RESEARCH ARTICLE

Gynaecological Cancer Mortality in Serbia, 1991-2010: A Joinpoint Regression Analysis

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Abstract

This descriptive epidemiological study aimed to analyse the mortality trends from gynaecological cancer in Serbia. Average annual percentage of change (AAPC) and the corresponding 95% confidence intervals (CIs) were computed for trend using joinpoint regression analysis. Nearly 25,000 gynaecological cancer deaths occurred in Serbia during the 1991-2010 period, with the average annual age-standardised mortality rate being 17.2 per 100,000 women. Increase of mortality was observed for cancer of the vulva and vagina (AAPC=+1.3%, 95% CI=0.1 to 2.6), ovarian cancer (AAPC=+0.8%, 95% CI=0.4-1.3) and for cervical cancer (AAPC=+0.7%, 95% CI=0.3 to 1.1). Mortality rates for gynaecological cancer overall declined in women aged 30-39 years, but mortality was increased in middle-aged women (for cervical cancer) and in the elderly (for ovarian cancer). Improvements to and implementation of the national cervical cancer screening programme conducted in 2013 and expected to be finalised in the following years throughout Serbia should contribute to improvement.

Keywords: Gynaecological cancer - mortality trend - joinpoint regression analysis - Serbia.

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Introduction

Gynaecological cancers (including the malignant neoplasms of cervix, uterine body and ovary) accounted for 489,025 deaths and were deemed accountable for 14.6% of all cancers among women in 2008 worldwide (International Agency for Research on Cancer, 2008; Forouzanfar et al., 2011; Jemal et al., 2011). Developing countries accounted for approximately 75% of the gynaecological cancer deaths (International Agency for Research on Cancer, 2008; Jemal et al., 2011). Geographic variations in cancer mortality for certain gynaecological sites have also been noticed (Arbyn et al., 2008; International Agency for Research on Cancer, 2008; Jung et al., 2010).

The most commonly diagnosed gynaecological cancer is cervical cancer, the fourth leading cause of cancer death in women worldwide, accounting for 8.2% (275,100) of the total cancer deaths among women in 2008 (International Agency for Research on Cancer, 2008). In recent decades, cervical cancer is a major public health problem in developing countries (Arbyn et al., 2008; Kimman et al., 2012; D'Souza et al., 2013), while in most of developed countries mortality from cervical cancer has been steadily declining (de Kok et al., 2011; Howlader et al., 2013). Worldwide, cervical cancer was the second most common cause of death among all female cancers in young women 15-44 years of age (Arbyn et al., 2008).

Overall mortality rates for gynaecological cancers declined between 1992 and 2010 in the United States, but progress has been uneven among the cancer types (Howlader et al., 2013). In all races, mortality from cervical and ovarian cancer has been on decline since 2001 by -1.7% and -1.6% per year, respectively. In the same period, mortality from cancer of the uterine body and uterus, part unspecified, increased by +0.4% per year. Mortality from uterine and ovarian cancers has been steadily declining over the last few decades in some European countries (Austria, Germany, Netherlands, Switzerland, Sweden), while mortality rates are still increasing in a few southern and eastern European countries (Latvia, Lithuania, Romania, Croatia) (Arbyn et al., 2008; Arbyn et al., 2010; La Vecchia et al., 2010; Kelava et al., 2012).

Based on the GLOBOCAN 2010 estimates, mortality from gynaecological cancer ranks Serbia among countries with the highest death rates in Europe (International Agency for Research on Cancer, 2008). The aim of this study was to assess temporal changes in mortality rates of gynaecological cancer in Serbian population over the 1991-2010 period.

Materials and Methods

Data sources

The study comprised the female 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 women who died of gynaecological cancer

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(site codes 179-184 revision 9 and C51-C58 revision 10 of the International Classification of Diseases to classify death, injury and cause of death) were obtained from the statistical office of the Republic of Serbia (unpublished data). Cervical cancer was classified as ICD-9 180 and ICD-10 C53 and ovarian cancer as ICD-9 183 and ICD-10 C56. Data for corpus uteri cancer classified as ICD-9 182 and ICD-10 C54, while data of "not otherwise specified" (NOS) classified as code ICD-9 179 and ICD-10 C55. Due to small number of deaths, the malignant neoplasms of placenta (code ICD-9 181 and ICD-10 C58) and the other and unspecified female genital organs (code ICD-9 184 and ICD-10 C57) were included in the analysis together in the observed period, adding to them malignant neoplasms of vulva and vagina which were specifically registered as the cause of death only since the 1997, as ICD-10 C51 and ICD-10 C52, respectively.

