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ORIGINAL ARTICLE

Trend in esophageal cancer mortality in Serbia, 1991-2015 (a population-based study): an age-period-cohort analysis and a joinpoint regression analysis

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Summary

Purpose: *Esophageal cancer mortality trends vary substantially across the world. This study assessed the trend of esophageal cancer mortality in Serbia.*

Methods: *A population-based study analyzing esophageal cancer mortality in Serbia in the period 1991-2015 was carried out based on official data. The annual percentage of change (APC), with the 95% confidence interval (CI), was computed using the joinpoint regression analysis. The age, period and birth cohort effects on the mortality from esophageal cancer were examined using the age-period-cohort analysis.*

Results: *In Serbia, esophageal cancer mortality trend significantly increased from 1991 to 2015 in men (APC=+0.9%, 95%CI=0.3 to 1.4), but nonsignificantly increased in women (APC=+0.4%, 95%CI=-0.6 to 1.4). The age-specific mortality rates were increasing with age, but this trend has only been significant in men in the 50-59 years age group (APC=+1.5%, 95%CI= 0.8 to 2.3). The age-period-cohort analysis suggested statistically non-significant period and cohort effects, and local drifts for both genders (p>0.05 for all).*

Conclusions: *The trend of esophageal cancer mortality should be elucidated in future analytical epidemiological studies in Serbia.*

Key words: *age-period-cohort analysis, esophageal cancer, joinpoint analysis, mortality trend*

Introduction

In 2012 worldwide, according to the GLOBOCAN estimates, there were 400,000 esophageal cancer deaths (4.9% of the total), which makes it the 6th most common cause of death from cancer for both genders together [1,2]. Over 80% of deaths (329,000 cases) occurred in less developed countries (225,000 in men, 114,000 in women), and over half the world total occurred in Eastern Asia (mainly China). The estimated 5-year survival rates for esophageal cancer are relatively low (≤20%) [1-5].

Esophageal cancer mortality rate was considerably higher among men (Men:Women sex ratio of 2.9) [1]. Mortality rates vary worldwide (differences were almost 20-fold in both genders equally), with highest rates among men in Eastern Asia (14.1/100,000) and women in Eastern Africa (7.3/100,000), and lowest rates in Western Africa (0.8/100,000 in men, 0.4/100,000 in women) [1,2].

Since the 1970s, trends in esophageal cancer mortality have been increasing in both sexes in some western countries (United Kingdom, Denmark)

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and in men in Australia, Canada and the United States, while decreasing trends were observed in both sexes in South Europe, Middle East and Eastern Asia [1].

At the end of the 20th and the beginning of this century, Serbia has undergone great social, political and economic changes. Until today, as a small country at the crossroads of Central and Southeast Europe, Serbia hosted nearly 1 million refugees since the beginning of civil wars. Our study aimed to determine trends in esophageal cancer mortality in Serbia.

Methods

Study design

For this population-based study, we used annual data on the underlying cause of death in Serbia to describe trend in esophageal cancer mortality for the period 1991-2015.

Data source

Death of esophageal cancer was defined according to the International Classification of Diseases (ICD) as code 150 of the IX edition (1991-1996 period) and code C15 of the X edition (1997-2015 period). Data about the deceased from esophageal cancer were obtained from Statistical Office National Statistics Data.

The medical certification of death represents an obligation in Serbia. National statistical data collection is carried out through the following two forms: Statistical form on death and Death certificate. A medical doctor (in a hospital or coroner) completed the death certificate. Regional Institutes of Public Health collect and control all death data according to the national standard that complies with the World Health Organization guidelines. The DEM-2 form contains data on the underlying cause of death from the Death certificate, entered with the appropriate code. Authorized medical doctors carry out the control of data in the regional Institute of Public Health, and then data are submitted to the Regional Registry. Data control is finally carried out at the Statistical Office of the Republic of Serbia. Data collection is performed for the current year, but the need for careful analysis requires that the time for publishing final data is delayed by up to 24 months from the reference year. The underlying cause of death was recorded according to the ICD at the time of death. During the period studied, two different revisions of the ICD were used, the IX revision was used until 1997 when the X revision was implemented.

