

CERVICAL CANCER IN THE AUTONOMOUS PROVINCE OF VOJVODINA, SERBIA, 2016–2021

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ABSTRACT

Background: Cervical cancer is a major global health problem, and one of the most common causes of cancer in women. This descriptive epidemiological study aimed to provide an overview of the cervical cancer incidence and mortality in Vojvodina.

Methods: The data from the Serbian Cancer Registry regarding the cervical cancer incidence and mortality for the period 2016–2021 were analyzed.

Results: During the observed 6-year period, the average age-standardized incidence rates of cervical cancer in Vojvodina and Serbia were 20.4 and 19.1 per 100,000 women, respectively. The average age-standardized incidence rates by the district of Vojvodina ranged from 16.8 to 30.2/100,000. The average age-standardized cervical cancer mortality rate in Vojvodina and Serbia was 7.0 and 6.6/100,000, respectively. The average mortality rates by the district of Vojvodina ranged between 5.6/100,000 and 9.9/100,000.

Conclusion: The cervical cancer incidence and mortality rates in Vojvodina exhibited significant variation across different districts and observed years, with their average values surpassing the national average. To improve the epidemiological situation of cervical cancer in Vojvodina, it is imperative to enhance the implementation of organized screening at the district level, coupled with intensified efforts to promote HPV vaccination throughout Vojvodina. Additionally, more research on screening coverage and vaccination rates and improved reporting cervical cancer cases and deaths are needed.

Key words: uterine cervical neoplasms; epidemiology; incidence; mortality; papillomavirus vaccines; Serbia

INTRODUCTION

Cervical cancer presents a major global health problem, as the fourth most common female cancer globally, just after breast, lung and colorectal cancer. According to estimates for the year 2022, over 662,000 women worldwide developed cervical cancer, and almost 349,000 died from it. The estimated age-standardized cervical cancer incidence rates vary widely across the globe, ranging from 2 to almost 96 per 100,000 women. Age-standardized mortality rates show similar variability, ranging from 1 to over 64/100,000 (1). In some of the most heavily affected countries, like Eswatini in Southern Africa, it is estimated that up to 6.5% of women will develop cervical cancer before they are 75 years old (2). Overall, about 88% of new cases and 91% of deaths are registered in low- and middle-income countries, with the highest incidence and mortality rates occurring in sub-Saharan Africa, Central America, and South-East Asia. This disparity is a result of numerous factors such as regional differences, inadequate vaccination, screening and treatment services, socioeconomic determinants and the presence of risk factors including the human immunodeficiency virus (HIV) infection (3,4).

The primary cause of precancerous and cancerous cervical lesions is infection with a high-risk or oncogenic human papillomavirus (HPV) strain. In fact, oncogenic strains of HPV, of which types 16 and 18 are most common, are considered to cause nearly 100% of cervical cancer cases, along with 90% of anal, 70% of vaginal, 50% of penile, 40% of vulvar and 13% to 72% cases of oropharyngeal cancers (5). After HPV,

smoking tobacco is the next significant risk factor for cervical cancer, with the risk of malignancy depending on the duration and intensity of the habit. HIV infection and long-term oral contraceptive use are also considered risk factors (6).

The Autonomous Province of Vojvodina is the northern province of the Republic of Serbia, bordering Croatia to the west, Hungary to the north, Romania to the east, and Bosnia and Herzegovina to the southwest (7). The province has about 1.7 million inhabitants, which corresponds to almost one-third of the population of Serbia. Vojvodina is divided into seven districts (North, West and South Bačka, North, Central and South Banat, and Srem), and 44 municipalities. The South Bačka District is the most populous one, containing the administrative centre of Vojvodina, the city of Novi Sad (8–10). The gross domestic product (GDP) per capita of Vojvodina in 2021 was 43.2% of the EU average, slightly below the average GDP per capita of the Republic of Serbia (44.8%), and significantly lower than the GDP per capita of the capital Belgrade (72.8% of the EU average) (11).

The aim of this study was to observe cervical cancer epidemiology in Vojvodina using the latest available data, spanning from 2016 to 2021.

