)	2,6	1999-2019	1,2 (-1,5 – 4,0)
50-59	18,8	1999-2019	-0,1 (-1,0 -0,8)	10,33	1999-2019	2,3* (1,3 – 3,2)
60-69	41,4	1999-2019	1,7* (0,7 – 2,7)	25,0	1999-2019	1,4* (0,5 – 2,2)
70+	42,4	1999-2019	4,6* (3,4 – 5,9)	34,8	1999-2008	8,2* (5,2 – 11,3)
					2008-2019	0,8 (-1,3 – 2,9)
					1999-2019	3,9* (2,8 – 5,1)
Standardizovana stopa	7,9	1999-2019	1,2* (0,8 – 1,6)	5,0	1999-2001	-13,3 (-28,8 – 4,3)
					2001-2007	5,5* (1,2 – 10,0)
					2007-2019	0,6 (-0,5 – 1,7)
					1999-2019	0,6 (-1,5 – 2,7)

Standardizovane stope prema populaciji sveta; APC – *Annual Percent Change*; AAPC – *Average Annual Percent Change* – prosečna procentualna godišnja promena; 95%IP – 95% interval poverenja; *APC/AAPC je značajno različit od 0 za alfa=0,05; joinpoint rezultati nisu prikazani za uzrast 0-29 jer je bilo manje od 5 slučajeva godišnje.



Grafikon 1. Joinpoint analiza (test paralelizma) kretanja stopa a) incidencije i b) mortaliteta od raka pankreasa, centralna Srbija, 1999-2019. godine

Tabela 4. Prosečne uzrasno-specifične i standardizovane stope mortaliteta (na 100.000) za rak pankreasa, joinpoint analiza kretanja stopa, centralna Srbija, 1999-2019. godine

Age groups	Men			Women		
	Mortality rates	Period	APC/AAPC (95% CI)	Mortality rates	Period	APC/AAPC (95% CI)
0-29	0	-	-	0	-	-
30-39	0.8	1999-2019	-5.0 (-12.0 – 2.5)	0.5	1999-2019	-10.1 (-20.2 – 1.3)
40-49	4.5	1999-2019	-1.0 (-2.6 – 0.6)	2.6	1999-2019	1.2 (-1.5 – 4.0)
50-59	18.8	1999-2019	-0.1 (-1.0 -0.8)	10.33	1999-2019	2.3* (1.3 – 3.2)
60-69	41.4	1999-2019	1.7* (0.7 – 2.7)	25.0	1999-2019	1.4* (0.5 – 2.2)
70+	42.4	1999-2019	4.6* (3.4 – 5.9)	34.8	1999-2008	8.2* (5.2 – 11.3)
					2008-2019	0.8 (-1.3 – 2.9)
					1999-2019	3.9* (2.8 – 5.1)
Standardized rate	7.9	1999-2019	1.2* (0.8 – 1.6)	5.0	1999-2001	-13.3 (-28.8 – 4.3)
					2001-2007	5.5* (1.2 – 10.0)
					2007-2019	0.6 (-0.5 – 1.7)
					1999-2019	0.6 (-1.5 – 2.7)

Standardized rates according to the world population; APC – Annual Percent Change; AAPC – Average Annual Percent Change; 95% CI-95% confidence interval; *AAPC is significantly different from 0 at the alpha=0.05 level; joinpoint results were not presented for age group 0-29 because there were less than 5 cases per year.

