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Prostate cancer mortality in Serbia, 1991–2010: a joinpoint regression analysis

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ABSTRACT

Background: The aim of this descriptive epidemiological study was to analyze the mortality trend of prostate cancer in Serbia (excluding the Kosovo and Metohia) from 1991 to 2010.

Methods: The age-standardized prostate cancer mortality rates (per 100 000) were calculated by direct standardization, using the World Standard Population. Average annual percentage of change (AAPC) and the corresponding 95% confidence interval (CI) was computed for trend using the joinpoint regression analysis.

Results: Significantly increased trend in prostate cancer mortality was recorded in Serbia continuously from 1991 to 2010 (AAPC = +2.2, 95% CI = 1.6–2.9). Mortality rates for prostate cancer showed a significant upward trend in all men aged 50 and over: AAPC (95% CI) was +1.9% (0.1–3.8) in aged 50–59 years, +1.7% (0.9–2.6) in aged 60–69 years, +2.0% (1.2–2.9) in aged 70–79 years and +3.5% (2.4–4.6) in aged 80 years and over. According to comparability test, prostate cancer mortality trends in majority of age groups were parallel (final selected model failed to reject parallelism, $P > 0.05$).

Conclusion: The increasing prostate cancer mortality trend implies the need for more effective measures of prevention, screening and early diagnosis, as well as prostate cancer treatment in Serbia.

Keywords joinpoint regression analysis, mortality, prostate cancer, trend

Introduction

In 2008, prostate cancer accounted for 258 133 deaths, took sixth place and was deemed accountable for 6.1% of all cancers among men worldwide.[1,2] Although the number of deaths from prostate cancer is almost the same in both developed and developing regions, the death rates from prostate cancer vary by >20 times around the world.[3]

The death rates from prostate cancer were high in the predominantly black population (Caribbean—26.3 per 100 000 and Southern Africa—18.5).[3] In 2008, mortality rates for prostate cancer were very low in Asia (i.e. in Eastern Asia—2.5 per 100 000) and intermediate in Australia/New Zealand and Europe (15.4 and 11.7, respectively).[3]

Since the 1990s, prostate cancer mortality rates have been declining in most developed countries (including the USA, the UK, Nordic countries, Western European countries, Australia).[4,5] Despite the persistent decline of prostate cancer in males in the USA (−3.3% per year in all races) and in higher resource countries within the European Union (in Luxembourg by −2.5%, Italy −0.8% per year), most countries in Central and Eastern Europe, such as Russia, Croatia and Slovenia, have shown a continuous rise (by +2.6, +1.8 and +1.5% per year, respectively).[4,5] The decreasing mortality trend for prostate cancer after 1990 may be attributed to the implementation of prostate-specific antigen (PSA) screening and improvements in treatment in developed countries.[6–9]

Most of the men who died of prostate cancer were aged 65 years or more.[4] In the oldest, in the age group of 85 years and

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over, mortality rates from prostate cancer are higher than in other malignancies in men.[10] The etiology of prostate cancer is not well understood, and older age, race (black) and family history of the disease were identified as risk factors for prostate cancer.[11–13] The results of numerous studies, which suggest an association between prostate cancer and hormonal status of an individual, sexual activity, personal and family medical history, vasectomy, obesity, alcohol consumption, smoking habits, occupational exposure to certain chemical substances and ionizing radiation, physical activity and diet, are not consistent.[14–16]

The aim of this study was to assess temporal changes in mortality rates of prostate cancer in the population of Serbia over the 1991–2010 period.

Methods

Data sources

This descriptive epidemiological study comprised the male population of the Republic of Serbia (all ages), during the period 1991–2010, excluding the Autonomous Province of Kosovo and Metohia, for which the data have been unavailable since 1998. Data on men who died of prostate cancer (site code 185 revision 9 and C61 revision 10 of the International Classification of Diseases to classify desease, injury and cause of death) were obtained from the Statistical Office of the Republic of Serbia.

