TRENDS IN PANCREATIC CANCER MORTALITY IN SERBIA: A JOINPOINT REGRESSION ANALYSIS

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ABSTRACT

Pancreatic cancer is a significant public health problem worldwide. It is currently ranked as the 12th most common malignancy and the 6th leading cause of cancer mortality. This study aimed to investigate sex-specific and age-specific pancreatic cancer mortality trends and disparities in the Serbia from 2000 to 2021. A descriptive epidemiological population-based study analyzing pancreatic cancer mortality was conducted. Age-standardized mortality rates (ASMRs) were calculated using the Segi's world standard population. Temporal trends for pancreatic cancer mortality were assessed using the joinpoint regression analysis. Age-standardized rate of pancreatic cancer in Serbia was 6.4/100,000 (7.9/100,000 in men, 5.1/100,000 in women). The rates were found to be 1.6 times higher in men than women. Pancreatic cancer mortality trend significantly increased from 2000 to 2010 in men (APC=+2.4%, 95%CI: 0.3 – 1.4), after 2010 rates nonsignificantly decline (APC=-0.4%; (95%CI: -2.5 – 0.5). In women, mortality trend significantly increased by +1.8% at an annual level (95%CI: 0.7–2.7). The mortality of pancreatic cancer increased by age. The joinpoint analysis showed a significant rising trend of mortality rates in all age groups 60+, with the highest average annual percent change being reported in the age groups 85+ (AAPC=+3.1 (95%CI: 1.6–4.5)). The provision of updated statistics on the occurrence and outcomes of pancreatic cancer, time trends among various population groups, along with a better understanding of its etiology and identification of causal changeable risk factors – are essential when it comes to the primary prevention of this particular disease.

Keywords: *Pancreatic cancer, age-standardized rates, mortality trend, joinpoint analysis.*

INTRODUCTION

Pancreatic cancer is a significant public health problem worldwide (1, 2). Despite advances in cancer therapy, pancreatic cancer is one of the most aggressive and most lethal malignancies, with the five-year survival rate less than 10% even in developing countries (3).

Globally, the number of new cases of pancreatic cancer has significantly increased for the past two decades (4), and it is currently ranked as the 12th most common malignancy (2.6% of all carcinomas) and the 6th leading cause of cancer mortality (4.8% of all carcinomas). In the year of 2022, pancreatic cancer caused 467,409 deaths globally, including 247,589 (52.9%) deaths among males and 219,820 (47.1%) deaths among females. Most of the deaths were recorded in Asia (212,243; 45.4% of the total), followed by Europe (138,644; 29.7%); whereas the least number of death cases was recorded in Africa (17,770; 3.8%) and Oceania (4,389; 0.9%). China (106,295), the US (49,491) and Japan (43,265) had the highest number of deaths from pancreatic cancer in 2022 among both sexes. Globally, the ASR of pancreatic cancer mortality was 4.2 per 100,000 (the ASR was 5.0/100,000 for men and 3.5/100,000 for women) with considerable variations in mortality rates by country and region (5). The age-standardized incidence and mortality rates are four to five times higher in countries with a high/very high Human Development Index (HDI) when compared to low/middle HDI countries.

Based on the estimates from the GLOBOCAN 2022, pancreatic cancer was the sixth most common malignant tumor in the Republic of Serbia, accounting for 3.4% of the total number of all malignant tumors (1,433 cases) and the standardized incidence rate of 7.6/100,000. In the year of 2022, 1,343 people died of pancreatic cancer in the Republic of Serbia (5.6% out of the total number of deaths caused by malignant tumors), whereas the standardized mortality rate was 6.9/100,000, which is why it is considered the fourth most common malignant tumor as regards the structure of mortality from malignant tumors (5).

The etiology of pancreatic cancer is complex and it is still insufficiently elaborated. Apart from unchangeable genetic factors, age and gender, there are a few significant modifiable pancreatic cancer risk factors such as the following: tobacco smoking, obesity, type 2 diabetes, alcohol consumption, physical inactivity, nutrition factors, chronic pancreatitis and exposure to certain chemicals, hypertension and high cholesterol level (2).