The study included the entire population of Serbia (about 7.2 million inhabitants in 2015), excluding the Autonomous Province of Kosovo and Metohija (for which since 1998 data are not available and which declared its independency in 2008) [6]. Serbia is among the countries with 'long-term refugees' crisis. Still, the refugee population data could not be set aside as a special contingent and were included in the Serbian population.

Statistics

We calculated three types of cancer mortality rates: crude, specific (age-specific and sex-specific) and standardized mortality rates. Mortality rates were expressed per 100,000 persons. Calculations were based on the 10-year age-group in which the cancer death occurred. The age-standardized rates (ASRs) were computed by methods of direct standardization, using the World Standard Population.

Temporal trends for esophageal cancer mortality were assessed using the joinpoint regression analysis (Joinpoint regression software, Version 4.5.0.1, available through the Surveillance Research Program of the United States National Cancer Institute), according to the method proposed by Kim et al. [7]. Joinpoint analysis models were based on regression with age-standardized mortality rates as the dependent variables and with year as the independent variable. Gender and age group were the by-variables. We used the Grid Search Method. The minimum number of observations between two joinpoints was 2, while the maximum joinpoints to enter the final model were 4. We selected a model where errors are assumed to have constant variance (homoscedasticity). The program assumes that the random errors in the regression model are uncorrelated and estimates the regression coefficients by ordinary least squares. The joinpoint regression uses a series of permutation tests (with 4499 randomly selected data sets) in order to provide a joined straight line between changes in trend (joinpoints) and to estimate change between joinpoints. An annual percentage of change (APC), along with the corresponding 95% confidence interval (95%CI), was calculated for each trend. The APC values that were statistically significant indicated a temporal change in mortality trend over the time period. We used the Monte Carlo Permutation method for tests of significance. The comparability test was conducted in order to determine the differences between pairs and to clarify whether two joinpoint regression functions are identical or whether the two regression mean functions are parallel. For the subgroups aged <40 years joinpoint results are not shown because fewer than 5 cases of esophageal cancer deaths occurred in each of the decennium in any year.

The United States National Cancer Institute statistical web tool was used according to the method proposed by Rosenberg et al. [8] for conducting the age, period and cohort analysis that attempts to assess the effects of age, period and birth cohort on the mortality rates from esophageal cancer. Cancer mortality data stratified by 5-year age groups (40 to 44, ... and 80 to 84), the same 5-year intervals for calendar periods (1991 to 1995, ... and 2011 to 2015) and birth cohorts (1906 to 1911, ... and 1971 to 1975) were used for the age-period-cohort analysis. The central age group, period and birth cohort were defined as the reference. Because the occurrence of esophageal cancer was zero or very rare in those aged below 40 years and those aged 85 years and above, and resultant rates were unstable, we therefore omitted these age groups from the analysis. The following parameters were provided by this analysis: longitudinal age curve, local drifts, net drift, period rate ratio, and cohort rate ratio. Longitudinal age curve represents the fitted age-specific rates in reference cohort adjusted for period effects. Local drifts represent annual percentage changes for each age group over time. Net drift indicates the overall annual percentage change over time. Period rate ratios represent the ratio of age-specific rates in each period relative to the reference period, and indicate changes in the esophageal cancer mortality rates over time that influenced all age groups simultaneously. Cohort rate ratios represent the ratio of age-specific rates in each cohort relative to the reference cohort, and indicate changes in the esophageal cancer mortality rates over time that influenced all persons with the same birth years. Wald test was used for the significance of the estimable functions.

For all tests, two-sided p value less than 0.05 was considered to indicate statistical significance.