Data on the number and composition of the population of the Republic of Serbia by sex and age were obtained from the population censuses in the years 1991 and 2002; for intercensus years, estimates published by the Statistical Office of the Republic of Serbia were used.

Statistical analysis

Two types of mortality rates (per 100 000) were calculated: age specific and age standardized. The age-standardized rates were calculated by direct standardization, using the World Standard Population. The analysis was conducted on the entire male Serbian population (~3.6 million persons), but the results are not shown for the subgroups aged <50 years, because fewer than 10 cases of prostate cancer deaths occurred in each of the decennium in any year. The age-specific rates, with the number of cases, were presented for the beginning and the end of the study period for the following age groups: 50–59, 60–69, 70–79 and 80+.

Mortality trend from prostate cancer was assessed using the joinpoint regression analysis (Joinpoint Regression Software, Version 4.0.4—May 2013; Statistical Methodology and Applications Branch, Surveillance Research Program of the US National Cancer Institute), according to the method proposed by Kim *et al.*[17] This method uses a statistical algorithm to define a best-fitting regression line through mortality data across time, determining how many, if any, joinpoints should be used to determine where significant changes take place.[17] Tests of significance used a Monte Carlo permutation method with 4499 replicates. The Annual Percentage Change (APC) with the corresponding 95% confidence interval (CI) was estimated for each identified trend, by fitting a regression line to the natural logarithm of the rates, using calendar year as a regression variable. The analysis began with the minimum number of joinpoints (e.g. 0 joinpoint, representing a straight line) and tested whether one or more joinpoints were significant. The Grid Search Method was selected.[18] The joinpoint analysis provided average annual percentage change (AAPC)—a summary measure over a fixed interval; for each AAPC estimate, we calculated the corresponding 95% confidence interval (95% CI).[19] For zero joinpoints, APC and AAPC are identical. In describing trends, the term 'increase' was used when the slope (positive APC or AAPC) of the trend was statistically significant. Significant differences by age were detected using a specific procedure—comparability test.[20] The test is applied to compare prostate cancer mortality rates between two age groups using tests of parallelism and coincidence of time trends. Test determines whether the two regression mean functions are parallel allowing different intercepts (test of parallelism) or whether two joinpoint regression functions are identical (test of coincidence). Two-sided *P*-values were considered to indicate statistical significance when they were <0.05.

Results

Figure 1 and Table 1 show the results of joinpoint regression analysis of prostate cancer mortality rates in Serbia, during the period 1991–2010. Nearly 14 000 prostate cancer deaths occurred in Serbia during observed period, with the average annual ASRs being 9.92 per 100 000. Between 1991 and 2010, the ASRs increased from 7.78 per 100 000 in 1991 to 12.92 per 100 000 in 2010. For mortality of prostate cancer, ASRs significantly increased between 1991 and 2010 by +2.2% per year (95% CI = 1.6–2.9). Joinpoint analysis of mortality did not identify any joinpoint.

Prostate cancer is predominantly a disease of older men. Seventy-three per cent of deaths were in patients aged 70 and older. Results of joinpoint regression analysis of prostate cancer mortality rates by age are presented in Table 1. In all age groups aged 50 and over, a significant rise in prostate cancer death rates was observed continuously from 1991 (by +1.9, +1.7, +2.0 and +3.5% per year, respectively).

