

## **CERVICAL CANCER IN THE REPUBLIC OF NORTH MACEDONIA (2014-2021): POTENTIAL DIFFERENCES BY AGE AND PLACE OF RESIDENCE**

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### **Abstract**

Cervical cancer remains an important problem affecting more than half a million women across the globe each year. This study aims to illustrate the demographic (age) and geographic (rural/urban place of residence) differences in cervical cancer incidence rates in the Republic of North Macedonia. For this reason, a cross-sectional analytical study of 1817 cervical cancer patients registered in the period from 2014 through 2021 was conducted. Analysis of newly diagnosed cases of cervical cancer (2014-2021) indicated an upward trend by place of residence and age groups. The geographic (rural/urban) analysis indicated that 1309(72.7%) cases were from urban areas, and 492(27.3%) from rural areas. The majority or 1261(69.4%) were aged  $\geq 50$  years. The proportion of women aged under 50 was significantly lower - 556(30.6%), but liable to increase. In selected statistical regions, analysis of several years did not indicate a significant urban/rural difference in the percentage of newly diagnosed cases of cervical cancer.

Although a significant part of the burden of cervical cancer can be alleviated through the HPV vaccination and timely screening, focused research on the geographic and socio-demographic specificities of the population must be conducted. Such research would provide a greater understanding of the nature of regional and sociodemographic disparities, which would in turn allow for the creation and improvement of programs for prevention, diagnosis and timely treatment of cervical cancer.

**Keywords:** cervical cancer; morbidity, mortality; urban, rural

### **Introduction**

Cervical cancer is the fourth most common type of cancer in women and the seventh most common type of cancer worldwide, and thus, one of the most pressing health issues in the world today. In 2020 alone, there were approximately 604,127 new cases of cervical cancer diagnosed globally, and 341,831 deaths resulting from this disease<sup>[1]</sup>. While in recent decades cervical cancer prevention and control has been effective in many developed countries due to screening initiatives and effective treatment methods, it is still the leading cause of cancer-related deaths among women in 42 countries, most of which are of low and middle-income.

To address this issue, the World Health Organization (WHO) launched their global initiative for the elimination of cervical cancer in 2020, aiming to reduce the incidence rates to less than 4 cases per 100,000 women annually in each country. This comprehensive effort

also seeks to mitigate international disparities related to this disease. The objective outlined in this initiative, known as “90-70-90”, envisions achieving the following set of targets by 2030: having 90% of girls vaccinated by the age of 15, ensuring that at least 70% of women undergo high-performance screening tests at least twice by the age of 45 and identifying 90% of women with cervical pre-cancer or cancer in need of treatment<sup>[3]</sup>.

There are, however, two primary challenges to consider: a) Due to the fact that HPV vaccines primarily target preadolescents or early adolescents, it may take several decades after their administration to fully observe their efficacy in the prevention of cervical cancer and thus the reduction of its incidence and mortality rates<sup>[4-6]</sup>, and b) The vaccine coverage in low and middle-income countries has thus far been very low.

Notably, data from March 2022 indicate that only 27% of low-income countries and 43% of middle-income countries have incorporated HPV vaccination into their regular immunization schedules<sup>[7]</sup>. Recent estimates reveal that a mere 12.2% of girls and women worldwide are covered by extant HPV vaccination programs (8). Progress in the reduction of incidence and mortality rates of cervical cancer has, on a global scale and in particular in low and middle-income countries, where a consistent 91% vs. 60% of cases are observed, has been very slow, with numerous countries reporting an increase in both rates over the course of the last decade<sup>[7]</sup>. Another concerning statistic is that while both the incidence and mortality rates of cervical cancer are highest among individuals aged 50 and above, the incidence among young women (aged 15-49) has seen a global increase, particularly in regions with a high socio-demographic development index<sup>[7]</sup>. Furthermore, while both the incidence and mortality rates of cervical cancer are highest among individuals aged 50 and above, the incidence among young women (aged 15-49) have seen a global uptick, particularly in regions with a high socio-demographic development index<sup>[9]</sup>. This increase can be attributed to a wide range of factors, including heightened HPV exposure, increased participation in screening, earlier engagement in sexual activity and a history of multiple sexual partners, among others. Aside from general vaccine unavailability, the lack of adequate early detection programs in impoverished nations are also a likely culprit for the elevated incidence and mortality rates of cervical cancer<sup>[10]</sup>. Nonetheless, given that the cause of cervical cancer incidence and mortality rates are complex and can greatly vary for each country, it is recommended to conduct a comprehensive analysis of the disparities and relevant factors in each country in order to develop a more effective treatment and prevention strategy.