This study aimed to investigate sex-specific and age-specific pancreatic cancer mortality trends and disparities in the Serbia from 2000 to 2021.

MATERIALS AND METHODS

Data sources

A descriptive epidemiological population-based study analyzing pancreatic cancer mortality was conducted. The data on pancreatic cancer mortality in Serbia (excluding the territory of Autonomous Province of Kosovo and Metohija) for the period 2000 – 2021, were obtained from the Statistical Office of the Republic of Serbia. The primary data source refers to the death certificates completed by a physician who determines the time and cause of death – based on which special statistical reports on death are completed (DEM-2) by health institutions. The annual number of deaths was collected in accordance with the codes listed in International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) (code C25) and it is stratified according to age and 5-year age groups. The data related to the exact number and structure of the population according to age and gender, used as the denominator in calculations of death indicators, were derived from the Statistical Office of the Republic of Serbia.

Statistical analysis

In this particular paper, we calculated the crude rates, age-specific rates and age-standardized rates (ASRs) of pancreatic cancer per 100,000 inhabitants. Gender-specific age-standardized mortality rates (ASMRs) were calculated using the Segi's world standard population.

In order to estimate mortality trends according to age groups and gender for the period 2000 – 2001, we used the linear regression and joinpoint regression analyses (Joinpoint Regression Program, Version 5.3.0.0, Statistical Research and Applications Branch, National Cancer Institute). The joinpoint regression analysis was employed to determine the Annual Percent Change (APC), the Average Annual Percent Change (AARC), complete with the points leading to significant changes in trends. All the results with the p-value less than 5% ($p < 0.05$) are considered statistically significant.

RESULTS

From 2000 to 2001, the total number of 22,488 pancreatic cancer deaths were reported in Serbia, which is why pancreatic cancer is considered the fourth most frequently occurring malignant tumor in the structure of malignant tumor mortality. Among the above-mentioned cases, 12,053 (53.6%) were males and 10,435 (46.4% %) were females. The average number of deaths was 1,022 (548 men and 474 women), whereas the average ASR of pancreatic cancer was 6.4/100,000 (7.9/100,000 in men, 5.1/100,000 in women). The rates were found to be 1.6 times higher in men than the ones detected among women.

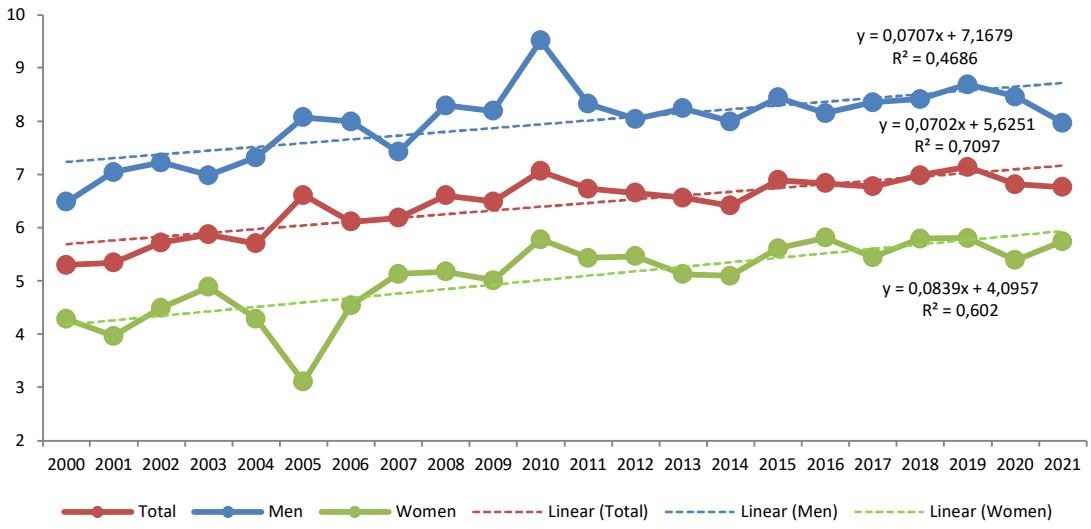
Estimates for death cases due to pancreatic cancer, crude rates and ASRs per 100,000 people from 2000 to 2021 are presented in Table 1.