Table 1. Esophageal cancer mortality in Serbia, 1991-2015

Year	*No.*	*Crude rates*	*Age-standardized rates*
1991	202	2.7	1.6
1992	197	2.6	1.5
1993	196	2.6	1.5
1994	225	3.0	1.7
1995	205	2.7	1.6
1996	217	2.8	1.7
1997	228	3.0	1.7
1998	260	3.4	2.0
1999	192	2.5	1.4
2000	253	3.4	1.9
2001	230	3.1	1.7
2002	239	3.2	1.7
2003	229	3.1	1.6
2004	223	3.0	1.6
2005	243	3.3	1.8
2006	246	3.3	1.8
2007	256	3.5	1.9
2008	275	3.7	2.0
2009	275	3.8	2.0
2010	298	4,1	2.2
2011	245	3.4	1.6
2012	274	3.8	1.9
2013	274	3.8	1.9
2014	253	3.5	1.7
2015	271	3.8	1.9
Overall	6,006	3.2	1.8

Results

In the period 1991-2015, 6,006 cases of esophageal cancer deaths in Serbia were estimated (Table 1). The average annual age-standardized mortality rate by World standard population was 1.8/100,000 (ASRs ranged from 1.6/100,000 in 1991 to 2.2/100,000 in 2010). The average annual ASR was 3.1/100,000 in men and 0.6/100,000 in women. Esophageal cancer was 5.2 times more common among men than women in Serbia.

The overall esophageal cancer mortality trend was significantly increasing by +0.8% yearly (Table 2). According to the comparability test, esophageal cancer mortality trends in men and women were parallel (final selected model failed to reject parallelism, p=0.4033) and not coincident (final selected model rejected coincidence, p=0.0002). In Serbia, esophageal cancer mortality trend (Figure 1) significantly increased from 1991 to 2015 in men (APC=+0.9%, 95%CI=0.3-1.4), but nonsignificantly increased in women (APC=+0.4%, 95%CI=-0.6 to 1.4).

The age-specific mortality rates from esophageal cancer were higher in men in all age groups (Table 3). Esophageal cancer mortality rates increased with age, except only for women aged 70-79 years. The mortality trend was significant only in men in the 50-59 years age group (APC= +1.5%, 95%CI= 0.8 to 2.3).

Table 2. Joinpoint regression analysis* of esophageal cancer mortality in Serbia, by age, 1991-2015

Age[†]	*Average annual*	*Year 1991*		*Year 2015*		*Number of joinpoints*	*APC*	*Lower 95% CI*	*Upper 95% CI*
		No of cases	*Rates*	*No of cases*	*Rates*				
				Age-specific rates[‡]					
40-49	1.4	7	0.8	10	1.1	0	+0.4	-1.5	2.3
50-59	5.6	58	5.3	62	6.1	0	+1.4*	0.7	2.1
60-69	9.4	84	9.1	97	9.8	0	+0.3	-0.5	1.2
70-79	10.8	37	10.9	73	12.3	0	+0.3	-0.3	0.9
80+	8.3	14	7.6	26	8.6	0	+0.8	-0.7	2.3
				Age-standardized rates[‡]					
All ages	1.8	202	1.6	271	1.9	0	+ 0.8*	0.3	1.4

* Statistically significant trend; [†] Joinpoint results are not shown for the subgroups aged <40 years, because fewer than 5 cases of esophageal cancer deaths occurred in each of the decennium in any year; [‡] per 100,000 people; APC= Annual Percentage Change; CI= Confidence Interval.

The age-period-cohort analysis of mortality from esophageal cancer in Serbia is illustrated in Figure 2. The risk of death from the esophageal cancer increased sharply with age until a peak of those aged 70-75 years and showed a decline thereafter. The local drift values were around 0 in almost all age groups, with slightly higher values at ages 50-59 years: the local drifts and the net drift were not statistically significant (p>0.05). The period effects remained relatively stable for the entire period: the period effect was not statistically significant (p>0.05). The risk of death from esophageal cancer increased for most of the birth cohorts: the cohort effect was not statistically significant (p>0.05).