In addition to the developmental disparities among countries, in-depth analyses conducted in each individual country reveal significant variations in cervical cancer mortality rates between rural and urban settings. Specifically, in many rural areas, the mortality rates either remain stable or see a slight increase, contrasting the decrease seen in urban areas. The reasons for these disparities are highly complex, with inadequacies in rural areas' healthcare systems emerging as a key factor<sup>[11]</sup>. Relevant literature substantiates the purported claim of significantly varying levels of healthcare quality between urban and rural areas in terms of coverage with early detection and prevention programs for cervical cancer<sup>[10]</sup> and limited access to healthcare services. The latter factor in particular significantly impacts the utilization of cervical cancer screening programs in North Macedonia. Both factors, however, should be taken into consideration, as they both serve as important indicators of timely and effective treatment opportunities<sup>[12]</sup>.

Another crucial group of factors that directly and proportionally impact cervical cancer incidence rates is that of illiteracy and multiparity (multiple births), which are prevalent in marginalized areas of economically underdeveloped nations. Geographical regions with high cervical cancer incidence and mortality rates often coincide with areas of

endemic human papillomavirus (HPV) infection, leading to a high prevalence of infection among both men and women<sup>[7,8]</sup>. The HPV subtypes prevalent in countries with high cervical cancer mortality (Asian, Latin American and African) are likely to pose a higher risk due to their greater oncogenic potential when compared to European types/subtypes<sup>[8,13]</sup>.

Despite the professional consensus regarding the importance of analyzing rural/urban disparities in the context of cervical cancer, scientific discussion on this issue in North Macedonia remains extremely sparse. Thus, this study was conducted with the intent of shedding light on age and urban-rural disparities in cervical cancer rates in the Republic of North Macedonia.

### **Materials and methods**

This study was conducted as part of the National Cervical Cancer Survey in the Republic of North Macedonia, employing a cross-sectional analytical approach. It is carried out annually by the Institute of Epidemiology and Biostatistics with Medical Informatics, Faculty of Medicine, Ss. Cyril and Methodius University, as a part of the Ministry of Health Cancer Control Program. This analysis took into consideration data collected during 2014-2021, or rather, it encapsulates the period from the implementation of the *National eHealth System in Republic of North Macedonia - "My Appointment"* ("Moj Termin") electronic database of the Ministry of Health.

For the purposes of this study, data of absolute number of cases, were collected from individuals who were registered in the "My Appointment" database by their attending physicians during the aforementioned period. These individuals sought healthcare services or interventions related to the diagnosis and treatment of cervical cancer. The diagnostic criteria according to the International Statistical Classification of Disease and Related Health Problems, Tenth Revision (ICD-10) code C53, was used to identify cases of cervical cancer. Population data, including gender, age and distribution across the eight statistical regions were obtained from the State Statistical Office of the Republic of North Macedonia annual official population records, which encompass the entire year up to December 31st. The estimate of the country's population was based on the last census of 2002 and for the period of interest of this study was with no major variations. This study aimed to provide a comprehensive overview of the national epidemiological landscape of cervical cancer from 2014 to 2021, taking into consideration both geographical and socio-demographic factors.