Table 1. Number of death cases, crude rates and ASRs (per 100,000) for pancreatic cancer in Serbia, 2000 – 2021.

Year	Total			Men			Women		
	N	Crude rate	ASR[a]	N	Crude rate	ASR[a]	N	Crude rate	ASR[a]
2000	747	9.94	5.30	401	10.97	6.48	346	8.96	4.28
2001	772	10.29	5.34	445	12.20	7.04	327	8.48	3.96
2002	835	11.13	5.72	466	12.78	7.22	369	9.58	4.49
2003	855	11.43	5.87	451	12.40	6.98	404	10.51	4.88
2004	852	11.42	5.70	476	13.12	7.32	376	9.81	4.29
2005	988	13.32	6.61	518	14.32	8.07	470	6.25	3.11
2006	910	12.28	6.11	520	14.43	7.99	390	10.24	4.54
2007	966	13.09	6.18	491	13.68	7.42	475	12.52	5.13
2008	1034	14.07	6.60	561	15.70	8.29	473	12.53	5.17
2009	1020	13.03	6.49	546	15.34	8.19	474	12.60	5.01
2010	1088	14.92	7.06	566	15.96	9.51	522	13.94	5.78
2011	1055	14.58	6.73	570	16.18	8.32	485	13.06	5.43
2012	1099	15.26	6.65	573	16.34	8.04	526	14.24	5.46
2013	1070	14.93	6.56	585	16.76	8.24	485	13.19	5.12
2014	1056	14.81	6.41	573	16.50	7.99	483	13.20	5.09
2015	1134	15.98	6.89	618	17.89	8.44	516	14.18	5.61
2016	1151	16.31	6.83	599	17.42	8.15	552	15.25	5.81
2017	1156	16.47	6.77	619	18.10	8.35	537	14.91	5.44
2018	1168	16.73	6.98	615	18.08	8.41	553	15.44	5.79
2019	1206	17.36	7.14	640	18.91	8.69	566	15.89	5.80
2020	1169	16.94	6.81	625	18.60	8.46	544	15.37	5.39
2021	1157	16.93	6.76	595	17.88	7.97	562	16.02	5.74
Overall	22488	14.15	6.43	12053	15.62	8.24	10435	12.55	5.06

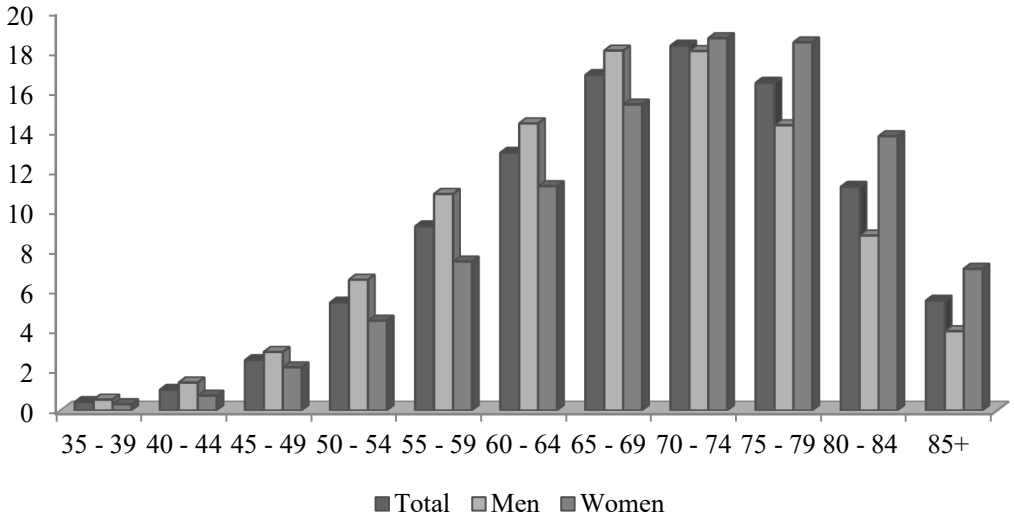
A significant rising trend in the mortality of pancreatic cancer was reported to be present in the population (y=0.0072x + 5.6251, p<0.001), during the observed period in both men (y=0.00707x + 7.1679, p=0.001) and women (y=0.0839x + 4.0957, p<0.001) (Figure 1).