Discussion

Mortality trend of esophageal cancer has been increasing in the last decades in Serbia, mainly due to the increase in mortality in men. The esophageal cancer mortality showed a non-significant period and birth-cohort effects.

Worldwide, esophageal cancer mortality varied noticeably [1-3]. The highest mortality rates from esophageal cancer in 2012 were found in less developed countries (about 20 per 100,000 in Malawi and Turkmenistan) [1]. The lowest rates were recorded in Western Africa (about 0.6 per 100,000). In the United States and Australia/New

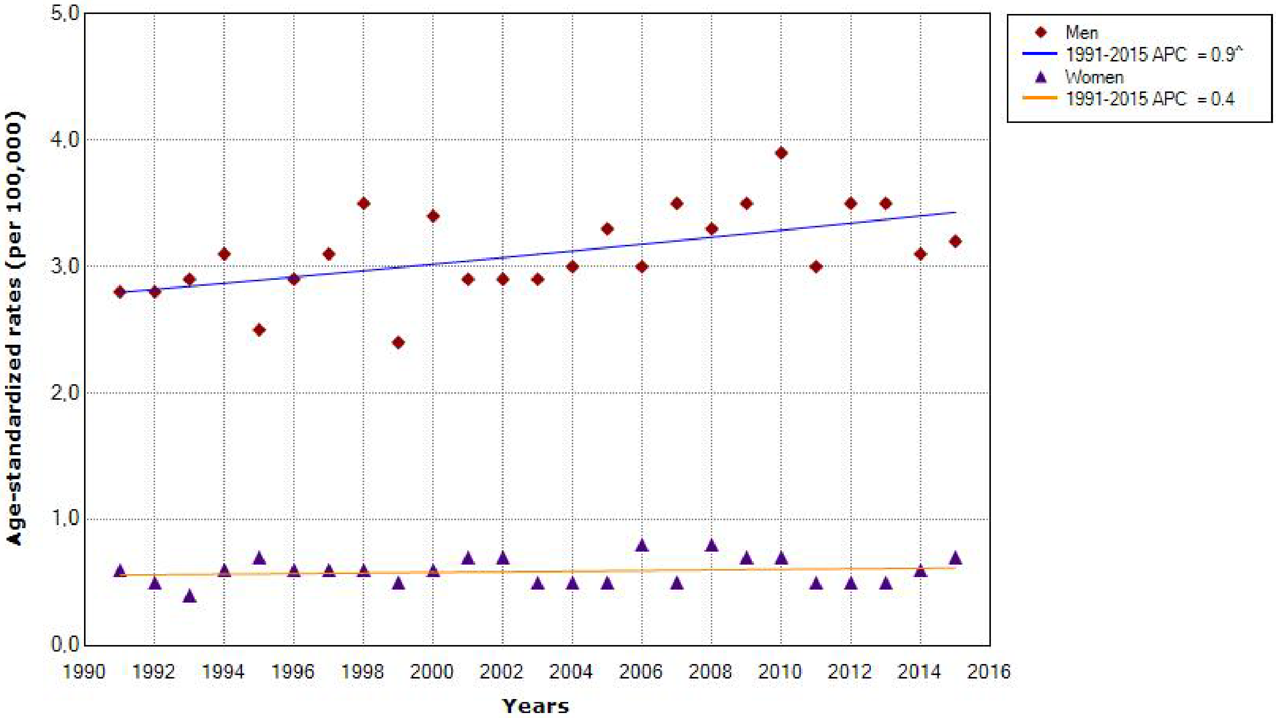

Figure 1. Trend in mortality of esophageal cancer in Serbia, by genders, 1991-2015: a joinpoint analysis; Men: 0 joinpoints versus women: 0 joinpoints