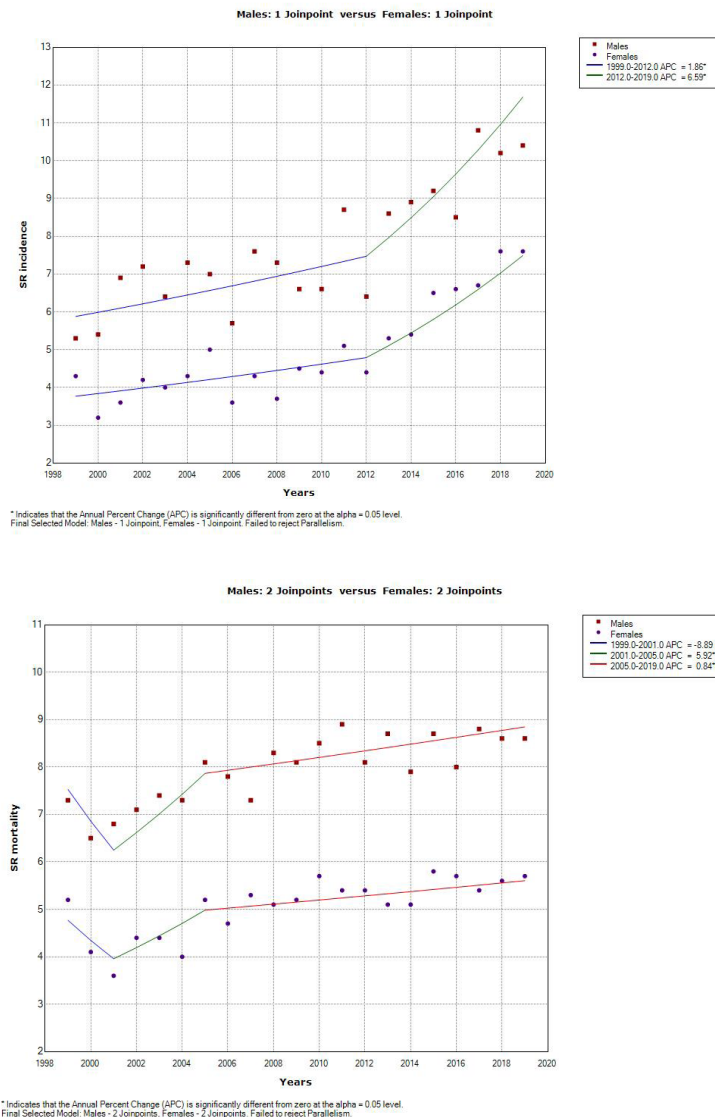


Figure 1. Joinpoint analysis (parallelism test) of trends a) incidence i b) mortality of pancreatic cancer, central Serbia, 1999-2019.

i gojaznost (2,4,13,14). Zemlje sa višim stopama incidencije i mortaliteta su češće imale veću prevalenciju pušenja, konzumiranja alkohola, fizičke neaktivnosti, gojaznosti, hipertenzije i visok holesterol (8). Ono što treba uzeti u obzir jeste i različita dostupnost dijagnostičkih procedura između razvijenih i nerazvijenih zemalja, kao i razlike u kvalitetu registara za rak. U razvijenijim zemljama veća incidencija može biti posledica veće dostupnosti zdravstvene zaštite i zdravstvene svesti. Osim toga, moguće je da su incidencija raka pankreasa i srodni faktori rizika potcenjeni u regionima sa nižim stepenom razvoja zbog manjeg prijavljivanja. Niže stope incidencije kod žena mogu se pripisati manjoj sklonosti ovom oboljenju ili izloženosti faktorima sredine, odnosno faktorima rizika, u manjoj meri.

Stope incidencije raka pankreasa rastu sa uzrastom. Posle 70+ se beleži najveća incidencija kod oba pola (2). Međutim, kod nas se u datom periodu beleži najveća stopa incidencije u uzrastu od 60-69 godina kod muškaraca (39,7 na 100.000), dok je kod žena stopa incidencije najveća u grupi starih 70 i više godina (25,7 na 100.000). U Kanadi je 99% obolelih bilo uzrasta 50 i više godina (15). Kina beleži najveću stopu incidencije u grupi starijih od 85 godina, kod oba pola (muškarci 59,8 na 100.000, žene 47,5 na 100.000) (16).

U periodu 1999-2019. godine u centralnoj Srbiji kod muškaraca se beleži značajan prosečan procentualni godišnji porast obolavanja od +2,9%, a kod žena +3,7%. Sličan trend porasta stopa incidencije beleži se i u drugim zemljama. *Huang et al.* (8) su, pored faktora povezanih sa nastankom raka pankreasa, analizirali i kretanje stopa incidencije i mortaliteta od raka pankreasa u 48 zemalja, u periodu od 2008. do 2017. godine. U Evropi 9 zemalja beleži porast stopa incidencije kod muškaraca, a najviše povećanje stopa beleži se na Islandu (AAPC, +8,8%), Kipru (+5,5%), i Francuskoj (+4,3%). Od ostalih regiona, najveći porast beleže Tajland (+4,5%) i Japan (+1,5%). Kod žena se porast beleži u 12 Evropskih zemalja, a najveće povećanje je na Malti (+6,0%), u Slovačkoj (+4,4%) i Francuskoj (+4,2%). Od ostalih zemalja uključenih u analizu najveći porast je na Novom Zelandu (+2,6%), u Japanu (+1,5%) i Južnoj Koreji (+1,7%). Jedino je Danska pokazala opadajući trend (-2,4%). U istoj studiji, u 18 zemalja opažen je porast stopa incidencije kod osoba od 50 i više godina, i to najviše

