

OBOLEVANJE I UMIRANJE OD RAKA DOJKE U MUŠKOJ I ŽENSKOJ POPULACIJI CENTRALNE SRBIJE U PERIODU 2009-2020.GODINE

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SAŽETAK

Uvod/Cilj: U 2020. godini, rak dojke je vodeći uzrok obolevanja na globalnom nivou kada se posmatraju oba pola zajedno, a zatim slede rak prostate i rak pluća. Međutim, rak dojke je veoma redak kod muškaraca. U okviru ove deskriptivne studije analizirano je obolevanje i umiranje od raka dojke u populaciji muškaraca i žena Centralne Srbije za period od 2009. do 2020. godine.

Metode: Podaci o obolelima i umrlima od raka dojke, kao i o broju stanovnika, po polu i uzrastu, preuzeti su iz publikovanog i nepublikovanog materijala Instituta za javno zdravlje Srbije „Dr Milan Jovanović Batut“. U okviru analize korišćene su opšte, specifične i standardizovane stope incidencije i mortaliteta. *Joinpoint* regresiona analiza je korišćena za analizu trenda kretanja obolevanja i umiranja.

Rezultati: U periodu 2009-2020. godine, prosečna standardizovana stopa incidencije (na 100.000) za rak dojke iznosila je 1,3 za muškarce i 65,3 za žene, a prosečna stopa mortaliteta (na 100.000) 0,4 za muškarce i 19,8 za žene. Tokom posmatranog perioda kod muškaraca dolazi do porasta standardizovane stope incidencije za 1,9% godišnje i stope mortaliteta za 2,4%, ali bez značajnosti. Kod žena značajno raste standardizovana stopa incidencije za 3,5% godišnje u periodu 2013-2020, a standardizovana stopa mortaliteta značajno opada za -0,5% godišnje u periodu 2009-2020. godine. Kod oba pola, stopa mortaliteta i incidencije raste sa godinama starosti, izuzev što je kod žena stopa incidencije za uzrast 70 i više godina bila niža u odnosu na stopu incidencije za uzrast 60-69 godina.

Zaključak: Neophodno je dalje unaprediti sprovođenje organizovanog skrininga za rak dojke kod žena na teritoriji Centralne Srbije, raditi na redukciji i/ili eliminaciji faktora rizika, kao i na podizanju svesti muškaraca da postoji mogućnost da mogu da obolele i od raka dojke.

Ključne reči: deskriptivna studija, rak dojke, muškarci, žene, incidencija, mortalitet, *joinpoint* regresiona analiza.

Uvod

Prvi put u svetu rak dojke je, 2020. godine, postao vodeći uzrok obolevanja među svim malignim tumorima i to kada se posmatraju oba pola zajedno, a peti je vodeći uzrok umiranja, iza raka pluća, raka kolorektuma, raka jetre i raka želuca (1). Posmatrajući oba pola zajedno, u 2020. godini, u svetu je registrovano 2.261.419 novih slučajeva raka dojke žena, što je 11,7% svih novoobolelih od malignih tumora, a umrlo je 685.000 što je 6,9% svih umrlih od malignoma (1).

Kada se globalno posmatra populacija žena, onda je rak dojke prvi vodeći uzrok obolevanja (čini 24,5% svih obolelih od malignih tumora) i umiranja (čini 15,4% svih umrlih od malignih tumora) (1). Ova bolest se često smatra bolešću žena, iako se javlja kod oko 1% muškaraca (2). To govori da je ovaj maligni tumor veoma redak u muškoj populaciji.

U mnogim studijama ukazano je da postoje velike razlike u stopama incidencije i mortaliteta za

INCIDENCE AND MORTALITY FROM BREAST CANCER IN THE MALE AND FEMALE POPULATION OF CENTRAL SERBIA IN THE PERIOD 2009-2020

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SUMMARY

Introduction/Aim: In 2020, breast cancer is the leading cause of morbidity globally when considering both sexes together, followed by prostate cancer and lung cancer. However, breast cancer is very rare in men. In this descriptive study, incidence and mortality from breast cancer was analyzed in the population of men and women in Central Serbia for the period from 2009 to 2020.

Methods: Data on patients and deaths from breast cancer, as well as the number of inhabitants, by gender and age, were taken from published and unpublished material of the Institute for Public Health of Serbia "Dr. Milan Jovanović Batut". General, specific and standardized incidence and mortality rates were used in the analysis. Joinpoint regression analysis was used to analyze trends in morbidity and mortality.

Results: In the period 2009-2020. In 2010, the average standardized incidence rate (per 100,000) for breast cancer was 1.3 for men and 65.3 for women, and the average mortality rate (per 100,000) was 0.4 for men and 19.8 for women. During the observed period, the standardized incidence rate for men increased by 1.9% per year and the mortality rate by 2.4%, but without significance. In women, the standardized incidence rate increases significantly by 3.5% per year in the period 2013-2020, and the standardized mortality rate significantly decreases by -0.5% per year in the period 2009-2020. years. In both sexes, mortality and incidence rates increased with age, except that in women the incidence rate for the age of 70 and over was lower compared to the incidence rate for the age of 60-69.

Conclusion: It is necessary to further improve the implementation of organized screening for breast cancer in women in the territory of Central Serbia, to work on the reduction and/or elimination of risk factors, as well as on raising the awareness of men that there is a possibility that they can also get breast cancer.

Key words: descriptive study, breast cancer, men, women, incidence, mortality, joinpoint regression analysis.

Introduction

In 2020, for the first time in the world, breast cancer became the leading cause of morbidity among all malignant tumors when both sexes are observed together and it is the fifth leading cause of death behind lung cancer, colorectal cancer, liver cancer and stomach cancer (1). Looking at both sexes together, 2,261,419 cases of female breast cancer were registered worldwide in 2020, which is 11.7% of all new cases of malignant

tumors, while 685,000 died, which is 6.9% of all deaths caused by malignant tumors (1).

When the female population is observed globally, breast cancer is the first leading cause of morbidity (accounting for 24.5% of all patients with malignant tumors) and death (accounting for 15.4% of all deaths from malignant tumors) (1). This disease is often considered as a disease of women, although it occurs in about 1% of men (2).

rak dojke kako unutar jedne zemlje, tako i između različitih zemalja i regiona (3). Najveće stope incidencije za rak dojke su u zemljama koje su prošle ekonomsku tranziciju, a izuzetno visoke stope mortaliteta i rastuća stopa incidencije su u zemljama u tranziciji (1). Procenjuje se da će doći do povećanja broj novoobolelih (za oko 40%) i broja umrlih (za oko 50%) od raka dojke do 2040. godine (3). Ovo je posledica daljeg porasta broja stanovnika i starenja populacije (3).

Neki od faktora rizika koji se dovode u vezu sa rakom dojke su pozitivna porodična anamneza za rak dojke, stariji uzrast (više od 40 godina), menstruacija u mlađoj dobi, menopauza u starijoj dobi, trudnoća u kasnijim godinama, korišćenje hormona (dugotrajna upotreba kontraceptiva ili hormonska terapija u postmenopauzi), gojaznost, prekomerno konzumiranje alkohola, pušenje, itd. (4). Jako se malo zna o epidemiologiji i etiologiji raka dojke kod muškaraca, u poređenju sa ženama (4,5).

Cilj ove studije je da se analizira kretanje obolevanja i umiranja od raka dojke kod muškaraca i žena u Centralnoj Srbiji za period od 2009. do 2020. godine.