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 inter-census years, estimates published by the statistical office of the Republic of Serbia were used. The age-standardized rates (per 100,000 people) were calculated by direct standardization, using the World Standard Population. Age-specific mortality rates were computed for 10-year age groups. The analysis was conducted on the entire female Serbian population (approximately 4 million persons), but the results are not shown for the subgroups aged <30 years, because fewer than 10 cases of a gynaecological cancer deaths occurred in each of the decennial in any year.

Statistical analysis

Joinpoint regression analysis was used to identify significant changes and trends in the data. 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. The analysis began with the minimum number of joinpoints (e.g., 0 joinpoint) and tested whether one or more joinpoints were significant. Two-sided P values were considered to indicate statistical significance when they were less than 0.05 (Kim et al., 2000). The most significant numbers of joinpoints are used and an annual percentage change (APC) is calculated for each slope (Clegg et al., 2009). In the final model, the joinpoint analysis provided average annual percentage change (AAPC); for each AAPC estimate we calculated the corresponding 95% confidence interval (95%CI). Significant differences by age and cancer site were detected using tests of parallelism and coincidence of time trends (Kim et al., 2004). Joinpoint analyses were performed using Joinpoint regression software (Version 4.0.4), available through the surveillance research program of the US National Cancer Institute.

Results

Nearly 25,000 gynaecological cancer deaths occurred in Serbia during the 1991-2010 period, with the average annual age-standardised mortality rate (ASR) being 17.2 per 100,000 women (Table 1).

Results of joinpoint regression analysis of gynaecological cancer mortality rates are presented in Table 2. The significant increase of mortality was observed for cancer of vulva and vagina (AAPC=+1.3%, 95% CI=0.1 to 2.6), ovarian cancer (AAPC=+0.8%, 95% CI=0.4-1.3) and for cervical cancer (AAPC=+0.7%, 95% CI=0.3 to 1.1). According to a comparability test, mortality trends for ovarian cancer and for other gynaecological cancers were parallel (P=0.779), but they significantly were different with the uterine cancer mortality trend (P=0.033).

Mortality trends for overall gynaecological cancers in Serbia were differed by age: the decreasing trend was observed in younger women (30-39 years of age: AAPC=-1.0, 95% CI=-1.8 to -0.1), but increased trend was recorded in all of older women (≥40 years old). In women 60-69 years old, non-statistically significant decrease in gynaecological cancer mortality rates observed during the period 1991-2000 (by -1.1% per year) was followed by a significant increase until 2010 (by +1.2% per year). In older age groups, trend for overall gynaecological cancers mortality rates was significantly increased by +0.6% per year from 1991 to onwards.

Increase in cervical cancer mortality in middle-aged women (40-59 years) was recorded during the entire period. In all younger age groups, trend for cancer from uterine body and uterus NOS significantly was decreased during whole period (by -7.7% per year, -4.4%, -1.4% and -1.5%, respectively).

Increased trend for ovarian cancer mortality was significant in older women (≥60 years old). In women 60-69 years-old, trend for mortality from ovarian cancer insignificantly was decreased by -0.7% per year from 1991 to 2002 and then significantly was increased by +4.5% per year from 2002 to 2010. There was one joinpoint in mortality trend for ovarian cancer among women aged ≥70 years: mortality was decreased by -3.0% (95% CI=-6.9 to 1.1) per year from 1991 to 1998 and then followed by significant increase by +5.2% per year (95% CI=3.3 to 7.1) until the end of the period in 2010.

ASRs from other gynaecological cancers (i.e. vulva and vagina) significantly was increased by +1.3% (95% CI=0.1 to 2.6) per year, continuously from 1991 to 2010.

Discussion

The average annual age-standardised mortality rate of 17.2 per 100,000 women, in the period 1991-2010, place Serbia among the European countries with the highest gynaecological cancers mortality rates. Our results show the increased mortality trends for cervical cancer, ovarian cancer and for other sites of gynaecological cancers (i.e. vulva, vagina). Cervical cancer affects middle-aged (40-59 years) women, while ovarian cancer is a more common cause of death in elderly women (60+ years). Moderate and insignificant changes in mortality in younger age groups could be promising.