Figure 1. Trends of age-standardized pancreatic cancer mortality rates in Serbia by sex, in the period 2000-2021.



Age groups that are most affected by the burden of pancreatic cancer mortality were the following: 70-74 (18.3%), 65-69 (16.8%) and 75-79 (16.4%). It is significant to emphasize that the number of death cases in men constantly surpasses the number of deaths in women until the age-group of 70-74 years, whereas after the age of 70 – women are more likely to die when compared to men. The majority of death cases were registered in the age group of 65-69 years, with the total number of 2,174 death cases (18.0%) in men, whereas 37,609 death cases (18.7%) were reported in women in the age group of 70-74 years (Figure 2).

Figure 2. Distribution of pancreatic cancer mortality by age groups in Serbia, 2000 - 2021.

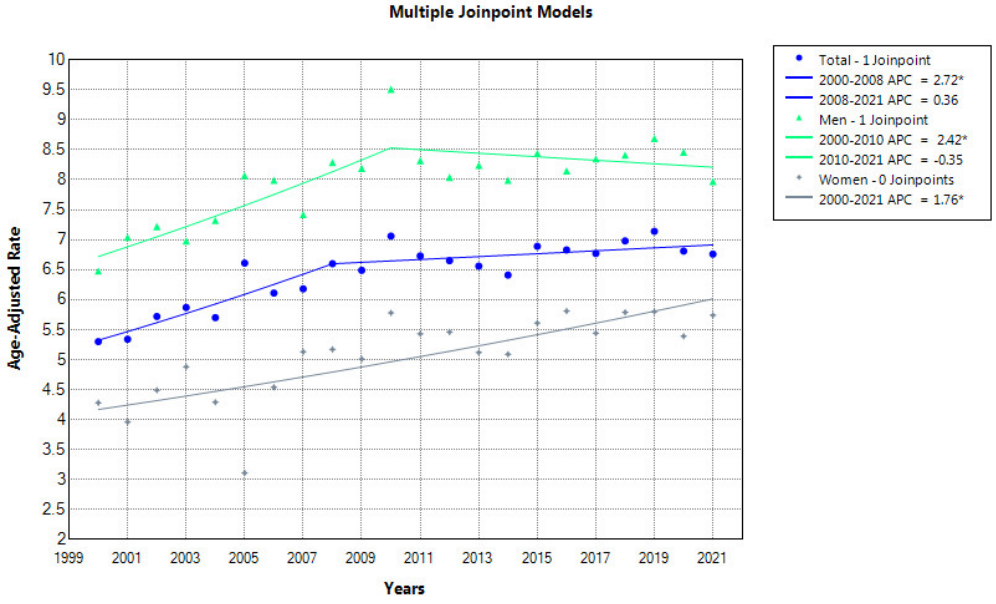


The joinpoint regression revealed a statistically significant increase in the mortality rates of pancreatic cancer for the total level, with an AAPC of 1.3% (95% CI: 0.9–1.6); p<0.001). More specifically, the joinpoint regression analysis identified one time point in which the trend significantly changed. An abrupt rise in the mortality rates was detected in the period from 2000 to 2008, by approximately 2.7% yearly (95% CI (1.7–6.2), p<0.001), followed by a slight, but not statistically significant decline in the mortality rates until the end of the observed period, with an average change of -0.4% per one year (95% CI: -0.8–0.8, p=0.331).

A similar trend in the mortality rates was reported in men as well (AAPC=0.95 (95% CI: 0.5–1.5; p=0.008). The mortality rates of pancreatic cancer in men were constantly increasing from 2000 to 2010, with an APC of 2.4% (95% CI: 1.4 – 5.5), which was considered to be statistically significant (p<0.001). After the year of 2010, there has been a decline in the above-mentioned mortality rates, with the APC of -0.4% (95% CI: -2.5 – 0.5). However, this change was not statistically significant (p=0.392).