Metode

Za ovu deskriptivnu studiju dobijeni su podaci o novoobolelima i umrlima od raka dojke (šifra

C50 prema Međunarodnoj klasifikaciji bolesti, X revizija), kao i o broju stanovnika, po polu i uzrastu, iz publikovanih i nepublikovanih materijala Instituta za javno zdravlje Srbije „Dr Milan Jovanović Batut”. Za period od 1999. do 2015. godine podaci su preuzeti iz registara za rak u Centralnoj Srbiji Instituta za javno zdravlje Srbije „Dr Milan Jovanović Batut”, a za period 2016-2020. godine korišćeni su nepublikovani podaci Instituta za javno zdravlje Srbije „Dr Milan Jovanović Batut”.

U cilju analize podataka korišćene su sirove, specifične i standardizovane stope incidencije i mortaliteta za rak dojke. 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) (6). U cilju analize kretanja stopa obolevanja i umiranja od raka dojke za period od 1999-2020. godine korišćena je *joinpoint* regresiona analiza (engl. *Joinpoint Regression Program, Version 4.9.0.1. February, 2022; Statistical Methodology and Applications Branch, Surveillance Research Program, National Cancer Institute*), prema metodu Kim i saradnika (7).

Rezultati

U Centralnoj Srbiji, u periodu od 2009. do 2020. godine, prosečno učešće obolelih od raka

Tabela 1. Procentualno učešće novoobolelih i umrlih od raka dojke među novoobolelima i umrlima od svih malignih tumora u muškoj i ženskoj populaciji, Centralna Srbija, 2009-2020. godine

Godine	Procentualno učešće novoobolelih od raka dojke među novoobolelima od svih malignih tumora		Procentualno učešće umrlih od raka dojke među umrlima od svih malignih tumora	
	Muškarci	Žene	Muškarci	Žene
2009	0,4	26,1	0,3	17,5
2010	0,5	25,2	0,4	18,6
2011	0,4	25,7	0,3	18,5
2012	0,4	25,8	0,2	18,0
2013	0,5	20,2	0,2	18,2
2014	0,3	21,3	0,3	17,9
2015	0,5	22,3	0,3	18,9
2016	0,3	23,3	0,4	18,9
2017	0,4	23,1	0,3	19,0
2018	0,4	24,2	0,2	17,5
2019	0,4	24,3	0,4	18,4
2020	0,6	23,0	0,4	19,5
2009-2020	0,4	23,7	0,3	18,4

This means that this malignant tumor is very rare in the male population.

Many studies have shown that there are large differences in the incidence and mortality rates for breast cancer both within one country and between different countries and regions (3). The highest incidence rates for breast cancer are in countries that have undergone economic transition, while extremely high mortality rates and increasing incidence rates are in transition countries (1). It is estimated that the number of new cases of breast cancer (by about 40%) and the number of deaths (by about 50%) will increase until 2040 (3). This is a consequence of the further growth of the population and aging (3).

Some of the risk factors associated with breast cancer are a positive family anamnesis of breast cancer, older age (more than 40 years), menstruation at a younger age, menopause at an older age, pregnancy at a later age, use of hormones (long-term use of contraceptive or hormone therapy in postmenopause), obesity, excessive alcohol consumption, smoking, etc. (4). Very little is known about the epidemiology and etiology of breast cancer in men compared to women (4,5).

The aim of this study to analyze trends in morbidity and mortality of breast cancer in men and women in Central Serbia from 2009 to 2020.

Methods

As part of this descriptive study, data on new cases and deaths caused by breast cancer (code C50 according to the International Classification of Diseases, X revision), as well as on the population number, sex and age, were obtained from published and unpublished materials of the Institute for Public Health of Serbia "Dr. Milan Jovanović Batut". For the period 1999 to 2005, data were taken from the registers for cancer in Central Serbia of the Public Health Institute "Dr Milan Jovanovic Batut", and for the period 2016-2020 were obtained from the unpublished data of the Institute of Public Health of Serbia "Dr Milan Jovanovic Batut".

In order to analyze the data, raw, specific and standardized incidence and mortality rates for breast cancer were used. Standardized incidence and mortality rates were calculated with the help of the direct standardization method, by using the standard world population according to Segi (1960) (6). In order to analyze trends in incidence and mortality rates for breast cancer for the period 1999-2020, the joinpoint regression analysis was used (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 of Kim and associates (7).

Table 1. Percent share of new cases and deaths from breast cancer among new cases and deaths from all malignant tumors in male and female population, Central Serbia, 2009-2020

Years	Percent share of new cases of breast cancer among new cases of all malignant tumors		Percent share of deaths from breast cancer among deaths from all malignant diseases tumors	
	Men	Women	Men	Women
2009	0.4	26.1	0.3	17.5
2010	0.5	25.2	0.4	18.6
2011	0.4	25.7	0.3	18.5
2012	0.4	25.8	0.2	18.0
2013	0.5	20.2	0.2	18.2
2014	0.3	21.3	0.3	17.9
2015	0.5	22.3	0.3	18.9
2016	0.3	23.3	0.4	18.9
2017	0.4	23.1	0.3	19.0
2018	0.4	24.2	0.2	17.5
2019	0.4	24.3	0.4	18.4
2020	0.6	23.0	0.4	19.5
2009-2020	0.4	23.7	0.3	18.4

Tabela 2. Broj novoobolelih i umrlih, standardizovane stope incidencije i mortaliteta (na 100.000 stanovnika) za rak dojke po polu, Centralna Srbija, 2009-2020. godine

Godine	Muškarci				Žene			
	Broj novoobolelih	Inc*	Broj umrlih	Mt**	Broj novoobolelih	Inc*	Broj umrlih	Mt**
2009	54	1,1	24	0,4	3307	71,5	1145	20,3
2010	71	1,5	32	0,6	3146	67,8	1197	21,4
2011	59	1,3	23	0,4	3293	69,7	1171	19,9
2012	61	1,3	19	0,3	3186	68,3	1175	20,2
2013	63	1,4	18	0,3	2515	50,5	1169	19,2
2014	37	0,8	22	0,4	2675	53,6	1180	19,3
2015	72	1,4	26	0,5	2966	60,9	1215	19,8
2016	50	0,9	35	0,6	3145	64,7	1238	20,1
2017	69	1,4	23	0,4	3211	65,6	1279	20,3
2018	57	1,2	22	0,4	3359	74,2	1181	18,9
2019	63	1,4	35	0,5	3377	73,4	1221	19,3
2020	102	2,2	33	0,6	3122	63,3	1256	19,5
2009-2020	63	1,3	26	0,4	3109	65,3	1202	19,8

Inc- stopa incidencije; *standardizovana stopa incidencije/100.000 prema populaciji sveta; Mt- stopa mortaliteta; **standardizovana stopa mortaliteta/100.000 prema populaciji sveta.

dojke među svim obolelima od malignih tumora je iznosilo 0,4% za muškarce i 23,7% za žene, a prosečno učešće umrlih od raka dojke među svim umrlima od malignih tumora je bilo 0,3% za muškarce i 18,4% za žene (Tabela 1).