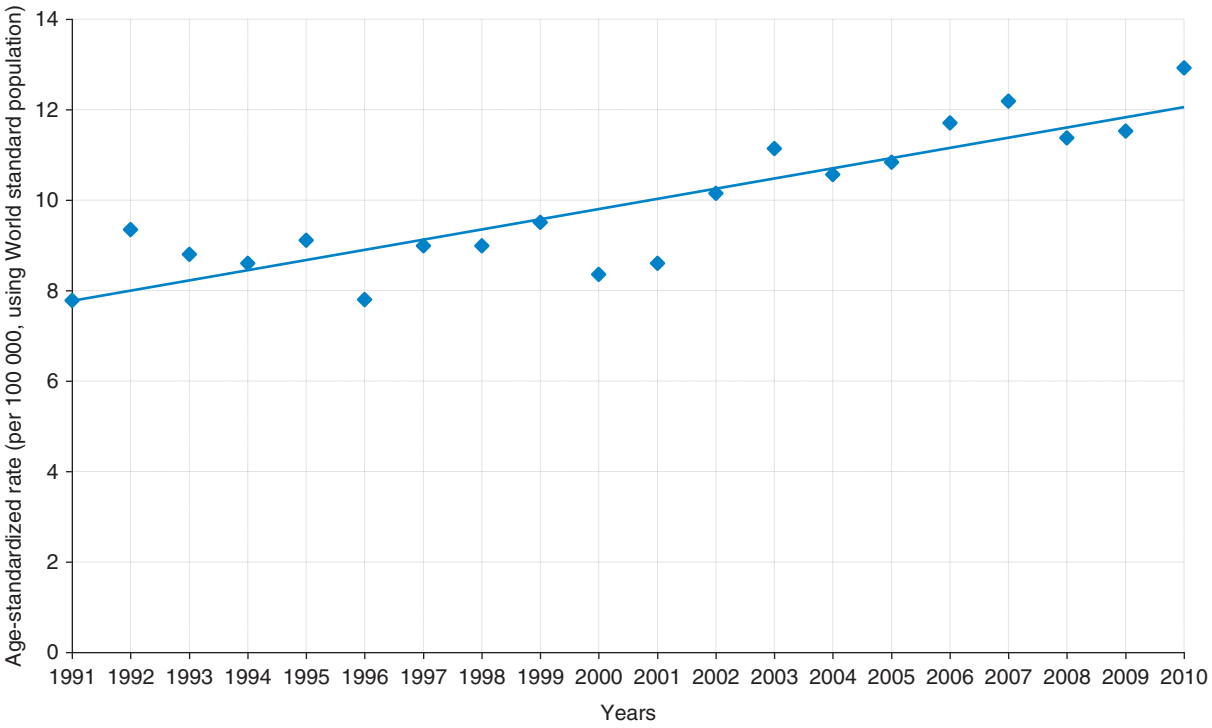

Fig. 1 Joinpoint regression analysis of prostate cancer mortality in Serbia, excluding the Autonomous Province of Kosovo and Metohia, 1991–2010.

Table 1 Joinpoint regression analysis[a] of prostate cancer mortality in Serbia, excluding the Autonomous Province of Kosovo and Metohia, by age, 1991–2010.

Age[b]		*Year 1991*		*Year 2010*		*Number of joinpoints*	*AAPC*[c]	*95% CI*[d]
		No of cases	*Rates*[e]	*No of cases*	*Rates*[e]			
Age-specific rates[e]								
Average annual								
50–59	6.04	19	3.57	40	7.21	0	+1.9[a]	0.1–3.8
60–69	38.70	138	35.49	174	51.13	0	+1.7[a]	0.9–2.6
70–79	148.32	163	118.89	522	197.91	0	+2.0[a]	1.2–2.9
80+	269.44	101	169.64	333	345.97	0	+3.5[a]	2.4–4.6
Age-standardized rates[e]								
Average annual								
All ages	9.92	427	7.78	1071	12.92	0	+2.2[a]	1.6–2.9

[a]Statistically significant trend.

[b]Joinpoint results are not shown for the subgroups aged <50 years, because fewer than 10 cases of prostate cancer deaths occurred in each of the decennium in any year.

[c]Average Annual Percent Change.

[d]CI, confidence interval.

[e]Per 100 000.

According to comparability test, only a trend in men aged 80+ years differed significantly from mortality trends in the age group 60–69 years (final selected model rejected parallelism, $P < 0.05$), while prostate cancer mortality trends in almost all of age groups were parallel (final selected model failed to reject parallelism, $P > 0.05$).

Discussion

Main finding of this study

Our results show an overall unfavorable trend for prostate cancer mortality in Serbia in recent two decades. This increase contrasts with the widespread decrease in prostate cancer mortality in many countries. Prostate cancer affects older men, especially after 70. The above mortality rates place Serbia among the countries with the intermediate prostate cancer mortality rates in Europe.