### **Statistical Analysis**

All data used for the purposes of this study were carefully arranged and organized into separate databases to ensure accuracy and minimize errors. The statistical analysis was conducted using the SPSS software package, version 22.0 for Windows (SPSS, Chicago, IL, USA). Qualitative variables were analyzed by calculating ratios, proportions and rates, and the results were presented as both absolute and relative numbers. In terms of quantitative variables, measures of central tendency (mean, median, minimum and maximum values) and measures of dispersion (such as standard deviation) were utilized. The frequency distribution was assessed using the Shapiro-Wilk W test. Proportions were compared using the Difference test. Statistical significance was determined using a two-tailed analysis with a significance level set at  $p < 0.05$ .

### **Results**

From 2014 to 2021, a total of 1817 new cases of cervical cancer were recorded in the national healthcare registry, with distribution shown in Table 1. In 2014, there were 399 cases, accounting for 21.9% of the total, while the remaining 1418 cases were diagnosed

between 2015 and 2017. The average age at the time of initial diagnosis was lowest in 2014 and 2017, with respective values of  $53.9 \pm 10.2$  and  $53.6 \pm 12.6$ . The age range was 28 to 80 years in the former and 19 to 84 years in the latter, with 50% of patients being younger than 55 years in the first group - Median IQR=55(46-61) and 53 years in the second group - Median IQR=53(46-63). The highest average age was observed in 2021, at  $58.9 \pm 11.59$  years, with a range of 26 to 91, and 50% of patients being younger than 61 years for the Median IQR=61(52-67).

Throughout the eight-year study period, there were a total of 11 cases (0.8%) diagnosed in individuals under the age of 29, 121 cases (8.5%) in those under 39, and 26 cases (1.8%) in individuals aged 80 and above.

Of the women diagnosed with cervical cancer between 2014 and 2021, the majority (69.4%, 1261 patients) were aged 50 or above, while the proportion of individuals under 50 years was significantly lower at 30.6% (556 patients). The proportion of individuals aged 50 or older varied from 78.4% in 2021 to 60.8% in 2019 (Table 1).

**Table 1.** Cervical cancer according to year of first diagnosis and age above/below 50 (2014-2021)

Age	Year of first diagnosis								Total
	2014	2015	2016	2017	2018	2019	2020	2021	
<50 years	138	48	34	58	103	81	44	50	556
	34.6%	28.1%	31.8%	36.9%	32.2%	29.2%	28.4%	21.6%	30.6%
≥50 years	261	123	73	99	217	196	111	181	1261
	65.4%	72.9%	68.2%	63.1%	67.8%	60.8%	71.6%	78.4%	69.4%
Total	399	171	107	157	320	277	155	231	1817
	22.0%	9.4%	5.9%	8.6%	17.7%	15.2%	8.5%	12.7%	100%

Sample analysis from the 1801 registered cases of cervical cancer from the period of 2014 to 2021 categorized as either urban or rural environments, revealed that majority, specifically 1309 cases (72.7%), were from urban environments, while 492 cases (27.3%) were from rural areas. The analysis of the absolute number of registered cases indicated a significantly higher newly diagnosed cervical cancer cases in urban areas compared to rural areas, both in the overall sample ( $p=0.0001$ ) and for specific years.

Concerning the entire sample during the period of 2014-2021 across all eight statistical regions, the analysis revealed that in seven of these regions, there was a significantly higher prevalence of newly registered cervical cancer cases in urban areas ( $p<0.05$ ). However, there was an exception in the Pelagonia region from 2015 to 2021, where a higher prevalence of newly diagnosed cases in rural areas was observed in 2016 through 2020, although the difference was not statistically significant ( $p>0.05$ ) (Table 2).

Further analysis showed no significant difference in the percentage distribution of newly diagnosed cases between urban and rural areas over several years. Specifically, this was observed in the Pelagonia region for all eight years, the Southeast region for four years (2014, 2016, 2018 and 2020), the Northeast region for two years (2017 and 2020) and the East region for one year (2020) (Table 2).

The analysis by year also revealed that in terms of the proportion of new cases originating from rural areas compared to urban areas the Pelagonia region stood out with higher numbers in 2016, 2017, 2018 and 2020. Additionally, an equal number of newly registered cases were observed in the Southeast region in 2017, the Southwest region in 2016 and the Northeast region in 2016 (Table 2).