The cervical cancer mortality between countries varies greatly, from the highest rates in Eastern African countries, Western Africa and Sub-Saharan Africa, to the

Table 1. Gynaecological Cancer Mortality Rates per 100,000 Women in Serbia, Excluding the Autonomous Province of Kosovo and Metohia, in 1991-2010 period.

Year	All		Uterus		Ovary		Others*	
	No.	ASRs	No.	ASRs	No.	ASRs	No.	ASRs
1991	1074	16.8	719	11.2	290	4.7	65	1.0
1992	1136	17.5	783	12.1	286	4.5	67	0.9
1993	1136	17.2	746	11.4	312	4.7	78	1.0
1994	1158	17.5	771	11.5	334	5.2	53	0.7
1995	1135	16.8	742	11.0	330	4.9	63	0.8
1996	1098	16.5	732	11.0	291	4.6	75	1.0
1997	1166	17.1	770	11.4	311	4.6	85	1.1
1998	1198	17.3	806	11.7	311	4.7	81	1.0
1999	1161	16.5	782	11.3	320	4.5	59	0.8
2000	1146	16.6	761	11.1	304	4.5	81	1.1
2001	1235	17.4	791	11.5	356	4.9	88	1.0
2002	1247	17.4	853	12.1	318	4.6	76	0.8
2003	1206	16.3	784	10.7	329	4.6	93	1.0
2004	1247	17.0	796	11.0	348	4.9	103	1.1
2005	1274	17.2	821	11.2	369	4.9	84	1.0
2006	1332	18.3	832	11.5	406	5.7	94	1.0
2007	1353	18.2	829	11.3	390	5.3	134	1.4
2008	1284	17.7	812	11.4	377	5.2	95	1.0
2009	1264	16.6	763	10.1	412	5.6	89	0.9
2010	1318	17.7	783	10.8	416	5.5	119	1.4
Overall	24168	17.2	15676	11.3	6810	4.9	1682	1.0

*ASR-Age standardized rate (per 100,000 women, using world standard population); Other cancers were included cancer of vulva, vagina, placenta and of other and unspecified female genital organs.

Table 1. Joinpoint Regression Analysis*† (of age-specific and age-standardized rates) of Gynaecological Cancer Mortality Rates per 100,000 Women in Serbia, Excluding the Autonomous Province of Kosovo and Metohia, by age, in 1991-2010 period.

	Age					
	30-39	40-49	50-59	60-69	70+	All ages
All gynaecological cancers						
AAPC	-1.0*	0.3	0.6	+0.1‡	+0.6*	0.2
(95%CI)	(-1.8 to -0.1)	(-0.5 to 1.0)	(-0.1 to 1.2)	(-0.3 to 0.6)	(0.1 to 1.2)	(-0.1 to 0.4)
Cervical cancer						
AAPC	-0.2	+1.3*	+2.1*	-0.1	-0.2	+0.7*
(95%CI)	(-1.7 to 1.3)	(0.4 to 2.2)	(1.3 to 2.8)	(-0.8 to 0.7)	(-1.1 to 0.7)	(0.3 to 1.1)
Corpus uteri/NOS						
AAPC	-7.7*	-4.4*	-1.4*	-1.5*	-0.5	-1.8*
(95%CI)	(-10.5 to -4.8)	(-7.0 to -1.7)	(-2.7 to -0.1)	(-2.1 to -0.8)	(-1.7 to 0.8)	(-2.4 to -1.3)
Ovarian cancer						
AAPC	0.4	0.6	-0.1	+1.3*,§	+2.5*,¶	+0.8*,††
(95%CI)	(-2.5 to 3.4)	(-0.4 to 1.5)	(-0.9 to 0.9)	(0.5 to 2.1)	(1.3 to 3.8)	(0.4 to 1.3)
Other cancers						
AAPC†††	-	0.9	2.8	1.2	1.9	+1.3*
(95%CI)		(-3.6 to 5.5)	(-0.4 to 6.0)	(-0.9 to 3.4)	(-0.3 to 4.1)	(0.1 to 2.6)