Broj novoobolelih od raka dojke u populaciji muškaraca Centralne Srbije je bio najveći 2020. godine i iznosio je 102, a najmanji 2014. godine i iznosio je 37 (Tabela 2). Broj umrlih muškaraca od raka dojke se kretao od 18 u 2013. godini do

33 u 2020. godini. Prosečna standardizovana stopa incidencije (na 100.000) za rak dojke za muškarce, u periodu 2009-2020. godine, je iznosila 1,3, a mortaliteta 0,4. U ženskoj populaciji Centralne Srbije najveći broj novoobolelih je zabeležen 2019. godine i iznosio je 3377, a najniži u 2013. godini 2515. Broj umrlih od raka dojke se kretao od 1145 u 2009. godini do 1238 u 2016. godini. Prosečna standardizovana stopa incidencije (na 100.000) za

Tabela 3. Prosečne uzrasno-specifične i standardizovane stope incidencije (na 100.000)** , joinpoint analiza kretanja stopa incidencije rakadojke popolu, Centralna Srbija, period 2009- 2020. godine

Uzrasne grupe (godine)	Muškarci			Žene		
	Inc	Period	APC (95%IP)	Inc	Period	APC (95%IP)
<30	0,03	-	-	1,9	2009-2020	-6,6 (-13,1-0,4)
30-39	0,5	2009-2020	2,2 (-19,4- 29,6)	41,6	2009-2020	1,9 (-1,4 -5,3)
40-49	1,5	2009-2020	6,7 (-6,2 -21,4)	137,3	2009-2020	0,5 (-3,0 -4,1)
50-59	3,7	2009-2020	-1,3 (-6,9- 4,6)	192,7	2009-2020	-1,2(-4,0- 1,7)
60-69	6,0	2009-2020	1,2 (-3,5 -6,2)	250,9	2009-2013 2013-2020	-7,2*(-12,4--1,6) 4,7*(2,2-7,3)
70+	8,2	2009-2020	2,7(-2,8 -8,4)	200,1	2009-2020	-0,4(-2,2- 1,5)
Ukupno	1,3**	2009-2020	1,9(-2,9-7,0)	65,3**	2009-2013 2013-2020	-6,8 (-13,9-0,9) 3,5*(0,1-7,1)

Inc – stopa incidencije; APC (engl. *Annual Percent Change*) – prosečna procentualna godišnja promena; 95%IP – 95% interval poverenja; * – APC je značajno različit od 0 za alfa=0,05.

Table 2. The number of new cases and deaths, standardized incidence and mortality rates (per 100,000) for breast cancer by sex, Central Serbia, 2009-2020

Years	Men				Women			
	Number of new cases	Inc*	Number of deaths	Mt**	Number of new cases	Inc*	Number of deaths	Mt**
2009	54	1.1	24	0.4	3307	71.5	1145	20.3
2010	71	1.5	32	0.6	3146	67.8	1197	21.4
2011	59	1.3	23	0.4	3293	69.7	1171	19.9
2012	61	1.3	19	0.3	3186	68.3	1175	20.2
2013	63	1.4	18	0.3	2515	50.5	1169	19.2
2014	37	0.8	22	0.4	2675	53.6	1180	19.3
2015	72	1.4	26	0.5	2966	60.9	1215	19.8
2016	50	0.9	35	0.6	3145	64.7	1238	20.1
2017	69	1.4	23	0.4	3211	65.6	1279	20.3
2018	57	1.2	22	0.4	3359	74.2	1181	18.9
2019	63	1.4	35	0.5	3377	73.4	1221	19.3
2020	102	2.2	33	0.6	3122	63.3	1256	19.5
2009-2020	63	1.3	26	0.4	3109	65.3	1202	19.8

Inc- incidence rate;*standardized incidence rate/100,000 according to the world population; Mt- mortality rate; **standardized mortality rate/100,000 according to the world population.

Results

In Central Serbia, from 2009 to 2020, of all cancer cases, the average share of breast cancer was 0.4% for men and 23.7% for women, while the average share of deaths from breast cancer among all deaths from malignant tumors was 0.3% for men and 18.4% for women (Table 1).

The highest number of new cases of breast cancer in the male population of Central Serbia was registered in 2020, and it amounted to 102,

while the lowest number was registered in 2014, when it amounted to 37 (Table 2). The number of men who died from bre. The average standardized incidence rates (per 100,000) of breast cancer in men was 1.3 in the period 2009-2020, while average standardized mortality rate was 0.4. In the female population of Central Serbia, the highest number of new cases was registered in 2019, when it amounted to 3377, while the lowest number was in 2013, 2515. The number of deaths

Table 3. Average age-specific and standardized incidence rates (per 100,000)**, joinpoint analysis of trends in incidence rates of breast cancer by sex, Central Serbia, for the period 2009-2020.

Age groups (years)	Men			Women		
	Inc	Period	APC (95%IP)	Inc	Period	APC (95%IP)
<30	0.03	-	-	1.9	2009-2020	-6.6 (-13.1-0.4)
30-39	0.5	2009-2020	2.2 (-19.4- 29.6)	41.6	2009-2020	1.9 (-1.4 -5.3)
40-49	1.5	2009-2020	6.7 (-6.2 -21.4)	137.3	2009-2020	0.5 (-3.0 -4.1)
50-59	3.7	2009-2020	-1.3 (-6.9- 4.6)	192.7	2009-2020	-1.2(-4.0- 1.7)
60-69	6.0	2009-2020	1.2 (-3.5 -6.2)	250.9	2009-2013 2013-2020	-7.2*(-12.4-1.6) 4.7*(2.2-7.3)
70+	8.2	2009-2020	2.7(-2.8 -8.4)	200.1	2009-2020	-0.4(-2.2- 1.5)
Total	1.3**	2009-2020	1.9(-2.9-7.0)	65.3**	2009-2013 2013-2020	-6.8 (-13.9-0.9) 3.5*(0.1-7.1)

Inc- incidence rate; APC - Annual Percent Change; 95%CI - 95% confidence interval; * - APC is significantly different from 0 for alpha=0.05.

rak dojke za žene, u periodu 2009-2020. godine, je iznosila 65,3, a mortaliteta 19,8.

U okviru posmatranog dvanaestogodišnjeg perioda dolazi do porasta standardizovane stope incidencije u muškoj populaciji za 1,9% godišnje, ali trend porasta nije bio značajan (Tabela 3, Grafikon 1a). Međutim kod žena je u periodu od 2009. do 2013. godine bio prisutan trend pada standardizovanih stopa incidencije raka dojke za -6,8% godišnje, a u periodu od 2013. do 2020. godine zabeležen je značajan porast stope incidencije za 3,5% godišnje (Tabela 3, Grafikon 1b). Kod muškaraca i žena raste stopa incidencije sa starenjem, izuzev što je kod žena stopa incidencije za uzrast 70 i više godina bila niža u odnosu na stopu incidencije za uzrast 60-69 godina. Kod muškaraca nije uočen značajan trend porasta ili opadanja stopa incidencije za rak dojke po uzrasnim grupama u posmatranom periodu, a kod žena je u uzrastu 60-69 godina zabeležen jedino statistički značajan pad stopa incidencije u periodu 2009-2013. godine za -7,2% godišnje, a potom u periodu 2013-2020. godine značajan trend porasta za 4,7% godišnje.

U okviru posmatranog dvanaestogodišnjeg perioda dolazi do porasta standardizovane stope mortaliteta u muškoj populaciji za 2,4% godišnje, ali trend porastanije bio značajan (Tabela 4, Grafikon 2a). Međutim kod žena je u periodu od 2009. do 2020. godine bio prisutan značajan trend pada standardizovanih stopa mortaliteta raka dojke za -0,5% godišnje (Tabela 4, Grafikon 2b). Kod muškaraca i žena raste stopa mortaliteta sa starenjem. Kod muškaraca nije uočen značajan trend porasta ili opadanja stopa mortaliteta za rak dojke po uz-

rasnim grupama za posmatrani period, a kod žena uzrasta 40-49 i 50-59 godina zabeležen je statistički značajan pad stopamortaliteta za -2,5% i -2,0%, kao i značajan porast stopa mortaliteta u uzrastu 70 i više godina za 2% godišnje.