MATERIALS AND METHODS

We conducted a descriptive epidemiological study using data from the Serbian Cancer Registry of the “Dr Milan Jovanović Batut” Institute of Public Health of Serbia, covering the period from 2016 to 2021. The data preceding 2016 were compiled in the now defunct Cancer

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Registry of Vojvodina and are not publicly available. The study focused on analyzing the age-standardized rates of cervical cancer incidence and mortality in Vojvodina with its districts and Serbia (excluding the Autonomous Province of Kosovo and Metohija). The Serbian Cancer Registry contains data collected from oncology institutes and clinics, hospitals and out-patient health institutions, pathology, hematology and other laboratories, death reports, health insurance funds, and targeted research. Malignancies in the Registry are classified according to the tenth Revision of the International Classification of Disease. We have only analyzed rates pertaining to cervical cancer (code C53). The age-standardized incidence and mortality rates presented in the Registry are standardized via direct standardization, using Segi's world population (12). The period average age-standardized incidence and mortality rates were calculated as arithmetic means of yearly rates. Comparisons of the cervical cancer incidence and mortality across different regions or calendar years of the same region were made using ratios multiplied by 100%. When comparing annual changes in a single region, the numerator is the current year, and the denominator is the previous year.

RESULTS

During the period from 2016 to 2021, the age-standardized incidence rates (ASIRs) in Vojvodina ranged from 10.8 in the North Bačka District (in 2019), to 39.0 cases per 100,000 women in the West Bačka District (in 2021) (Figure 1).

The average ASIRs of cervical cancer in Vojvodina and Serbia for the study period were 20.4 and 19.1 per 100,000 women, respectively. The average ASIR values by district ranged between 16.8/100,000 in the South Banat District and 30.2/100,000 in the West Bačka District (Figure 2).

The age-standardized mortality rates (ASMRs) in the districts of Vojvodina ranged from 0 in the Central Banat District (in 2019) to 13.7 per 100,000 women in the North Banat District (in 2017) (Figure 3).

The average ASMRs in Vojvodina and Serbia in the period were 7.0 and 6.6 per 100,000 women, respectively. The districts of Vojvodina had six-year average ASMR values in the range from 5.6/100,000 in the Srem District to 9.9/100,000 in the North Banat District (Figure 4).

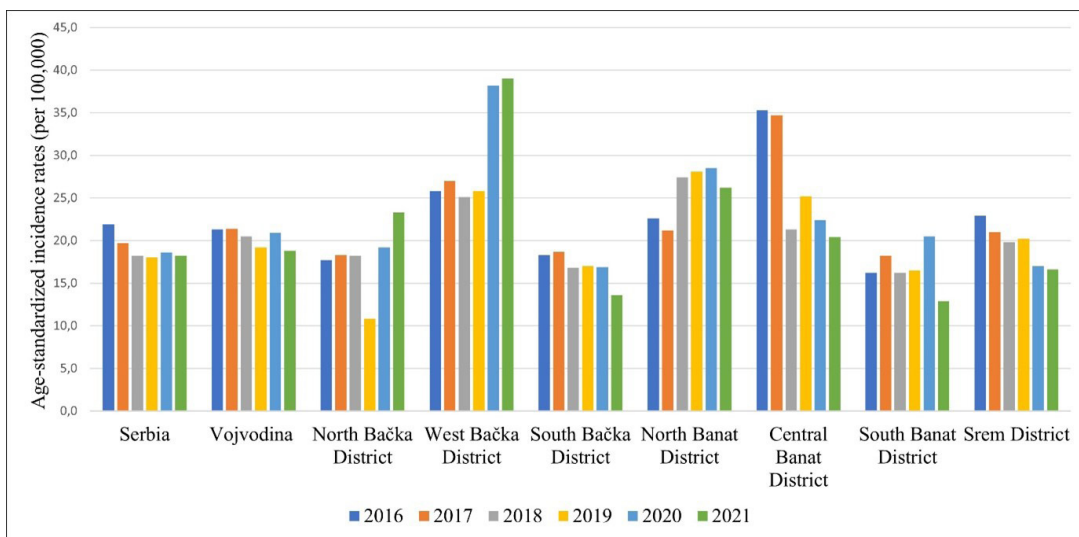


Figure 1. Age-standardized incidence rates for cervical cancer in Serbia, Vojvodina, and the districts of Vojvodina, 2016-2021.