na Islandu, Malti i Francuskoj. Kod mlađih od 50 godina došlo je do porasta stopa incidencije u 8 zemalja (Nemačka, Švedska, Holandija, Ujedinjeno Kraljevstvo, Kanada, Češka, Turska i Australija). Porast stopa incidencije kod mlađih od 40 godina zabeležen je u četiri zemlje (Holandija, Kanada, Framžncuska i Ujedinjeno Kraljevstvo).

U periodu od 1999-2019. godine u centralnoj Srbiji je prosečna standardizovana stopa mortaliteta (na 100.000) za muškarce iznosila je 7,9, a za žene 5,0. Vrednosti stopa mortaliteta od raka pankreasa u svetu značajno variraju. Najviše stope mortaliteta beleže Zapadna Evropa (8,6 na 100.000 kod muškaraca, i 7,8 kod žena), Severna Amerika (8,0 muškarci i 6,5 žene), Centralna, Istočna i Severna Evropa, Australija i Novi Zeland (17). Više od 50% smrtnih ishoda od raka pankreasa registrovano je u visoko razvijenim zemljama (53,9%, 251.333 smrtna ishoda). Mortalitet od raka pankreasa raste sa uzrastom, skoro 90% smrtnih ishoda je nakon 55 godina starosti. U našoj studiji, najveće vrednosti stopa mortaliteta, kod oba pola, zabeležene se u uzrastu od 70 i više godina. Slične vrednosti stopa incidencije i mortaliteta od raka pankreasa pokazatelji su upravo fatalne prirode ove bolesti (2,18). Procenjuje se da 80-90% pacijenata ima neresektibilni tumor, jer se bolest otkrije tek u uznapređovalom stadijumu. Zbog svoje asimptomatske prirode, rak pankreasa se često otkrije tek tokom obdukcije. Osim toga, trenutni hemioterapijski režimi su često neefikasni za tumore koji se otkriju u uznapređovalom stadijumu (18). Još uvek nema markera za ranu detekciju, pa samim tim ni efikasnih skrining programa, koji bi zasigurno doprineli smanjenju stopa mortaliteta.

U centralnoj Srbiji u periodu 1999-2019. godine se beleži značajan porast standardizovanih stopa mortaliteta od +1,2% godišnje kod muškaraca, dok se kod žena beleži porast od 0,6% godišnje, ali on nije bio značajan. U istraživanju Huang i saradnika (8) u periodu 2008-2017. godine do porasta stopa mortaliteta od raka pankreasa kod muškaraca došlo je u tri evropske zemlje: Rusiji (+0,7%), Španiji (+0,6%), i Nemačkoj (+0,6%). Porast beleže Filipini (+4,2%), Tajland (+4,1%) i Čile (+1,8%). Kad se posmatraju stope mortaliteta kod žena, 14 zemalja je zabeležilo uzlazni trend. Od Evropskih zemalja Malta, Slovačka, i Litvanija imale su najveće vrednosti porasta.

Europe. This difference in incidence rates between different countries is not completely clear, but it may be the consequence of different environmental factors, as well as the exposure to risk factors, such as smoking, dietary factors and obesity (2,4,13,14). Countries with higher incidence and mortality rates had more frequently higher prevalence of smoking, alcohol consumption, physical inactivity, obesity, hypertension and high cholesterol (8). One should also take into consideration the availability of different diagnostic procedures between developed and undeveloped countries, as well as differences regarding the quality of cancer registries. In developed countries, higher incidence may be the result of greater availability of health care and health awareness. Beside, the incidence of pancreatic cancer and related risk factors may be underestimated in regions with lower level of development because the disease is reported less. Lower incidence rates in women may be attributed to the fact that women are less prone to this disease, or are less exposed to environmental factors, or risk factors.