Statistically significant trend; †Joinpoint results are not shown for the age subgroups <30, because there were less than 10 cases in any year; average annual percent change; CI-Confidence interval; NOS-Cancer of uterus, part unspecified; other cancers include cancer of vulva, vagina, placenta and of other and unspecified female genital organs. ‡One joinpoint, for all gynaecological cancers in 60-69 years old women: Trend 1 (1991-2000): annual percent change (APC) (95% CI)=-1.1 (-2.3 to 0.0); Trend 2 (2000-2010): APC (95% CI)=+1.2(0.2 to 2.2). §One joinpoint, for ovarian cancer in 60-69 years old women: Trend 1 (1991-2002): (APC) (95% CI)=-0.7 (-2.0 to 0.7); Trend 2 (2002-2010): APC (95% CI)=+4.5*(2.3 to 6.8). ¶One joinpoint, for ovarian cancer in 70 and over years old women: Trend 1 (1991-1998): (APC) (95% CI)=-3.0 (-6.9 to 1.1); Trend 2 (1998-2010): APC (95% CI)=+5.2*(3.3 to 7.1). ††One joinpoint, for ovarian cancer trend in overall: Trend 1 (1991-2002): (APC) (95% CI)=-0.2 (-1.2 to 0.8); Trend 2 (2002-2010): APC (95% CI)=+2.5*(0.9 to 4.1); †††Joinpoint results are not shown for the 30-39 age subgroup, since there were less than 10 cases in any given year.

low rates in Northern America, Australia, some Middle Eastern countries (International Agency for Research on Cancer, 2008). In Europe, low rates are observed in the Scandinavia, Southern and Western Europe, while the highest mortality was observed in Romania and Serbia. A decline in the cervical cancer mortality recorded in most of developed countries, as Sweden (Bergstrom et al., 1999), England (Arbyn and Geys, 2002), Belgium (Bray et al., 2005). Mortality from invasive cervical cancer in the United States of America decreased significantly in all races in the 2000-2010 period, by -1.3% per year in women younger 50 and decreased by -1.9% in women 50+ years old (Howlader et al., 2013). Downward mortality trend for cervical cancer in the United States of America and West and North European countries is associated with the introduction of an organised mass screening

programme (de Kok et al., 2011). The high mortality rates and unfavourable trends of cervical cancer in developing countries are largely due to the lack of smear test screening that would provide for detection of precancerous cells and early stage cervical cancer (Bray et al., 2005). Increase in cervical cancer mortality in middle-aged women has also been observed in Serbia since 1991, as in countries with limited resources. Cervical cancer prevention in Serbia has relied on opportunistic screening, characterised by high coverage in younger and low coverage in middle-aged and older women (Ministry of Health Republic of Serbia, 2007). Improvements and implementation of the National Cervical Cancer Screening Programme were done in 2013 and are expected to be finalised in the following years throughout Serbia.

Mortality depends on incidence and survival and mortality differences may reflect differences in either or both of these factors. In Serbia, as in countries with limited resources, less than a third of cervical cancer cases are discovered in early stage of illness, whilst in most patients later stages are found (Ministry of Health Republic of Serbia, 2007; Gyenwali et al., 2013; Razak et al., 2013). One of the postulated environmental risk factor known to cause cervical cancer is smoking. Tobacco exposure in Serbia is high. In 2000, 38.1% of Serbian women were smokers, whereby the highest percentage of smokers was recorded in the 35 to 44 year-old group. Cervical HPV infection was detected in 19.1% of asymptomatic young women with normal cytology in Serbia (Knezevic et al., 2012). Both HPV prophylactic vaccines are registered, but not integrated in the national immunisation programme in Serbia.

The opposite trends in cervical cancer mortality in developed and in developing countries should be interpreted very carefully for several reasons. Variations in quality of mortality statistics are one of the possible explanations for these differences and might be associated with the way used to of determine cause of death, cause of death coding, presence of symptoms and underdefined conditions in the structure of total mortality, frequency of autopsy. The percentage of uterine cancer cases (cervical and uterine body cancers) and deaths attributed to the third category, i.e. Uterus NOS, varies among countries and times (Arbyn and Geys, 2002). The question remains how changes in the death rate from cervical or uterine body cancers in Serbia may be associated with a reduction in Uterus NOS rate due to improved cause-of-death determination (Mathers et al., 2005). In some countries (Howlader et al., 2013), mortality data do not distinguish among cervical, uterine and uterus NOS cancers, which makes it difficult to perform international comparisons.