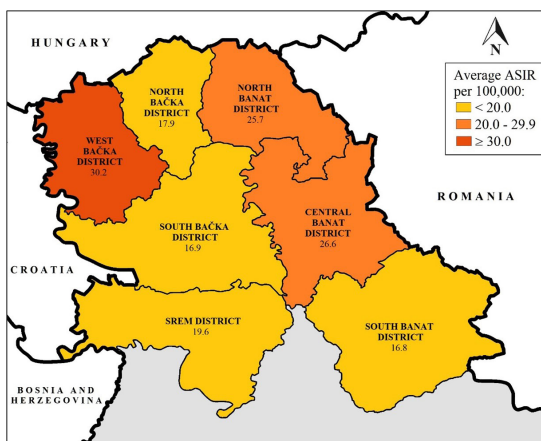


Figure 2. Average age-standardized cervical cancer incidence rates by district of Vojvodina, 2016-2021.

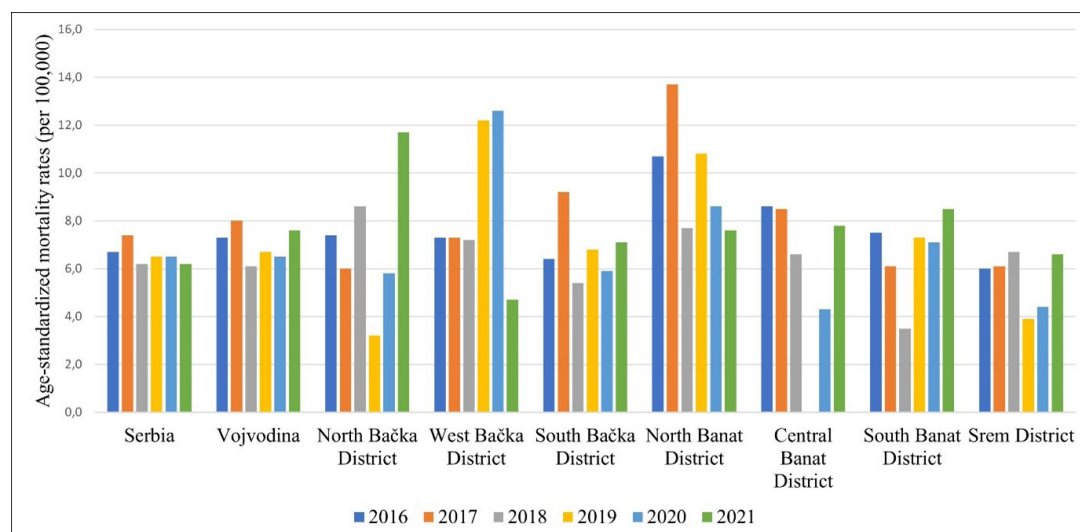


Figure 3. Age-standardized mortality rates of cervical cancer in Serbia, Vojvodina, and districts of Vojvodina, 2016-2021.

DISCUSSION

Most European countries have lower age-standardized cervical cancer incidence and mortality rates than the global average. According to the 2022 International Agency for Research on Cancer (IARC) estimates, cervical cancer is the sixth most frequent female cancer in Europe with an average ASIR of 10.6 per 100,000, and the sixth most common cause of cancer death in women, with an average ASMR of 3.8 per 100,000 (1). However, there is a noticeable discrepancy in the burden of cervical cancer across the continent. While Western European countries traditionally exhibit low incidence and mortality rates, Eastern European countries, including Serbia, demonstrate higher values (13).

In 2020, it was estimated that Serbia had the third highest age-standardized incidence and mortality rates in Europe, after Montenegro and Romania (3). Comparing the data from the Serbian Cancer Registry with the current estimates for Europe, the 2016-2021 average cervical cancer ASIR was 80% higher than the European average (19.1 vs 10.6/100,000). As for mortality, the six-year average ASMR was 74% above the average rate in Europe (6.6 vs 3.8/100,000). Underlining these high rates, cervical cancer is the fourth most frequent female cancer and the fifth most common cause of death due to cancer in women in Serbia (12).