Incidence rates of pancreatic cancer increase with age. The highest incidence is reported in both sexes after the age of 70 (2). However, in the given time period of our study, the highest incidence rate was registered in the age group 60-69 years in men (39.7 per 100,000), while in women the incidence rate was the highest in the group of patients aged 70 and older (25.7 per 100,000). In Canada, 99% of patients were aged 50 and older (15). In China, the highest incidence rate was registered in the group of patients older than 85 in both sexes (men 59.8 per 100,000 and women 47.5 per 100,000) (16).

In the period 1999-2019 in central Serbia, the significant average annual increase of 2.9% was registered in men, and in women it was +3.7%. A similar trend of increase in incidence rates was reported in other countries. Huang et al. (8) analyzed, beside factors related to the occurrence of pancreatic cancer, trends in incidence and mortality rates in 48 countries, in the period 2008-2017. In Europe, nine countries reported the increase of incidence rates in men, and the highest increase was reported in Iceland (AAPC, +8.8%), Cyprus (+5.5%), and France (+4.3%). As far as other regions are concerned, the highest increase is reported by Thailand (+4.5%) and Japan (+1.5%). In women, the increase is reported in 12 European countries, while the highest increase is in Malta

(+6.0%), Slovakia (+4.4%) and France (4.2%). Of other countries included in the analysis, the highest increase is in New Zealand (+2.6%), Japan (+1.5%), and South Korea (+1.7%). Only Denmark reported a trend of decrease (-2.4%). In the same study, in the group of people aged 50 and older, the increase in incidence rates was noted in 18 countries, and the highest increase was in Iceland, Malta and France. In people younger than 50, there came to the increase of incidence rates in 8 countries (Germany, Sweden, Holland, United Kingdom, Canada, Czechia, Turkey and Australia). The increase in incidence rates in people younger than 40 was noted in four countries (Holland, Canada, France and United Kingdom).

In the period 1999-2019, in central Serbia, the average standardized mortality rate (per 100,000) was 7.9 for men, and 5.0 for women. The values of mortality rates of pancreatic cancer vary significantly in the world. The highest mortality rates are registered in Western Europe (8.6 per 100,000 in men and 7.8 in women), North America (8.0 men and 6.5 women), Central, Eastern and Northern Europe, Australia and New Zealand (17). More than 50% of deathly outcomes caused by pancreatic cancer were registered in highly developed countries (53.9%, 251,333 deaths). Mortality of pancreatic cancer increases with age, and almost 90% of deaths was after 55 years of age. In our study, the highest mortality rates in both sexes were noted in the age group 70 years and older. Similar values of incidence and mortality rates of pancreatic cancer show the fatal nature of this disease (2,18). It has been estimated that 80-90% of patients have unresectable tumors due to the advanced stage of diagnosis. Due to its asymptomatic nature, pancreatic cancer is often detected only after autopsy. Additionally, the current chemotherapeutic regimen is often ineffective for tumors that are detected at advanced stages (18). There are no markers for early detection, and therefore, no efficient screening programs which would certainly contribute to the decrease in mortality rates.

In central Serbia in the period 1999-2019, a significant annual increase of +1.2% in standardized mortality rates was reported in men, and in women the increase of 0.6% was registered annually, but it was not significant. In the study of Huang and associates (8) in the period 2008-2017, there came to the increase of mortality rates of pancreatic