Unlike men, what was observed in women was a continuously rising trend in mortality of pancreatic cancer by 1.8% at an annual level (95%CI: 0.7–2.7. p=<0.001). The joinpoint regression analysis did not identify a single time point in which the trend in mortality rates of women significantly changed (Figure 3).

Figure 3. Trend in mortality of pancreatic cancer in Serbia, 2000 – 2021.



The mortality of pancreatic cancer increased by age both in men and in women. The highest ASR among men was in the age group of 80-84 years (77.9±18.1) and among women in the same age group (65.2±12.2).

The joinpoint analysis showed a significant rising trend of mortality rates in all age groups 60+ during the whole study period, with the highest AAPC being reported in the age groups 85+ (AAPC=+3.1 (95% CI: 1.6–4.5)). The age specific mortality rates in males increased significantly by +1.1% (95% CI: 0.1–2.2) yearly in the age group 60–64, +1.75% (95% CI 1.00-2.5) yearly in the age group 65–69, +1.59% (95% CI: 0.6–2.6) yearly in the age group 70–74 and +2.10% (95% CI: 0.6–3.6) yearly in the age group 75-79. A decreasing trend in the mortality of pancreatic cancer was recorded only in males aged 40 – 44, 45 – 49, 50 – 54 and 55 – 59 years, but these changes were not considered to be statistically significant.

The rate for women increased significantly in the age groups of 55–59, 65–69, 70–74, 74–79, 80–85, and 85+ years. The corresponding AAPC values are 1.9% (95% CI: 0.6–3.2), 2.1% (95% CI: 0.6-3.7), 0.9% (95% CI: 0.01–1.9), 2.9% (95% CI: 0.3–3.6), 2.1% (95% CI: 0.7–3.42), and 4.4% (95% CI: 2.1–6.4) (Table 2).

Table 2. Joinpoint regression analysis* of pancreatic cancer mortality by age in Serbia, 2000 - 2021.

	Total		Men		Women	
	ASR±SD	AAPC[a] (95% CI[b])	ASR±SD	AAPC[a] (95% CI[b])	ASR±SD	AAPC[a] (95% CI[b])
25 - 29	0.2±0.2		0.1±0.2		0.2±0.3	
30 - 34	0.3±0.3		0.3±0.4		0.3±0.5	
35 - 39	0.4±0.4	-0.9 (-4.5-2.9)	1.2±0.7		0.3±0.5	
40 - 44	2.1±0.6	-1.3 (-3.6-1.2)	3.1±1.5	-1.5 (-4.3-1.5)	1.4±0.7	
45 - 49	5.01±1.2	0.4 (-1.4-2.4)	6.3±2.0	-0.5 (-2.5-1.6)	3.9±1.8	2.1 (-2.4-7.1)
50 - 54	10.4±1.2	0.1 (-0.8-0.9)	13.8±4.2	-0.1 (-1.9-1.7)	7.8±1.5	0.5 (-1.2-2.3)
55 - 59	18.7±2.1	0.1 (-0.8-1.1)	24.5±3.9	-0.7 (-1.9-0.5)	13.3±2.4	1.9* (0.6-3.2)
60 - 64	27.8±3.0	1.2* (0.5-1.8)	35.2±5.1	1.1* (0.1-2.2)	20.7±4.1	1.7 (-0.2-3.7)
65 - 69	40.0±5.5	1.7* (1.1-2.4)	50.6±7.4	1.* (1.0-2.5)	30.2±5.8	2.1* (0.6-3.7)
70 - 74	52.2±6.1	1.6* (0.6-2.6)	63.5±9.8	1.6* (0.6-2.6)	42.9±6.6	0.9* (0.01-1.8)
75 - 79	62.1±9.4	2.5* (1.2-3.7)	71.3±14.5	2.1* (0.6-3.6)	53.7±9.0	2.9* (0.3-3.6)
80 - 84	70.4±10.0	1.7* (0.7-2.8)	77.9±18.1	1.5 (-1.1-4.3)	65.2±12.2	2.1* (0.7-3.4)
85+	63.3±11.4	3.1* (1.6-4.5)	68.2±22.9		57.9±13.3	4.4* (2.1-6.4)

[a]AAPC – Average Annual Percent Change
[b]CI – Confidence Interval
* Statistically significant trend

DISCUSION

Despite the rapid progress of advanced medical technology, pancreatic cancer still remains to be one of the deadliest malignant tumors (3). A close parallel that can be drawn between the incidence and mortality rates of pancreatic cancer reflects the fatal nature of this disease. There are several reasons why pancreatic cancer has such a high mortality rate such as the following: late diagnosis, aggressive nature, a lack of effective screening and limited treatment options (11).