While cervical cancer presents a major health problem in Serbia, the northern province of Vojvodina is, on average, more affected - the average age-standardized incidence rate during the 2016-2021 period was 6.8% higher than the Serbian average (20.4 vs 19.1/100,000), and the average age-standardized mortality rate was likewise 6.1% above the national average (7.0 vs 6.6/100,000). Compared to European countries, the ASIR in Vojvodina during the analyzed period was 92% higher compared to the European average (20.1 vs 10.6/100,000), while the ASMR was 84% higher (7.0 vs 3.8/100,000). When compared to some similarly sized countries in the region, this disparity becomes

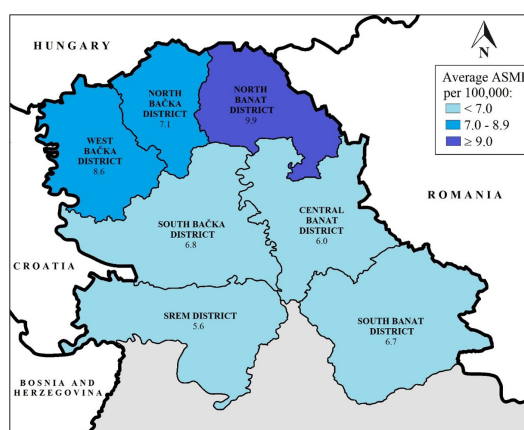


Figure 4. Average age-standardized cervical cancer mortality rates by district of Vojvodina, 2016-2021.

even larger. The 6-year average ASIR in Vojvodina was more than two times higher than the 2016-2020 average incidence rate in neighboring Croatia (20.4 vs 9.0/100,000), and three times higher (20.4 vs 6.8/100,000) than the average in Slovenia during the same time period (14,15). Additionally, the average ASMR in Vojvodina was nearly four times higher than in Slovenia (7.0 vs 1.8/100,000) during this 5-year period (15).

During the period from 1991 to 2011, the average ASMR in Serbia was 7 per 100,000 women, with values steadily and significantly increasing from 6.1 (in 1991) to 8.2/100,000 (in 2008) (16). Collated with this, the average ASMR in Serbia has fallen by 6% from the 1991-2011 average, while the current average ASMR in Vojvodina is equal to that value. This clearly shows that preventive efforts, including organized screening and HPV vaccination, both initially introduced in 2008 in Serbia, have failed to produce a significant effect, and require further improvement.

Considering the average cervical cancer incidence rates in the period 2016-2021 by district, the West Bačka District had the highest average ASIR (30.2/100,000), 58% higher than the country aver-

age. Additionally, the Central Banat District and the North Banat District also had higher incidence rates than the average in Vojvodina (26.6 and 25.7/100,000, respectively), while the Srem District had an average ASIR below the average in Vojvodina but higher than the Serbian average (19.6/100,000). The districts of North Bačka, South Bačka and South Banat had an ASIR lower than the country average (17.9, 16.9 and 16.8/100,000, respectively).

Regarding the mortality rates, there was a similar distribution across the districts of Vojvodina during the observed 6-year period. The highest average mortality rate was recorded in the North Banat District (9.9/100,000), which was 48% above the average ASMR in Serbia during the 2016-2021 period. The districts of West Bačka and North Bačka exhibited higher cervical cancer mortality compared to both the provincial and national averages (8.6 and 7.1/100,000, respectively). The South Bačka District and the South Banat District had slightly higher rates than the Serbian average (6.8 and 6.7/100,000, respectively), while the average ASMR in the Central Banat District was below the average rate in Serbia (6.0/100,000). The lowest average cervical cancer mortality (5.6/100,000 women) was registered in the Srem District. It should be noted that the data show an exceeding variability of mortality rates, with multiple per-year changes of over 50%, including a district which reported zero deaths (Central Banat District in 2019), which could indicate an issue with cervical cancer reporting.

With this in mind, the areas most affected by cervical cancer within Vojvodina are the districts of West Bačka, Central Banat and North Banat. Proving this point, the average ASIR in West Bačka was 1.8 times higher than the incidence rate in the South Bačka District, and the ASMR in the district of North Bačka was also 1.8 times higher than the average rate in the Srem District. Such regional disparities point to a need for further research into potential causes, including socioeconomic characteristics, screening coverage and vaccination rate in these districts.