Table 3. Joinpoint analysis: trends* in age-specific esophageal cancer mortality rates, men and women in Serbia, 1991-2015

Age[†]	*Men*			*Women*		
	Average annual age-specific rate[‡]	*Period*	*APC (95% CI)*	*Average annual age-specific rate*[‡]	*Period*	*APC (95% CI)*
40-49	2.4	1991-2015	0.1 (-1.8 to 2.1)	0.5		
50-59	10.1	1991-2015	1.5* (0.8 to 2.3)	1.5	1991-2015	0.4 (-1.2 to 2.1)
60-69	17.1	1991-2015	0.3 (-0.6 to 1.2)	2.8	1991-2015	0.2 (-1.5 to 1.9)
70-79	19.0	1991-2015	0.7 (-0.2 to 1.5)	5.0	1991-2015	-0.8 (-2.2 to 0.6)
80+	14.1	1991-2015	1.2 (-1.0 to 3.3)	5.3	1991-2015	1.7 (-0.5 to 3.8)

* Statistically significant trend; † Joinpoint results are not shown for the subgroups aged <40 years, because fewer than 5 cases of esophageal cancer deaths occurred in each of the decennium in any year in both sexes, as well as in women aged 40-49; ‡ All the rates are presented as number of deaths per 100,000 people; APC= Annual Percent Change; CI= Confidence Interval.