The pancreatic cancer-related mortality rates vary significantly, depending on the region and population (12). The highest burden is notified in the regions with a very high and high HDI, despite the fact that these regions were reported to have better medical resources, whereas the reduced burden was reported in regions with a medium and low HDI, which is in accordance with the findings obtained from the previous research studies (12, 13, 14).

In the year of 2022, the highest ASRs were recorded in Western Europe (7.92) and Eastern Europe (7.08), whereas the least mortality rates were registered in South Central Asia (1.12) and Middle Africa (1.50). There are significant differences observed in the mortality rates reported among the countries. In the year of 2022, the highest standardized mortality rates of pancreatic cancer were reported in Hungary (9.61/100,000), Uruguay (9.41/100,000), the Czech Republic (8.55/100,000), Latvia (8.42/100,000) and Finland (8.41/100,000), whereas the lowest mortality rates were registered in Malawi (0.44/100,000), Vanuatu (0.55/100,000), Sierra Leone (0.65/100,000), Pakistan (0.67/100,000) and Rwanda (0.7/100,000) (5). The above-mentioned differences may be explained due to the increased proportions of the ageing population and its unhealthy lifestyle habits, complete with the higher prevalence of metabolic risk factors in countries with a higher HDI. On the other hand, it is possible that the pancreatic cancer-related incidence, mortality rates and risk factors are underestimated in the regions with a lower HDI due to underdevelopment of the mechanism of cancer reporting (7, 15, 16).

The rise in pancreatic cancer-related mortality rates has been noticed in almost all countries worldwide ever since 1991, particularly among women and those older than 50 years (7, 17). Favourable trends in the mortality rates of pancreatic cancer were reported in Canada only (an annual

decline of 0.4% in men and 0.2% in women) and Mexico (an annual decline of 0.7% in men and 0.8% in women). Turkmenistan showed the greatest rise in mortality rates in both sexes (AAPC = +10.0% in men and AAPC = +6.4% in women).

What was shown in a study conducted by Tana *et al*., was a slow, but continuously rising trend in the mortality rates of pancreatic cancer, with an annual increase of 0.23% in the period from 1999 to 2020 in the United States. Possible factors listed as the ones contributing to the rising trend in mortality rates were related to the population ageing and the increasing prevalence of obesity (19).

The findings of our study indicated a significant increase in the trend of pancreatic cancer-related mortality rates in both men and women for the past two decades. One study that was previously conducted in Serbia showed that in the period from 1991 to 2010 pancreatic cancer caused the rise in mortality rates, with an annual increase of 1.6% in men and annual increase of 2.2% in women.

It is estimated that the incidence and mortality rates of pancreatic cancer will continue to grow in the following 20 years in both men and women. By 2030, pancreatic cancer may become the second leading cancer-related death cause (20, 21). The greatest rise in fatal outcomes is expected to be found in regions with a medium and low HDI. It is estimated that the mortality rates of pancreatic cancer in Africa will be increased by 17,744 deaths in the year of 2040, with the growth rate of 114.8%, meaning that its rates will simultaneously be considered the highest ones worldwide. The above-mentioned rates will be followed by Latin America and the Caribbean (a rise of 109%). However, in 2040, the growth of mortality rates of 31.6% will be the lowest in Europe (22). This alarming rising trend in the incidence and mortality rates of pancreatic cancer emphasizes the need to use more advanced diagnostic tools and introduce earlier cancer screening programs along with more effective treatment options.