What is already known on this topic

In 2008, the mortality of prostate cancer varied greatly between countries, from the highest rates in Caribbean countries (Barbados—61.7 per 100 000) and Southern Africa (Zambia—24.7), to the lowest rates in some countries in Eastern Asia (India—2.5).[3] In Europe, high rates have been observed in the Baltic countries (Estonia—22.0) and the Nordic countries (Sweden—19.9), and then in Southern Europe (Croatia—14.0) and Western Europe (the Netherlands—13.9); the lowest mortality was observed in Moldova (6.6).[3] The majority of developed countries have shown a decline in the prostate cancer mortality in the last two decades—Switzerland (by −3.2% per year), Finland (−3.1%).[5] In contrast, a rise in prostate cancer mortality was noticed in most of the developing countries—Moldova (+6.5%) and Russia (+2.6%).[5] Even though there is still no consensus on the benefits of screening in the prevention of prostate cancer, the reduction in prostate cancer mortality in Western countries may be attributed to availability and use of screening with a PSA test and to improved treatment, while the increased mortality in developing countries probably reflects changes in lifestyle that accompany industrialization, including increased consumption of animal fat, obesity and physical inactivity.[7,9] The benefits and harms of prostate cancer screening, however, are still estimated.[21]

There is still reluctance to use PSA test as a sole indication for biopsy in Serbia, which can be linked to a lot of curable prostate cancer cases being missed, especially among the oldest men.[22] Some unfavorable changes in lifestyle that can influence the increased risk for prostate cancer occurred in Serbia in the last decades. UN Security Council sanctions between 1992 and 1995, economic crisis, war, disintegration of the country, NATO bombing in 1999, nearly half a million refugees and internally displaced persons, have had a considerable impact on lifestyle as well as on the functioning of the health services in Serbia. The 2006 National Health Survey revealed that tobacco exposure is high in Serbian population (without data for Kosovo and Metohia): 38.1% of men were smokers, with >78.7% of everyday smokers consuming >20 cigarettes per day, with an average smoking period of 21.1 years.[23] In 2006, 18.3% of adult male population in Serbia were obese (body mass index ≥30), significantly more than in 2000 (17.4%).[23] Everyday alcohol consumption was recorded for 7.2% of men. Ilic *et al.*[15] found that occupational physical activity during the year preceding the disease, occupational exposure to asbestos, dyes and lacquers, bitumen, fertilizers and certain other agents, nephrolithiasis and 'other' diseases in the medical history (i.e. diabetes mellitus) were significantly related to prostate cancer.

What this study adds

This study provides the first nationwide estimates of prostate cancer mortality in Serbia in last two decades. The mortality of prostate cancer in Serbia is increasing, contrary to the trends in developed countries. This mortality trend implies the need for more effective measures of prevention, screening and early diagnosis, as well as prostate cancer treatment in Serbia.

Also, this study enables comparison with other countries thanks to quality of data and comprehensive coverage by death registration system across the country.[24,25]

Limitations of this study

The World Health Organization assessed the quality of data on the cause of death in Serbia as moderate.[24] Percentage of unknown and ill-defined cancer deaths (3.8%) for the most recent year indicated that cause-of-death data in Serbia were of moderate quality.[26] The proportion of cases with uncertain death cause (revision 9 codes 780–799 and revision 10 codes R00–R99) was on average 6.8% in the observed period, with a non-significant decreasing trend ($P = 0.137$), enabling a good assessment of mortality trend for prostate cancer.[25]

The PSA testing is still not recommended as national prostate cancer screening test in Serbia.[22] Therefore, the lacking of the data on PSA testing in Serbia, which could be used to explain the mortality trends, is a limitation of our study. Differences in prostate cancer mortality rates between countries could in part be due to variations in prevalence of the risk factors, as well as in the variations in the availability and use of screening with a PSA test and treatment.

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