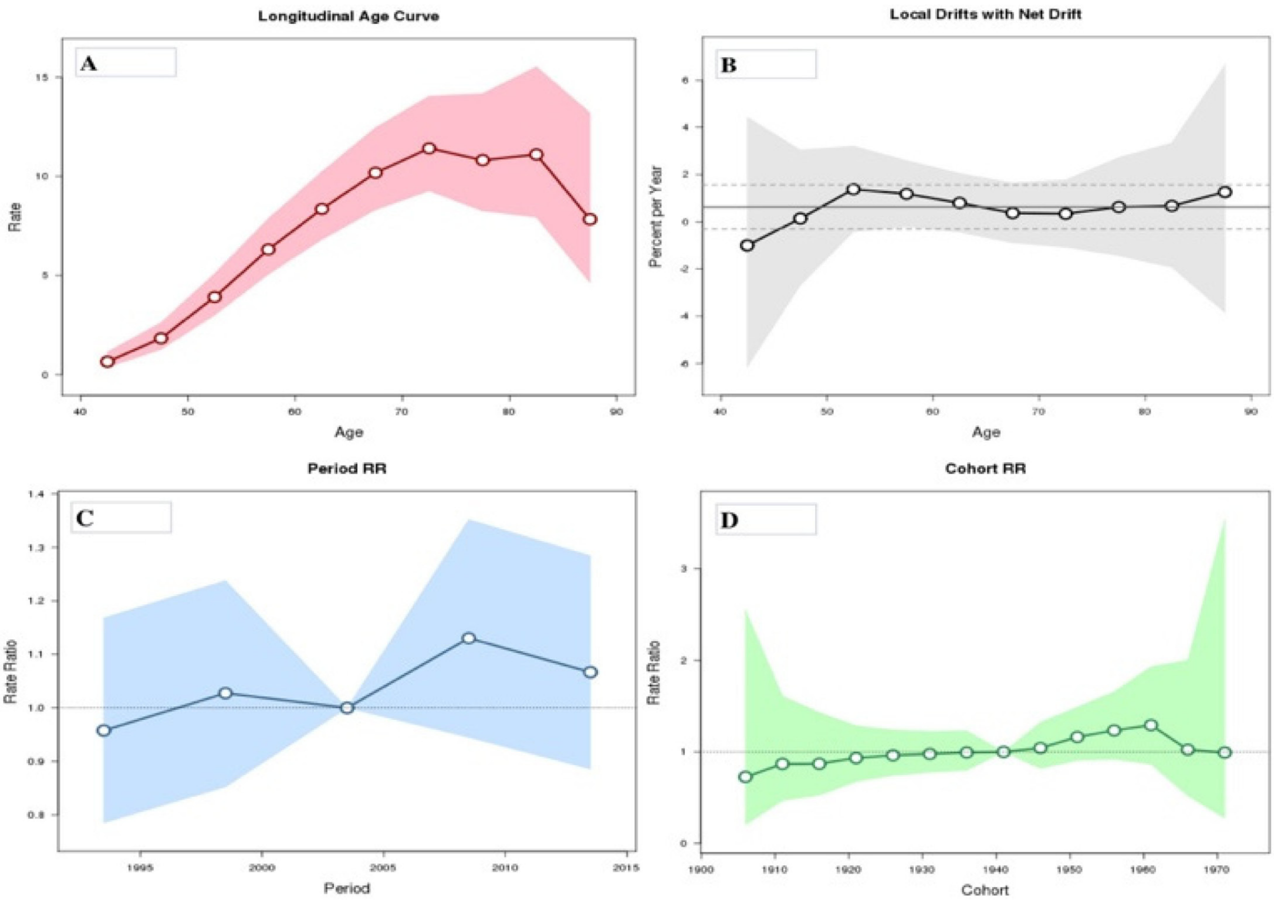

Figure 2. Esophageal cancer mortality rates in Serbia, 1991-2015: an age-period-cohort analysis. **A:** Longitudinal age curve of esophageal cancer mortality rates (per 100,000 people) and 95% confidence intervals (the area colored in *pink*). **B:** Local drift value: age group-specific annual percent change (%) and 95% confidence intervals (the area colored in *grey*). **C:** Period effects for the esophageal cancer mortality rates and 95% confidence intervals (the area colored in *blue*); RR – rate ratio. **D:** Cohort effects for the esophageal cancer mortality rates and 95% confidence intervals (the area colored in *green*); RR – rate ratio.

Zealand the mortality rate was 2.9 per 100,000. The highest rates in Europe were recorded in the United Kingdom (5.6 per 100,000) and the lowest in Georgia (0.6 per 100,000). Intermediate rates in the European region (about 2.7 per 100,000) were seen in the Russian Federation, followed by Finland, Spain and Serbia (around 1.9 per 100,000). Similar to other countries [9], the mortality rates of esophageal cancer in women in Serbia are approximately 5 times lower than those observed in men. Worldwide, the mortality of esophageal cancer correlated with increasing age [10,11]. Similar to the Serbian population, the majority of deceased were older than 50 years. Based on the share of persons aged 65+ years in the total population (19.6% in 2011 versus 18.7% in 2002), Serbian population can be classified in the group of very old populations [6]. Some of the international variations and gender differences could be attributed to the prevalence of esophageal cancer risk factors [1]. The causes of esophageal cancer are still insufficiently clarified, although certain risk factors have been identified, such as smoking, alcohol use, genetic factors, diet [12,13]. World Health Organization estimates indicate that in 2013 the prevalence of tobacco smoking among men aged 15 years or more was 73.3% in Indonesia, 59.8% in the Russian Federation, 44.6% in Serbia, 24.6% in Finland [14]. In women, the highest prevalence of tobacco smoking was recorded in Serbia (39.7%), followed by Croatia (32.7%), the Netherlands (24.2%) and the Russian Federation (22.7%), while the lowest prevalence was found in India (2.3%), China (1.9%), and Bangladesh (0.9%). Besides the highest smoking prevalence, the highest smoking intensity was also recorded in China and Eastern and Southern Europe. Average alcohol consumption strongly correlated with mortality rates of esophageal cancer in past decades in the United States, France and the United Kingdom [15]. In Serbia, 4.7% of the population (men six times more than women, ie 8.3% vs 1.3%) drank on a daily basis in 2013 [16]. Besides, it is always a question whether the differences were real or partialy a consequence of variations in the process of registering causes of death [17].