Analyzing year-to-year changes in the cervical cancer incidence and mortality rates, it can be observed that ASIRs consistently fell for multiple years in Serbia (from 21.9 to 18.2/100,000), the South Bačka District (from 18.3 to 13.6/100,000), the Central Banat District (from 35.3 to 20.4/100,000), and the Srem District (from 22.9 to 16.6/100,000). On the other hand, ASIRs have increased in the North Bačka District (from 17.7 to 23.3/100,000), the West Bačka District (from 25.8 to 39.0) and the North Banat District (from 22.6 to 26.2/100,000). Regarding the mortality rates, the ASMR of cervical cancer in Serbia slightly dropped during the observed period (from 6.7 to 6.2/100,000). However, the mortality rates in Vojvodina and its districts show large year-to-year variations, and a trend cannot be discerned.

Given the significant burden of cervical cancer in Serbia and following the results of a pilot study conducted

in the Braničevo District, the Serbian government implemented a decentralized screening program in 2008, which was further improved in 2012 and 2013. The target demographic encompasses women aged 25 to 64, with a goal of achieving over 75% coverage. Cervical cytology-based screening (Papanicolaou test) is used, with one test performed every 3 years, after 2 previous negative results in the span of a single year (17). According to a report by the National Cancer Screening Office, 25,370 women from the territory of Novi Sad were invited to participate in cervical cancer screening during 2016, which represented 71.1% of the target population; 93.8% of this number had a Papanicolaou test performed, resulting in a total coverage by examination of 66.7%. By comparison, on the territory of Belgrade and for the same period, 35% of the target population was invited to participate, and only 16.7% of women aged 25–64 years were ultimately covered by examination (18). Currently, the screening coverage for cervical cancer in Serbia is estimated to be between 35% and 68%, though there is no published data for individual regions, including Vojvodina (19). More detailed and up-to-date data regarding screening coverage in different parts of the country is needed in order to assess the potential implications on the cervical cancer incidence and mortality rates.

While Papanicolaou testing has significantly contributed to cervical cancer prevention worldwide, there are several limitations of this screening method, including suboptimal sensitivity and dependence on the cytologist's skill and experience. The prime candidate for replacing Pap testing as the cervical cancer screening method of choice is HPV-based screening, i.e. the detection of viral DNA in exfoliated cervical cells (20). HPV based screening is characterized by a high sensitivity and a very high negative predictive value of nearly 100%, according to multiple studies. As a result, a five-year disease-free rate after a negative HPV test is considered to be equivalent to a two-year disease-free rate after a Papanicolaou test. However, it is important to note that lower specificity and a higher number of false-positive results present a downside for HPV screening, increasing referrals for colposcopy and causing unnecessary psychological morbidity to women (21). Previously, HPV testing was considered a costlier alternative to cervical cytological examination; however, according to recent data from the Netherlands, HPV-based screening was proven to be more effective and less expensive than the previous cytological screening program (22). An example of successful implementation of HPV testing is Turkey, which increased screening coverage from 3% to 35% in just five years, after replacing cytology-based screening with HPV-based screening (23). Currently, HPV testing has not been implemented in Serbia, nor are there plans to use it as a primary screening test in the foreseeable future. Yet, considering the significant cervical cancer burden in the country, the aforementioned advantages of the method, and the experience from other countries,

adopting HPV testing as a primary screening test would be expected to provide a significant improvement in cervical cancer screening, coupled with a long-term reduction in cost.

Alongside a carefully structured screening program for cervical cancer, another important preventive measure is vaccination against HPV. The effectiveness of HPV vaccination in cervical cancer prevention has been clearly demonstrated. In a large-scale study conducted in Scotland, vaccinated women showed an almost 90% reduction in the prevalence of cervical intraepithelial neoplasia (CIN) grade 3 and grade 2, and an almost 80% reduction in CIN grade 1 prevalence, at 20 years of age, compared to unvaccinated women (24). An efficacy study conducted in Denmark, Sweden, Norway, and Finland showed no cases of high-grade cervical dysplasia linked to HPV types 16 or 18 among vaccinated women, resulting in a vaccine effectiveness of 100%, which was demonstrated for over 12 years post-vaccination (25). The HPV vaccines in use have demonstrated an acceptable safety profile, with no consistent evidence of an increased risk of any side effects of special interest, and with a highly favorable risk-benefit ratio (26). Additionally, HPV vaccination helps reduce the incidence of genital warts, which are predominantly caused by low-risk HPV types 6 and 11 and are among the most common sexually transmitted infections globally (27).