Najvažniji sredinski faktor rizika za rak pankreasa je pušenje. Pušači imaju skoro dva puta veći rizik da obole od raka pankreasa (3,13,19). Rizik za obolevanje raste sa dužinom pušenja i brojem dnevno popušanih cigareta (19). Prema rezultatima meta-analize relativni rizik za rak pankreasa za sadašnje pušače bio je 1,7, a za bivše 1,2, i ostaje povišen bar 10 godina od prestanka pušenja (20). Da je pušenje značajan faktor u nastanku raka pankreasa pokazuje i studija u Kanadi, gde se sa opadanjem broja pušača beleži značajan pad stope incidencije od -10% godišnje kod muškaraca (15). Kao i kod drugih malignih tumora povezanih sa pušenjem, međunarodne razlike u trendovima mortaliteta odražavaju različitu prevalenciju pušenja. Dok prevalencija pušenja u mnogim razvijenim zemljama opada, s druge strane ostaje visoka ili raste među ženama i u zemljama u razvoju. Prema podacima Nacionalnog istraživanja o zdravlju stanovništva u Republici Srbiji u 2019. godini, izloženost duvanskom dimu u Srbiji je visoka. Prevalencija navike pušenja duvanskih proizvoda (svakodnevno ili povremeno), u populaciji uzrasta 15 i više godina, iznosila je 31,9% (21). Nešto veći procenat pušača zabeležen je kod muškaraca (33,9%) nego kod žena (30,1%).

Osim pušenja, u populaciji Srbije rasprostranjeni su i drugi značajni faktori rizika za rak pankreasa. Konzumiranje alkohola je značajan faktor rizika za rak pankreasa (2,3). Alkohol konzumira 49,3% stanovnika Srbije, više muškaraca (65,0%), nego žena (35,2%) (21). Konzumiranje hrane bogate masnoćama povećava rizik od raka pankreasa, kao i prekomerna telesna težina i gojaznost (2). U Srbiji je 2019. godine, na osnovu indeksa telesne mase više od polovine (57,1%) stanovništva uzrasta 15 i više godina bilo prekomerno uhranjeno, odnosno pregojazno (36,3%) i gojazno (20,8%) (21). Prevalencija gojaznosti u Srbiji se neznatno razlikovala u odnosu na 2013. godinu (21,2%), ali je značajno veća u odnosu na 2006. godinu (17,3%). Osim toga, svakodnevno je povrće konzumiralo 50,2% stanovnika, a voće 39,4%. Skoro dve trećine stanovništva (64,6%) starosti od 18 do 64 godine ispunjavalo je preporuke Svetske zdravstvene organizacije za izvođenje fizičke aktivnosti koja utiče na poboljšanje zdravlja. Prema istom istraživanju 7,8% ispitanika navelo je da ima dijabetes, koji takođe predstavlja rizik za nastanak raka pankreasa (21).

Prema našim rezultatima uočava se da su stope incidencije niže u odnosu na stope mortaliteta.

Slično je zabeleženo i u istraživanju koje je obuhvatilo period 1960-2003. godine u Švedskoj (22). To se može pripisati niskoj specifičnosti prijavljenih umrlih. Moguće je i da je izvestan broj smrtnih slučajeva pogrešno klasifikovan kao primarni rak pankreasa. Pretpostavlja se da je to zato što oboljenje nije dijagnostikovano za vreme života pacijenta, ali se prepoznalo kao uzrok smrti na obdukciji, ili bolest nije prijavljena Registru za rak. Međutim, poslednjih godina kod nas se primećuje da je broj obolelih veći od broja umrlih, što možda govori u prilog tome da se ovo oboljenje ranije dijagnostikuje i uspešnije leči nego na početku ispitivanog perioda.

Jedan od nedostataka studije mogao bi da bude i sam kvalitet podataka u registrima za rak, pre svega zbog težine postavljanja dijagnoze ovog oboljenja. Podaci o stadijumu tumora, kao i o njegovoj veličini u trenutku dijagnoze nisu dostupni. Porast stopa incidencije mogao bi da bude posledica i boljih mogućnosti za dijagnostiku koje su se vremenom razvijale. Dodatne epidemiološke studije, koje bi uključile i identifikaciju faktora rizika, kao što su pušenje, konzumiranje alkohola, fizička aktivnost i gojaznost u budućnosti bile bi značajne.

Zaključak

U centralnoj Srbiji u periodu 1999-2019. godine stope incidencije i mortaliteta su u porastu kod oba pola. U cilju redukcije umiranja akcent treba staviti na ranom otkrivanju poremećaja zdravlja (skriningu), kao i blagovremenom lečenju primenom savremenih terapija. Neophodna su dalja istraživanja za identifikaciju potencijalnih faktora rizika za nastanak ove bolesti. U cilju prevencije nastanka ove bolesti neophodna je edukacija stanovništva o zdravim stilovima života. U budućnosti bi trebalo raditi na edukaciji lekara i starijeg stanovništva o prevenciji, simptomima i poboljšanju primarne zdravstvene zaštite u gerijatrijskom dobu.