Diskusija

U Centralnoj Srbiji, za period 2009-2020, prosečna standardizovana stopa incidencije (na 100.000) za rak dojke je iznosila 1,3 za muškarce i 65,3 za žene, a prosečna standardizovana stopa mortaliteta 0,4 za muškarce i 19,8 za žene. Prema podacima GLOBOCAN-a za 2020. godinu, regioni sa najvišim stopama incidencije za rak dojke žena su Australija/Novi Zeland (95,5/100.000), Zapadna Evropa (90,7/100.000), Severna Amerika (89,4/100.000) i Severna Evropa (79,6/100.000), a sa najnižim Centralna Amerika (39,5/100.000), Istočna (33,0/100.000) i Srednja Afrika (32,7/1000.000) i Južna i Centralna Azija (26,2/100.000) (1). Najviše stope mortaliteta za rak dojke žena su zabeležene u Melaneziji (27,5/100.000), Zapadnoj Africi (22,3/100.000), Mikroneziji/Polineziji (19,6/100.000) i na Karibima (18,9/100.000), a najniže u Istočnoj Aziji (9,8/100.000), Centralnoj Americi (10,4/100.000), Australiji/Novom Zelandu (12,1/100.000) i Severnoj Americi (12,5/100.000) (1). Prema ovim podacima Centralna Srbija pripada zemljama sa srednje visokim stopama incidencije i visokim stopama mortaliteta za rak dojke kod žena. Zemlja sa najvišom stopom incidencije je Belgija, a sa najvišom stopom mortaliteta je Barbados. U visoko razvijenim zemljama visoke stope incidencije za rak dojke dovode se u vezu

Tabela 4. Prosečne uzrasno-specifične i standardizovane stope mortaliteta (na 100.000)** , *joinpoint* analiza kretanja stopa mortaliteta raka dojke po polu, Centralna Srbija, period 2009-2020. godine

Uzrasne grupe (godine)	Muškarci			Žene		
	Mt	Period	APC (95%IP)	Mt	Period	APC (95%IP)
<30	0,01	-	-	0,2	2009-2020	-6,7(-27,4– 20,1)
30-39	0,05	-	-	6,2	2009-2020	-0,0(-2,5–2,5)
40-49	0,4	2009-2020	12,2 (-24,9–67,7)	21,5	2009-2020	-2,5*(-4,1 – 2,8)
50-59	1,0	2009-2020	-8,0 (-18,6– 4,1)	56,2	2009-2020	-2,0*(-2,6 – 1,3)
60-69	2,0	2009-2020	4,6 (-7,7 –18,4)	87,7	2009-2020	0,4 (-1,6 –0,7)
70+	5,1	2009-2020	2,4 (-2,4 –7,6)	142,6	2009-2020	2,0*(1,1–2,8)
Ukupno	0,5**	2009-2020	2,4 (-2,6 –7,5)	19,9**	2009-2020	-0,5*(-1,1 – 0,0)

Mt–stopa mortaliteta; APC (engl. *Annual Percent Change*) – prosečna procentualna godišnja promena; 95%IP – 95% interval poverenja; * - APC je značajno različit od 0 za alfa=0,05.

from breast cancer ranged from 1145 in 2009 to 1238 in 2016. The average standardized incidence rate (per 100,000) for women, in the period 2009-2020, was 65.3, while the average standardized mortality rate was 19.8.

Within the twelve-year period, there came to the increase in the standardized incidence rate in the male population by 1.9% per year, but the trend of increase was not significant (Table 3, Graph 1a). However, in the period 2009 to 2013, in women, there was a downward trend in standardized breast cancer incidence rates by -6.8% per year, and in the period from 2013 to 2020, a significant increase in the incidence rate by 3.5% per year was registered (Table 3, Graph 1b). In men and women, the incidence rate increases with age, except that in women the incidence rate was lower at the age of 70 and older compared to the incidence rate at the age of 60-69. In men, no significant trend of increase or decrease in the incidence rate of breast cancer was noticed in the observed period, while in women aged 60-69, a statistically significant decrease in the incidence rate was registered in the period 2009-2013, by -7.2% per year, and then in the period 2013-2020, a significant trend of increase of 4.7% a year was registered.

Within the observed twelve-year period, there came to the increase in the standardized mortality rate in the male population by 2.4% per year, but the trend of increase was not significant (Table 4, Graph 2a). However, from 2009 to 2020, in women there was a significant downward trend in standardized breast cancer mortality rates by -0.5% per year (Table 4, Graph 2b). For men and

women, the mortality rate increases with age. In men, a significant trend of increase or decrease in the mortality rate by age groups was not noticed in the observed period, while in women aged 40-49 and 50-59 a statistically significant decrease in the mortality rate of -2.5% and -2.0% was registered, as well as a significant increase of 2% per year in the mortality rate was registered in the age group 70 and over.

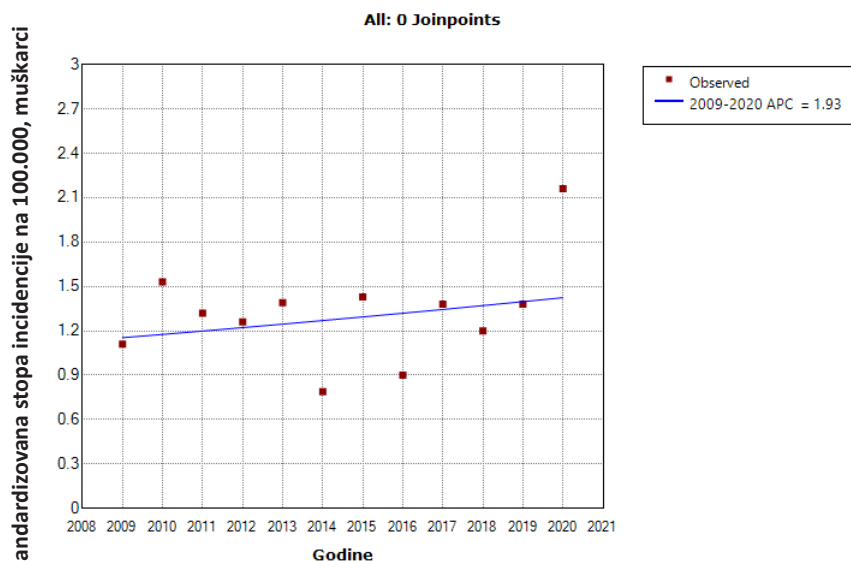
Discussion

In Central Serbia, the average standardized incidence rate (per 100,000) for breast cancer amounted to 1.3 for men and 65.3 for women in the period 2009-2020, while the standardized mortality rate was 0.4 for men and 19.8 for women. According to GLOBOCAN data for 2020, regions with the highest incidence rates for breast cancer were Australia/New Zealand (95.5/100,000), Western Europe (90.7/100,000), North America (89.4/100,000), North Europe (79.6/100,000), while the lowest rates were in Central America (39.5/100,000), Eastern (33.0/100,000) and Middle Africa (32.7/100,000) and South and Central Asia (26.2/100,000) (1). The highest mortality rates for breast cancer were registered in Melanesia (27.5/100,000), Western Africa (22.3/100,000), Micronesia/Polynesia (19.6/100,000), and Caribbean (18.9/100,000), while the lowest rates were in East Asia (9.8/100,000), Central America (10.4/100,000), Australia/Zealand (12.1/100,000) and North America (12.5/100,000) (1). According to these data, Central Serbia belongs to the countries with moderately high incidence rates and high mortality rates for breast cancer in women. Belgium is the country with the highest incidence