Mortality rates from uterine body cancer were decreased markedly in western and southern European countries, both in pre- and postmenopausal women (Bray et al., 2005b). Postmenopausal mortality rates were highest in Eastern Europe, with increased trend among women in Latvia, Russia and Moldova. While in the last decade recorded mortality from uterine body and uterus NOS cancer increased (by +0.4% per year) in all races in the USA (Howlader et al., 2013), women in Serbia showed decreased death rates (by -1.8% per year) during the 1991-2010 period. Changes in reproductive factors (e.g. nullyparity, older age at last birth), oral contraceptives use and hormonal replacement therapy, obesity, diabetes mellitus, smoking and alcohol use are the main factors that influenced changes in endometrial cancer occurrence (dos Santos Silva et al., 1995; Lindemann et al., 2008). The decreasing trend of mortality from uterine body and uterus NOS cancers in Serbia during the period observed can be probably attributed to some changes in reproductive and lifestyle factors. Oral contraceptives were used by about every tenth woman (11.6%) aged 20-24 years and by every eighth woman (13.1%) in the age group of 45-49 years (Rasevic, 2008). But, among women in Serbia the use of menopausal hormone therapy was very low, less than 1.0% (International Menopause Society, 2014).

Ovarian cancer mortality has been increasing in most of the Eastern and Southern European countries, especially in Greece, Bulgaria, Poland, Spain (Bray et al., 2005; International Agency for Research on Cancer, 2008; Kelava et al., 2012). High ovarian cancer mortality could be explained by absence of specific symptoms, undeveloped techniques of early detection, with the possibility of high-risk group identification to optimise the use of follow-up still being explored (Lea and Miller, 2001). The aetiology of ovarian cancer is not clearly understood. The established risk factors for ovarian cancer are age, family history and reproductive factors, while the possible risk factors are the fertility drugs use, hormonal replacement therapy, oral contraceptives, obesity (dos Santos Silva et al., 1995). Some of the possible risk factors for ovarian cancer are frequent in Serbia (Ministry of Health Republic of Serbia, 2007). In 2006, about 18.0% of women were obese and 29.5% were overweight (Ministry of Health Republic of Serbia, 2007). During the same period, decreased fertility was inversely related to increased mortality from ovarian cancer ($r=-0.509$, $p<0.05$), with an increase in age at first birth having also occurred (Statistical Office of the Republic of Serbia, 2001-2011).

Although vulvar cancers occur two to three times more frequently than vaginal cancers, they are still sparse (Sankaranarayanan and Ferlay, 2006). The mortality rates from vulvar and vaginal cancers are very low, but increased trends are important public health problems (International Agency for Research on Cancer, 2008). The etiology of vulvar and vaginal cancers are not understood well. Except for vaginal cancer, which is associated with maternal diethylstilbestrol exposure, numerous studies have shown an association between vulvar and vaginal cancer with age, HPV and HIV infection, smoking, high-risk sexual behaviours, genetic susceptibility (Trimble et al., 1996; Verloop et al., 2010). In Serbia, among women aged 19 to 31 years with normal cervical cytology, high prevalence of high-risk HPV types was detected (type 16 was the most frequent -23.1%) (Knezevic et al., 2012). Also, this study confirmed significant association between increasing number of sexual partners and HPV positivity. Vaginal and vulvar cancers have known precancerous lesions, but currently no evidence exists to suggest any screening tests (Bae-Jump et al., 2007).

Strengths and limitations of the study

This study provides the first nationwide estimates of gynaecological cancer mortality in Serbia in the last two decades. Mortality rates were based on the data that cover entire Serbia in general. As always, the important question is the reliability of the causes of death reported in the national statistics. Taking into account timeliness, completeness and coverage, the quality of the registration and classification of causes of death in Serbia was deemed moderate according to the assessment of the World Health Organization (Mathers et al., 2005). The relationship of the observed changes in mortality with some of the postulated risk factors for gynaecological cancers was also assessed.

We had no reliable data on incidence, treatment and survival of gynaecological cancers during the observed period. A further limitation is the lingering question whether and how much the increasing cervical cancer mortality in Serbia could be attributed to the lack of national screening. Finally, the lack of complete and precise data on presence of risk factors for gynaecological cancers occurrence, as and the considerable economic issues and insufficient health education in Serbia, made it impossible to examine their impact on the changes in the mortality.

In conclusion, our results showed the increased trend for cervical cancer, ovarian cancer and other gynaecological cancer mortality in Serbia. These unfavorable mortality trends indicates the extremely urgent need for the systematic improvement of both primary and secondary prevention measures, as well as the need for development of adequate resources and infrastructure for gynaecological cancer control in Serbia.

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