In the Republic of Serbia in 2008, an official recommendation for HPV vaccination for all children before their first sexual experience was given, but the cost was not covered by health insurance at the start of vaccination. In 2020, the Institute for Public Health of Vojvodina, in collaboration with the Healthcare Centre of Novi Sad, conducted a promotional campaign, targeting the population of the city of Novi Sad. Aiming to increase awareness about the HPV vaccine and increase vaccination rates, quadrivalent HPV vaccines were provided free of charge for girls aged 12–19 years. The following year, the program was modified to be gender neutral, and boys in the same age group were included as well. This promotional campaign ended in 2021, and during its course, approximately 1,400 teenaged girls and boys in Novi Sad were vaccinated with two or three doses of the HPV vaccine, depending on the age of the recipient. In 2022, the nonavalent HPV vaccine was introduced in the national immunization program and started to be implemented nationwide for males and females aged 9–19 years, free of charge (28). There is no officially published data regarding current HPV vaccine coverage in Vojvodina or Serbia, but a study published in 2018 reported that only 2% of Serbian children aged 9–18 were vaccinated with a single dose or more (29). This is quite low, especially when compared to some countries in the region like Croatia and Slovenia. Today, vaccine coverage is expected to be higher, especially since the HPV vaccine was included in the national immunization program in 2022, but the exact number is not available.

Regarding the experiences from countries in the region, the introduction of HPV immunization in Slovenia serves as a notable example. In this country, the HPV vaccine was introduced in 2007 and officially included in the national vaccination program in 2009. Initially, it was offered as a non-mandatory vaccine only for girls aged 11–12 years and provided free of charge. By 2018, 59.3% of eligible girls in Slovenia were fully vaccinated. Subsequently, in 2019, the Slovenian HPV vaccination program was expanded to include boys aged 11–12 years, with HPV vaccine coverage among this population reaching 14.7% during the school year of 2021/22 (30). In Croatia, the first HPV vaccines were registered in 2007, but were initially not covered by health insurance. In the following years, HPV vaccination was provided free of charge in some counties of this country. In 2016, HPV vaccination was added to the national immunization program in Croatia, covered by health insurance, and recommended for both boys and girls aged 14–15 years. A catch-up campaign was started in 2019, targeting unvaccinated people younger than 25 years of age. As a result of these efforts, in the school year of 2019/2020, 38% of first-grade high school female students and 24% of male students (aged 15–16 years) were fully vaccinated. A recent 2023 survey showed that 18.3% of the target cohort aged 18–25 years (25.0% of women and 11.7% of men) were vaccinated against HPV (31).

A public health measure that could improve cervical cancer prevention is the replacement of the current voluntary HPV vaccination program in Serbia with a mandatory one. Mandatory vaccination would be a fast way to increase vaccine uptake, especially if raising awareness and promotional campaigning fail to produce results. Yet, the numerous ethical implications and economic issues would first have to be discussed, and the potential effect on the public trust must be taken into consideration beforehand (32).

CONCLUSION

The cervical cancer incidence and mortality rates in Vojvodina exhibited significant variation across different districts and observed years, with their average values surpassing the national average. In response to this challenge, numerous strategic initiatives are currently being implemented on a national level. An organized cervical cancer screening program was established in 2008 and underwent further enhancement in 2012 and 2013, although the target coverage of 75% has not yet been achieved. The widespread implementation of HPV vaccination, as one of the most effective specific preventive measures, has only begun recently throughout the country, and its impact remains to be observed. To improve the epidemiological situation of cervical cancer in Vojvodina, it is imperative to enhance the implementation of organized screening at the district level, coupled with intensified efforts to promote HPV vaccination throughout Vojvodina. More research on screening coverage and vaccination rates across

different regions of Serbia is needed, in order to adequately plan public health measures and gauge their effectiveness. Additionally, improvements in cervical cancer reporting are necessary, as the data from the Serbian Cancer Registry regarding Vojvodina show a potential issue with reliability.

Declaration of interests

The authors declare no conflict of interest.

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