Table 4. Average age-specific and standardized mortality rates (per 100,000)** , joinpoint analysis of trends in mortality breast cancer rates by sex, Central Serbia, period 2009-2020

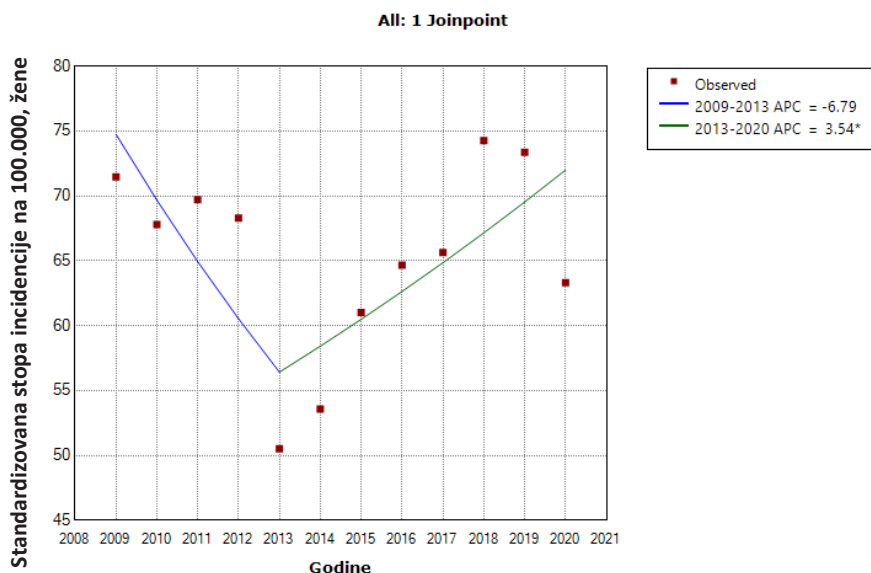
Age groups (years)	Men			Women		
	Mt	Period	APC (95%IP)	Mt	Period	APC (95%IP)
<30	0.01	-	-	0.2	2009-2020	-6.7 (-27.4– 20.1)
30-39	0.05	-	-	6.2	2009-2020	-0.0(-2.5–2.5)
40-49	0.4	2009-2020	12.2 (-24.9-67.7)	21.5	2009-2020	-2.5*(-4.1 – 2.8)
50-59	1.0	2009-2020	-8.0 (-18.6– 4.1)	56.2	2009-2020	-2.0*(-2.6 – 1.3)
60-69	2.0	2009-2020	4.6 (-7.7 –18.4)	87.7	2009-2020	0.4 (-1.6 –0.7)
70+	5.1	2009-2020	2.4 (-2.4 –7.6)	142.6	2009-2020	2.0*(1.1–2.8)
Total	0.5**	2009-2020	2.4 (-2.6 –7.5)	19.9**	2009-2020	-0.5*(-1.1 – 0.0)

Mt – mortality rates; APC - Annual Percent Change; 95%CI - 95% confidence interval; * - APC is significantly different from 0 for alpha=0,05.



a) muškarci

* Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level
Final Selected Model: 0 Joinpoints.



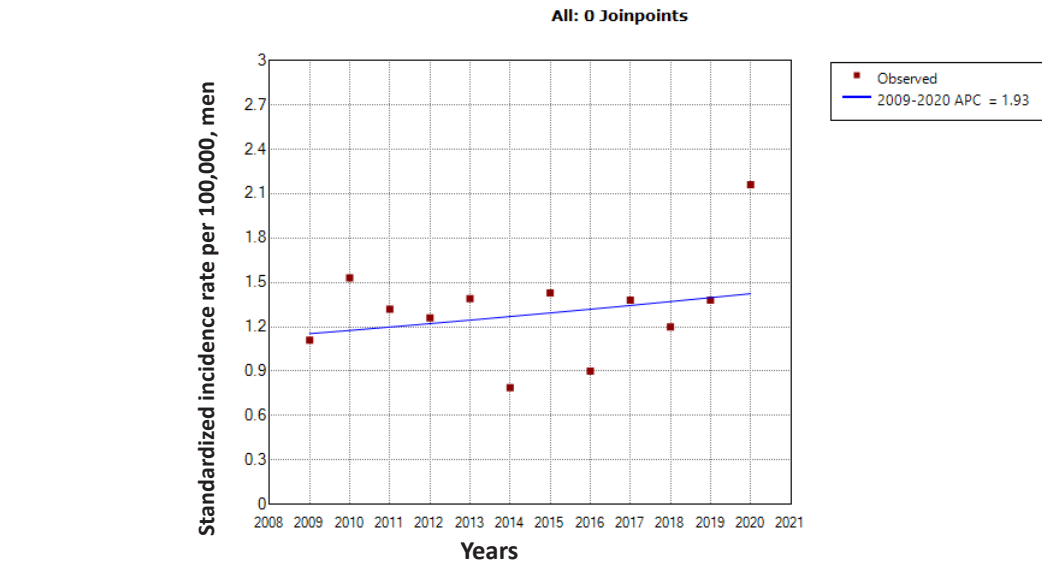
b) žene

* Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level
Final Selected Model: 1 Joinpoint.

Grafikon 1. Joinpoint analiza kretanja standardizovanih stopa incidencije raka dojke po polu, Centralna Srbija, period 2009-2020. godina

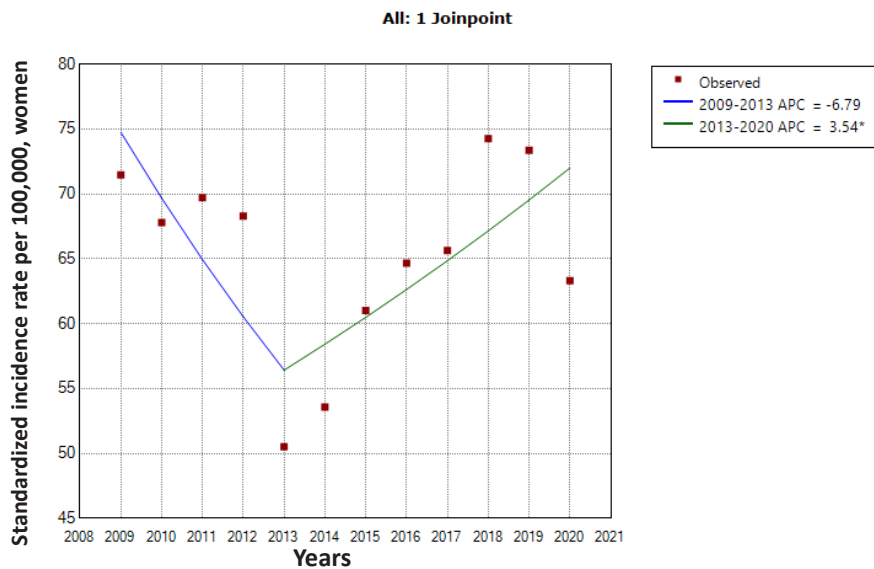
sa organizovanim sprovođenjem skrininga za rak dojke koji doprinosi ranijoj detekciji malignoma, životnim navikama (gojaznost, fizička neaktivnost i prekomerno konzumiranje alkohola), kao i sa faktorima vezanim za reproduktivno zdravlje: upotreba oralnih kontraceptiva, hormonska supstituciona terapija u menopauzi, kasna menopauza, ređe dojenje, manji broj živorođene dece i drugo) (8). U2020. godini standardizovane stope incidencije u razvijenim zemljama bile su skoro dva puta veće u odnosu na one u zemljama u razvoju (3). Smatra se da su visoke stope incidencije ovog tumora u ekon-