Konflikt interesa

Autori su izjavili da nema konflikta interesa.

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cancer in men in three European countries: Russia (+0.7%), Spain (+0.6%) and Germany (+0.6%). The increase was reported in the Philippines (+4.2%), Thailand (+4.1%) and Chile (+1.8%). As for the mortality rates in women, 14 countries registered increasing mortality trends. Of the European countries, Malta, Slovakia, and Lithuania had the highest values of increase.

Smoking is the most important environmental risk for pancreatic cancer. The risk of getting pancreatic cancer is about twice as high among people who smoke (3,13,19). The risk of getting the disease increases with smoking duration and the number of cigarettes smoked per day (19). According to the results of meta-analysis, the relative risk of getting pancreatic cancer for current smokers was 1.7, and 1.2 for ex-smokers, and it stayed elevated at least 10 years after they quit smoking (20). A study in Canada showed that smoking was a significant factor for pancreatic cancer, where the decrease in the number of smokers was correlated with the decrease in incidence rates of -10% annually in men (15). As in other malignant tumors associated with smoking, international differences in mortality trends reflect different prevalence of smoking. While the prevalence of smoking decreases in many developed countries, it remains high or increases among women or in developing countries. According to the data of the National research on the population health in the Republic of Serbia in 2019, the exposure to tobacco smoking (every day or occasionally), in the population aged 15 years and older, amounted to 31.9% (21). Higher percentage of smokers was registered in men (33.9%) in comparison to women (30.1%).

In addition to smoking, in the population of Serbia, there are other significant risk factors for pancreatic cancer. Alcohol consumption is a significant risk factor for pancreatic cancer (2,3). Alcohol is consumed by 49.3% of population in Serbia, more by men (65.0%) than by women (35.2%) (21). Consuming food rich in fats increases the risk of pancreatic cancer, as well as overweight and obesity (2). In 2019, in Serbia, according to the body mass index, more than half of the people aged 15 and more were overweight (57.1%), pre-obese (36.3%) and obese (20.8%) (21). The prevalence of obesity in Serbia was slightly different in comparison to 2013 (21.2%), but it was significantly higher in comparison to 2006 (17.3%).

Additionally, 50.2% of residents consumed vegetables every day, and 39.4% consumed fruit. Almost two thirds of the population (64.6%) aged 18 to 64 years satisfied the recommendations of the World Health Organization for doing physical activity which improves health. According to the same study, 7.8% of participants reported to have diabetes, which is also a risk factor for pancreatic cancer (21).

According to our results, incidence rates were lower than mortality rates. Similar findings were noted in the study which included the period 1960-2003 in Sweden (22). This may be attributed to the low specificity of reported deaths. It is possible that a certain number of deaths were wrongly classified as a primary pancreatic cancer. It is assumed that this happens because the disease was not diagnosed during patient's lifetime, but was recognized as a cause of disease during autopsy, or the disease was not reported to the Cancer Registry. However, in recent years it has been noted that the number of new cases is higher than the number of deaths, which possibly speaks in favor of the fact that this disease is diagnosed earlier and treated more successfully than at the beginning of the examined period.

One of the weaknesses of this study may be the quality of data in Cancer Registries, first of all, because the disease is hard to be diagnosed. The data about tumor stages, as well as about its size at the moment of diagnosis are not available. The increase in incidence rates may be the consequence of better diagnostic possibilities that have developed over time. Additional epidemiological studies, which would include the identification of risk factors, such as smoking, alcohol consumption, physical inactivity and obesity, would be significant in the future.

Conclusion

In the period 1999-2019 in central Serbia, incidence and mortality rates increased in both genders. The accent should be put on the early detection of disorders (screening), and on timely treatment using modern therapies, which is aimed at the reduction of dying. Further research is necessary for the identification of risk factors for the occurrence of this disease. The education of population about healthy lifestyles is necessary in order to prevent this disease. In the future,

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education of physicians and older residents about prevention, symptoms and the improvement of primary health care of the elderly should be encouraged.

Competing interests

The authors declare no competing interests.

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