The prevailing patterns of an increase in the pancreatic cancer incidence and mortality rates are closely associated with the process of globalization, urbanization, economic growth and changes in the age-related population structure (15). Due to epidemiological studies, it is known that geographical differences in the existing pancreatic cancer burden may be explained by variations in the prevalence of some of the essential lifestyle and metabolic risk factors such as the following: tobacco smoking, obesity, alcohol consumption, nutrition factors, type 2 diabetes mellitus (23, 24). Therefore, comprehensive understanding of risk factors for developing pancreatic cancer is of enormous practical importance for the efficient prevention of pancreatic cancer (3).

Meta-analysis provided strong evidence, pointing out that tobacco smoking was one of the main risk factors associated with pancreatic cancer. 11-32% of all death cases caused by pancreatic cancer was primarily attributed to active smoking (25). One large European study that included 2,009 cases and 1,532 controls confirmed the fact that active smokers were at a 72% higher risk of developing pancreatic cancer when compared to those who had never smoked (26). Although there was a decline in the pancreatic cancer-related mortality rates due to tobacco use in the period from 1990 to 2019, with a reduction of 20% reported in men and 6% in women (408), smoking continues to be a public health concern. Bearing in mind the existing differences in the smoking rates reported between men and women, this particular fact can provide at least a partial explanation of the gender-based differences observed in the prevalence of pancreatic cancer.

Globally, there has been a 3.5-fold increase in the number of death cases caused by pancreatic cancer, that can be attributed to metabolic risk factors, ranging from 22,091 death cases reported in 1990, to 77,215 deaths reported worldwide in 2019. North America and Central Europe were reported to have the highest age-standardized mortality rates (ASMRs) caused by pancreatic cancer that can be attributed to the high fasting plasma glucose (FPG) levels and high BMI, estimated in 2019, respectively (25). A pooled analysis of 14 cohort studies demonstrated that the respondents with a higher body mass index (BMI) were at a 40% higher risk of developing pancreatic cancer when compared to those whose BMI was stable (26), whereas the previous epidemiological studies indicated that obesity was associated with approximately 1.5-fold increased risk of developing pancreatic cancer (27, 28).

In Europe, the number of adult patients with diabetes has been increasing with the population growth and ageing (29). Therefore, if no additional measures are to be undertaken, it is expected that poor control of blood glucose levels will give its own increasing contribution to pancreatic cancer-related deaths (30).

The examination of mortality trends according to specific categories, such as gender and age groups, represents a highly significant aspect of comprehensive assessment of pancreatic cancer burden, complete with formulating and enforcing various prevention strategies. Globally, pancreatic cancer incidence and mortality rates are higher in men than in women (9). Our study demonstrated that there was a rise in the pancreatic cancer mortality trends reported in both sexes, with the significant increase in mortality rates among women occurring in a slightly quicker and earlier manner when compared to men. This particular pattern tends to follow the global trend of a greater rise in the female mortality rates (7), ranging from 0.78 to 5.83% when compared to the range of 0.55 to 4.20% detected in men. The most evident rise in female mortality rates is attributable to the greater prevalence of obesity among women, complete with the incidence of metabolic syndrome occurring more frequently with ageing (31).

Our analysis of the age-related distribution confirmed the results of previous studies underlying that the epidemiological pancreatic cancer burden was reported to be gradually increasing with ageing. Concerning the fact that pancreatic cancer is a disease typically found in older people, old age was identified as an independent risk factor (25).

Approximately 90% of newly diagnosed patients belonged to the older age group of 55 years and over, with the majority of them being in the seventh or eighth decade of life (18, 21, 32). Globally, the highest number of death cases was reported in the age group of 65-69 years in men, whereas the peak number of deaths among women was reported in the age group of 75-79 years (12).

CONCLUSION

Our study observed an increase in pancreatic cancer mortality rates during the studied period in Serbia. Taking into consideration the population ageing and an increase in the prevalence of specific risk factors, complete with the fact that pancreatic cancer screening is not currently recommended, pancreatic cancer burden still continues to be a major public health challenge. However, the provision of updated statistics on the occurrence and outcomes of pancreatic cancer, time trends among various population groups, along with a better understanding of its etiology and identification of causal changeable risk factors – are essential when it comes to the primary prevention of this particular disease.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest

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