omski razvijenim zemljama posledica velike zastupljenosti faktora rizika u tim populacijama (3). Nasuprot ovome žene slabije razvijenih zemalja imale su za 17% veću smrtnost od raka dojke, za razliku od žena u razvijenim državama (3). Veća smrtnost je rezultat nepravovremenog postavljanja dijagnoze bolesti, ali na prvom mestu nesprovođenja organizovanog skrininga - mamografije. Takođe, kod žena jevrejskog porekla (Aškenazi) visoka je učestalost BRCA1 i BRCA2 antigena što vodi većoj učestalosti raka dojke u Izraelu i nekim delovima Evrope (9).



a) males

* Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level
Final Selected Model: 0 Joinpoints.



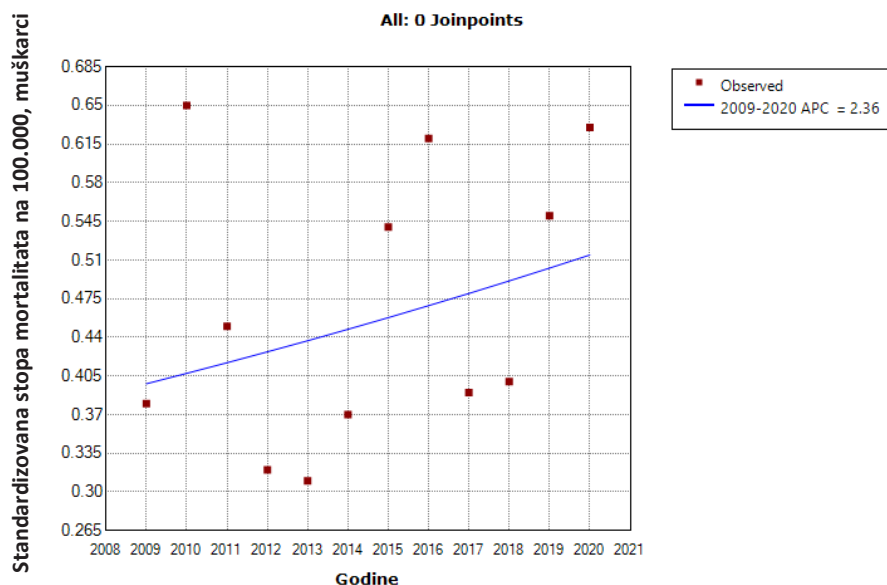
b) females

* Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level
Final Selected Model: 1 Joinpoint.

Graph 1. Joinpoint analysis of trends in standardized mortality rates for breast cancer by sex, Central Serbia, period 2009-2020

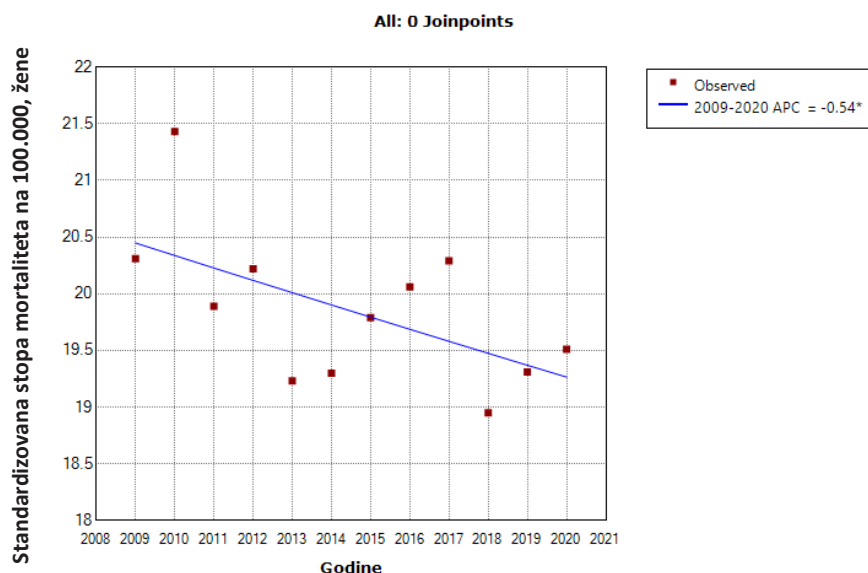
rate, while Barbados has the highest mortality rate. In highly developed countries, high incidence rates for breast cancer are associated with the organized screening for breast cancer which contributes to the early detection of cancer, habits (obesity, physical inactivity and excessive alcohol consumption), as well as with factors related to reproductive health: use of oral contraceptives, hormone replacement therapy in menopause, late menopause, rarer breastfeeding, smaller number of live born children), etc. (8). In 2020, standardized incidence rates in developed countries were almost two times higher in comparison to

developing countries (3). High incidence rates for this tumor in economically developed countries are considered to be the consequence of presence of risk factors in these populations (3). In contrast, mortality rates were higher for 17% in women from less developed countries, in comparison to women in developed countries (3). Higher mortality is the result of untimely diagnosis of this disease, but in the first place not conducting organized screening – mammography. Also, women of Jewish origin (Ashkenazi) have a high frequency of BRCA1 and BRCA2 antigens, which leads to a higher frequency of



a) muškarci

* Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level
Final Selected Model: 0 Joinpoints.



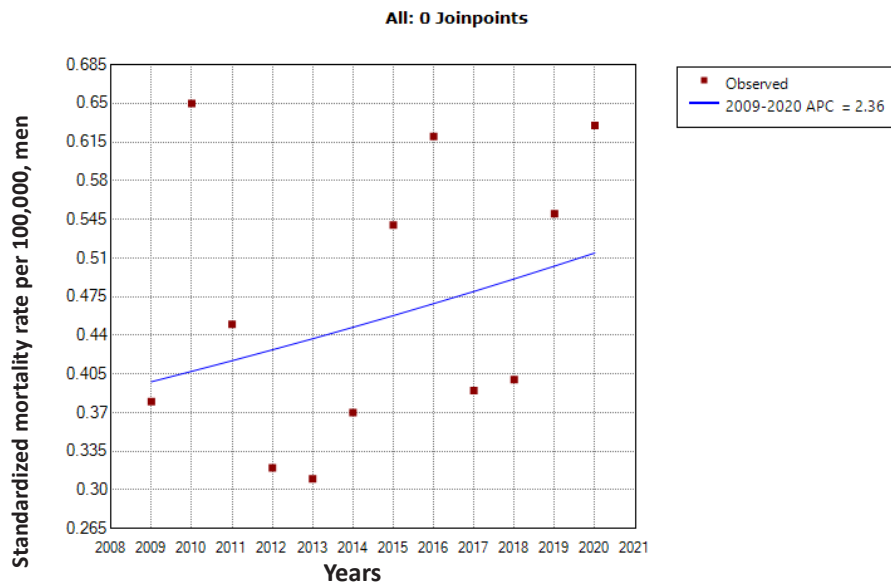
b) žene

* Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level
Final Selected Model: 0 Joinpoints.