In the last decades of the 20th century, esophageal cancer mortality was increasing in both genders (USA, European countries, Japan, China) [1,3,9]. Since 2000, a declining trend in mortality of esophageal cancer was registered in both genders in most developed countries of North America, Western and Southern Europe [9]. A strongly decreasing risk for esophageal cancer among Japanese immigrants in the United States may be attributed to the high alcohol consumption among men in Japan [18]. Some countries (Norway, Germany, Poland) had opposite mortality trends in men and women [1]. A marked increase in mortality trend was registered in Iceland (+40% in men, +14% in women) and Malta (+34% in men, +105% in women). Like some neighboring countries (Bulgaria, Romania), Serbia has an increase in overall esophageal cancer mortality. The lack of statistical significance for the mortality rates of esophageal cancer among the female population in Serbia was mostly caused by the smaller number of cases. The differences in esophageal cancer mortality trends between countries suggest differences in the distribution of a variety of risk factors among different groups and over time [19,20]. Between the two National Health Surveys in Serbia, in 2006 and 2013, there was a significant increase in the percentage of obese population (from 17.3% to 21.2%) [16]. Also, the surveys showed that a considerably higher percentage of overweight persons was recorded in all age groups over 45 years. A particular risk was drinking large quantities of alcohol per occasion (more than 6 alcoholic drinks) at least once a week which was practised by 4.3% of the population of Serbia (7.8% of men and 1% of women), and at least once a month which was practised by 16% of the population (27% of men and 6% of women). Also, to better understand the factors contributing to the observed differences, it is necessary to provide data about the frequency of different subtypes of esophageal cancer by gender. The period and cohort relative risks remained unchanged for the Serbian population. Nevertheless, esophageal cancer mortality pattern is not equally deployed, reflecting the differences in prevalence of risk factors among groups and over time.

Strengths and limitations of the study

This study provides the first nationwide estimates of mortality of esophageal cancer in Serbia. This study includes the entire Serbian population with temporal trends analyzed by both joinpoint regression and age-period-cohort analysis. Of course, there is always a question of data quality. Based on the timeliness, completeness (100%) and coverage (97%) of registration and the proportion of deaths assigned to ill-defined causes (8%), the WHO assessed the registration of death data in Serbia as having medium quality [21]. In this study, there were no variations either in the trend of total esophageal cancer mortality or in the trend of esophageal cancer mortality in males. The joinpoint analysis indicated a continuing significant increasing trend in total mortality from esophageal cancer in Serbia, as well as a continuing significant increasing trend in mortality rates in males only. Therefore, one could hardly assume that changes in the registration of death could have affected men alone, and that there were no effects on the trend of dying from esophageal cancer in women. Small numbers raise statistical issues, particularly in mortality from esophageal cancer in women in Serbia. There are no data about esophageal cancer incidence for the entire Republic of Serbia, which should be used for explaining the increasing mortality trends during the whole observed period.

The limitation of our study is absence of separate data on esophageal cancer deaths among refugees that could possibly confound the mortality pattern in Serbia. Namely, refugees have the same rights to health care (such as preventive, diagnostic and therapeutic procedures) as all the citizens of Serbia, and special surveillance is not conducted for the health status of refugees. Another lack of this study relates to the inherent limitations of the age-period-cohort analysis (such as collinearity among age, period and cohort effects, or ecological fallacy). In the applied log-linear model in this study, dropping observations from a particular year with the count of esophageal cancer deaths being zero from the analysis might shift or affect the detection or location of joinpoints, affecting the analysis (particularly in women). Finally, the main drawback of observational studies, such as our study, is the inability to explain international variations in the esophageal cancer mortality.

Conclusion

The trend in esophageal cancer mortality has been increasing in Serbia in the last decades, mainly due to the increase in mortality trend in men. Further research will allow a clarification of trends and help in future cancer control.

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Conflict of interests

The authors declare no conflict of interests.

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