Grafikon 2. Joinpoint analiza kretanja standardizovanih stopa mortaliteta raka dojke po polu, Centralna Srbija, period 2009-2020. godina

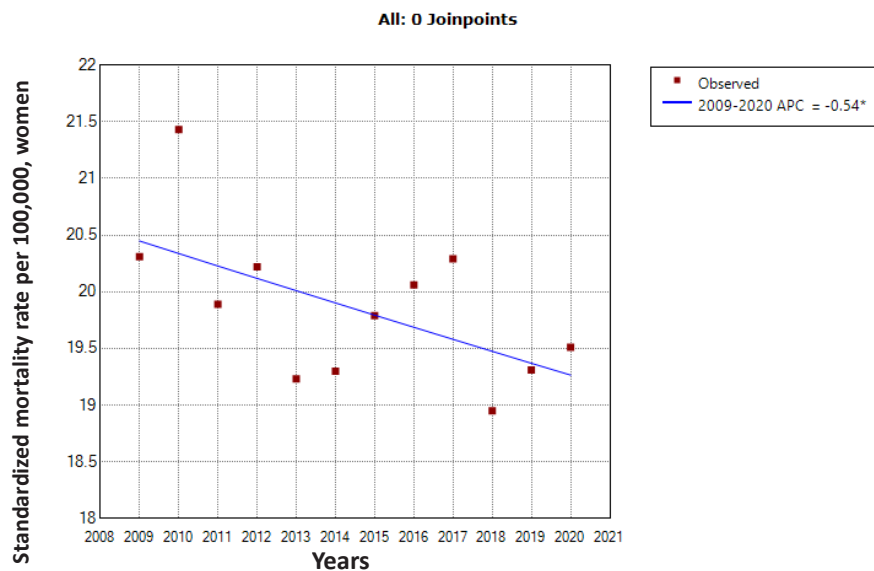
U Centralnoj Srbiji prosečna standardizovana stopa incidencije za rak dojke muškaraca je bila 50,2 puta manja od stope incidencije za žene, a prosečna standardizovana stopa mortaliteta 49,5 puta manja od stope mortaliteta za žene. U 2017. godini, u Sjedinjenim Američkim Državama (SAD) standardizovana stopa incidencije za rak dojke kod muškaraca je iznosila 1,3/100.000, što je oko 97 puta manje u odnosu na standardizovanu stopu incidencije kod žena (125,1/100.000), a stopa mortaliteta je bila 68,6 puta manja (muškarci – 0,3/100.000, a žene – 19,9/100.000)(10). Kod

muškaraca rak dojke čini manje od 1% svih malignih tumora i manje od 1% svih malignih tumora dojke (11). Neki od faktora rizika za nastanak raka dojke kod muškaraca su starenje, neravnoteža androgena/estrogena, izloženost zračenju i porodična istorija raka dojke (11,12). Od mutacija u genima najčešće se javlja mutacija gena BRCA2 (11,12). Najveći problem predstavlja činjenica da nije razvijena svest o mogućnosti nastanka ovog malignog tumora kod muškaraca. Iz navedenog razloga obično se lekaru javljaju kada je maligni tumor uznapredovao, što vodi većoj smrtnosti.



a) males

* Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level
Final Selected Model: 0 Joinpoints.



b) females

* Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level
Final Selected Model: 0 Joinpoints.

Graph 2. Joinpoint analysis of trends in standardized mortality rates for breast cancer by sex a) men and b) women, Central Serbia, period 2009-2020

breast cancer in Israel and some parts of Europe (9). In Central Serbia, the average standardized incidence rate for breast cancer in men was 50.2 times lower than the incidence rate in women, while the standardized mortality rate was for 49.5 times lower than the mortality rate in women. In 2017, in the United States of America (USA), the standardized incidence rate for breast cancer in men amounted to 1.3/100,000, which is almost 97 times less in comparison to the standardized incidence rate in women (125.1/100,000), while the mortality rate was for 68.6 times lower (men

– 0.3/100,000, women – 19.9/100,000) (10). In men, breast cancer accounts for less than 1% of all malignant tumors and less than 1% of all malignant breast tumors (11). Some of the risk factors for breast cancer in men are aging, androgen/estrogen imbalance, exposure to radiation, and family history of breast cancer (11,12). The BRCA gene mutation occurs most frequently of all gene mutations (11,12). The biggest problem is the fact that awareness about the possibility of this malignant tumor in men has not been developed. For the above-mentioned reason, they usually

Neke studije ukazuju da muškarci sa rakom dojke imaju veći rizik od nekih drugi malignih tumora.

U Centralnoj Srbiji, kod oba pola, prosečne uzrasno-specifične stope incidencije (na 100.000) su niske pre 30. godine života, a najviše su kod muškaraca u uzrastu 70 i više godina (8,2) i kod žena 60-69 godina (250,9), u periodu od 2009. do 2020. godine. Prosečno uzrasno specifična stopa mortaliteta za žene i muškarce raste sa godinama starosti i najvećaje kod osoba uzrasta ≥ 70 godina (142,6/100.000 - žene i 5,1/100.000 - muškarci) (10). Najveće stope incidencije i mortaliteta (na 100.000) kod muškaraca u Americi su u uzrastu 80 i više godina (8,30 i 2,68). Takođe, uočava se da je najveći procenat muškaraca sa smrtnim ishodom usled raka dojke u uzrastu 60-69 godina (10). Upravo zbog toga što je ovaj tumor redak i zbog nepostojanja skrining programa većina muškaraca bude dijagnostikovana u starijem životnom dobu i sa uznapređovalom bolešću, što značajno pogoršava prognozu (13).

U populaciji žena Centralne Srbije dolašlo je do značajnog porasta standardizovane stope incidencije u periodu 2013-2020. godine za 3,5% godišnje, a u muškoj populaciji za 1,3% godišnje, ali porast nije bio značajan. Nije uočena značajna promena kretanja trendova incidencije raka dojke po uzrasnim grupama kod oba pola, sem kod žena u uzrastu 60-69 godina gde je prisutan značajan pad stope incidencije za 7,2% godišnje u periodu 2009-2013, da bi potom došlo do značajnog porasta od 4,7% godišnje u periodu 2013-2020. Međutim, kod žena dolazi do značajnog pada stope mortaliteta tokom posmatranog dvanaestogodišnjeg perioda i to za -0,5% godišnje i za 2,4% godišnje kod muškaraca, ali trend porasta nije bio značajan.

Mnoge epidemiološke studije pokazuju da je trend incidencije karcinoma muške dojke u porastu (14), a stope mortaliteta su u zemljama centralno-istočne Evrope i Latinske Amerike u porastu za razliku od pada u severozapadnoj Evropi, Rusiji i SAD-a (za čak 10-40%) (15). Kod žena, dolazi do brzog porasta incidencije raka dojke u Severnoj Americi, Evropi i Okeaniji, tokom osamdesetih i devedesetih godina XX veka (16), a što se dovodi u vezu sa porastom obuhvata ženske populacije mamografijom i sve većom prevalencijom faktora rizika u populaciji (17). Međutim, u ranim 2000. godinama dolazi do pada incidencije raka dojke žena što se može objasniti manjim korišćenjem

hormonske supstitucione terapije u postmenopauzi padom obuhvata skriningom - mamografijom (18,19). Od 2007. godine, ponovo dolazi do porasta incidencije raka dojke žena (20,21) usled primene sve boljih skrining metoda. Takođe se u ovom vremenskom periodu uočava da su među obolelima od raka dojke sve češće prisutni tumori sa pozitivnim receptorima na estrogen (22). Češća pojava pozitivnih receptora na estrogen kod raka dojke dovodi se u vezu sa sve većom prevalencijom gojaznosti u populaciji, kao i sa činjenicom da se mamografijom prvenstveno otkriva baš ova vrsta sporo rastućeg malignoma (23). Obrnuta situacije je zabeležena u nerazvijenim zemljama (Afrika, Južna Amerika i Azija), gde je uočen trend porasta obolevanja od raka dojke zbog prihvatanja zapadnih stilova života (brza hrana, fizička neaktivnost, itd.), veće zaposlenosti žena što je dovelo do rađanja manjeg broja dece i odlaganja rađanja u kasnijim godinama života (3).

Nasuprot trenda incidencije, trend mortaliteta od raka dojke kod žena u razvijenim zemljama opada od 1980. godine (23). Ovo je posledica stalnog razvoja novih vidova lečenja i skrining programa. Upravo zbog toga došlo je do povećanja broja žena koje žive sa rakom dojke i u 2020. godini iznosio je oko 7,8 miliona (3). Sa druge strane stope mortaliteta pokazuju porast u subsaharskoj Africi i među najvišima su na globalnom nivou (24).

Petogodišnje preživljavanje obolelih od ovog tumora varira od 85-90% u razvijenim zemljama do 66% u 12 zemalja subsaharske Afrike (25,26). Najniže petogodišnje preživljavanje je zabeleženo u Ugandi i iznosi samo 12%. Visoke stope mortaliteta u subsaharskoj Africi i drugim nerazvijenim zemljama su pre svega posledica kasnog otkrivanja oboljenja, nedostupnosti adekvatnog načina lečenja i nepristupačnost zdravstvene zaštite (27). U razvijenim zemljama sveta stope mortaliteta od raka dojke kod muškaraca su konstantno veoma niske i variraju između 0,3-0,4/100.000 u periodu od 1970. do 1990, a potom sledi njihov blag pad (28).

Neophodno je dalje sprovođenje analitičkih studija sa ciljem otkrivanja faktora rizika za nastanak ovog malignog tumora i sprovođenja adekvatnih preventivnih programa.

Zaključak

Trend porasta standardizovanih stopa incidencije i mortaliteta kod muškaraca, u periodu

come to the doctor when the malignant tumor has advanced, which leads to higher mortality. Some studies have indicated that men with breast cancer have a higher risk of some other malignant tumors.

In Central Serbia, in both sexes, the average age-specific incidence rates (per 100,000) are low before the age of 30, while the highest rates are in men aged 70 and older (8.2) and in women aged 60-69 (250.9) in the period 2009 to 2020. The average age-specific mortality rate for women and men increases with age and it is highest in persons aged ≥ 70 (142.6/100,000 – women and 5.1/100,000 – men) (10). The highest incidence and mortality rates (per 100,000) in men in America are at the age of 80 and over (8.30 and 2.68). Also, it has been observed that the highest percentage of men with deathly outcome caused by breast cancer is between the ages 60-69 (10). Due to the fact that this tumor is rare and due to the lack of screening programs, most men are diagnosed with advanced disease at an older age, which significantly worsens the prognosis (13).

In the female population of Central Serbia, there came to the significant increase in the standardized incidence rate in the period 2013-2020 for 3.5% per year, while in the male population for 1.3% per year, but the increase was not significant. There was no significant change of trends in incidence rates for breast cancer according to age groups in both sexes, except in women aged 60-69, where a significant decrease in incidence for -7.2% was observed in the period 2009-2013. However, a significant decrease in mortality rate in women was observed during the twelve-year period, that is, for -0.5% per year and for 2.4% per year in men, but the trend of increase was not significant.

Many epidemiological studies have indicated that the trend in the incidence of breast cancer in men is on the rise, while the mortality rates increased in countries of Central-Eastern Europe and Latin America in contrast to the decrease in Western and North Europe, Russia and the USA (for even 10-40%) (15). In women, there came to the rapid increase in the incidence of breast cancer in North America, Europe and Oceania, during the 1980s and 1990s (16), which is associated with the increase in the proportion of women who have undergone mammography and the increasing prevalence of risk factors in the population (17). However, in the early 2000s, there was a decline

in the incidence of breast cancer in women, which can be explained by the lower use of hormone replacement therapy in postmenopause and the decline in the proportion of women covered by screening – mammography (18,19). Since 2007, there has been an increase in the incidence of breast cancer in women (20,21) due to the application of more efficient screening methods. Also, in this period, it was observed that tumors with positive estrogen receptors were increasingly present among breast cancer patients (22). The more frequent occurrence of positive estrogen receptors in breast cancer is related to the increasing prevalence of obesity in the population, as well as to the fact that mammography primarily detects this type of slow-growing malignancy (23). The reverse situation was observed in underdeveloped countries (Africa, South America and Asia), where the increase in the incidence of breast cancer was observed due to the acceptance of Western lifestyle (fast food, physical inactivity, etc.), higher employment of women, which led to fewer births and delayed childbearing (3).

Contrary to the trend of incidence, the trend of mortality from breast cancer in women in developed countries has decreased since 1980 (23). This is the consequence of the constant development of new types of treatment and screening programs. This is precisely why the number of women living with breast cancer has increased, and in 2020 it was around 7.8 million (3). On the other hand, mortality rates show the increase in sub-Saharan Africa and are among the highest at the global level (24).

Five-year survival from this tumor varies between 85-90% in developed countries to 66% in 12 countries of sub-Saharan Africa (25,26). The lowest five-year survival was registered in Uganda and it was only 12%. High mortality rates in sub-Saharan Africa and other underdeveloped countries are primarily the result of late detection of disease, unavailability of adequate treatment and inaccessibility of health care (27). In developed countries, mortality rates of breast cancer in men are constantly very low and vary between 0.3-0.4/100,000 in the period from 1970 to 1990, followed by the slight decline (28).

It is necessary to carry out further analytical studies with the aim of revealing risk factors for the occurrence of this malignant tumor and implementing adequate preventive programs.

2009-2020.godine, zahteva uvođenje edukativnih programa ucilju upoznavanja muške populacije sa mogućnošću obolevanja i umiranja od ovog malignoma, kao i sa faktorima rizika i mogućim preventivnim merama. U populaciji žena porast trenda incidencije za rak dojke od 2013. godine ukazuje na neophodnost redukcije ili eliminacije faktora rizika (gojaznosti, fizičke neaktivnosti), kao i unapređenje sprovođenja organizovanog skrininga, odnosno mamografije, a trend pada umiranja na pravovremeno otkrivanje i adekvatno lečenje.

Konflikt interesa

Autori su izjavili da nema konflikta interesa.

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Conclusion

The trend of the increase in standardized incidence and mortality rates in men, in the period 2009-2020 requires the introduction of educational programs aimed at informing the male population about the possibility of this disease and death caused by this malignancy, as well as about risk factors and possible preventive measures. Since 2013, in the female population, the increase in the incidence of breast cancer has indicated the necessity to reduce or eliminate risk factors (obesity, physical inactivity), as well as to improve the implementation of organized screening, that is, mammography, while the trend of the decrease in mortality has indicated the timely detection and adequate treatment.

Competing interests

The authors declared no competing interests.

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