**Table 2.** Distribution of cervical cancer according to year of first diagnosis, city/village and statistical region (2014-2021)

Parameters	Statistical regions								Total N (%)	
	1 N (%)	2 N (%)	3 N (%)	4 N (%)	5 N (%)	6 N (%)	7 N (%)	8 N (%)		
2014	City	32 68.1%	38 80.9%	25 62.5%	29 56.9%	43 82.7%	19 55.9%	24 88.9%	90 89.1%	300 75.2%
	village	15 31.9%	9 19.1%	15 37.5%	22 43.1%	9 17.3%	15 44.1%	3 11.1%	11 10.9	99 24.8%
	p <sup>1</sup>	0.0004*	0.000*	0.0253*	0.1634	0.000*	0.3305	0.00*	0.000	p <sup>2</sup> =0.00006*
2015	City	7 70.0%	15 75.0%	14 73.7%	14 70.0%	19 82.6%	9 60.0%	11 78.6%	42 84.0%	131 76.6%
	village	3 30.0%	5 25.0%	5 26.3%	6 30.0%	4 17.4%	6 30.0%	3 21.4%	8 16.0%	40 23.4%
	p <sup>1</sup>	0.0019*	0.0016*	0.0035*	0.00*	0.00*	0.0986	0.0025*	0.0000*	p <sup>2</sup> =0.638473
2016	City	7 70.0%	13 76.5	3 50.0%	9 52.9%	9 75.0%	3 42.9%	3 50.0%	28 87.5	75 73.7%
	village	3 30.0%	4 23.5%	3 50.0%	8 47.1%	3 25.0%	4 57.1%	3 50.0%	4 22.5%	32 26.3%
	p <sup>1</sup>	0.0019*	0.00*	1.000	0.7352	0.0143*	0.5952	1.000	0.00	p <sup>2</sup> =0.092109
2017	City	11 78.6%	12 80.0%	9 81.8%	4 50.0%	17 73.9%	8 44.4%	13 61.9%	35 77.8%	109 70.8%
	village	2 21.4%	3 20.0%	2 18.2%	4 50.0%	6 26.1%	10 55.6%	8 38.1%	10 22.2%	45 29.2%
	p <sup>1</sup>	0.00*	0.002*	0.00*	1.000	0.0012*	0.5016	0.1230	0.0000	p <sup>2</sup> =0.095778
2018	City	21 95.5%	28 66.7%	26 65.0%	17 56.7%	28 82.4%	15 45.5%	20 69.0%	68 82.9%	223 71.5
	village	1 4.5%	14 33.3%	14 35.0%	13 433%	6 17.6%	18 54.5%	9 31.0%	14 17.1%	89 28.5%
	p <sup>1</sup>	0.0000*	0.0022*	0.0073*	0.2933	0.00*	0.4647	0.0038*	0.000*	p <sup>2</sup> =0.000143*
2019	City	13 59.1%	21 77.8%	18 75.0%	15 65.2%	24 82.8%	14 51.9	25 75.8%	72 83.7%	202 74.3%
	village	9 40.9%	7 22.2%	6 25.0%	8 34.8%	5 17.2%	13 48.1%	8 24.2%	14 16.3%	70 16.7%
	p <sup>1</sup>	0.0019*	0.000*	0.000*	0.0392*	0.00*	0.7801	0.0000*	0.00*	p <sup>2</sup> =0.026013*

2020	City	9	3	10	10	10	9	6	43	100
		81.8%	33.3%	71.4%	45.5%	62.5%	45.0%	60.0%	81.1%	64.5%
	village	2	6	4	12	6	11	4	10	55
		18.2%	66.7%	28.6%	54.5%	37.5%	55.0%	40.0%	18.9%	35.5%
	p <sup>1</sup>	0.0384*	0.4647	0.0021*	0.5016	0.0018*	0.4026	0.5016	0.0000*	p <sup>2</sup> =0.07645
2021	City	11	15	11	18	26	10	20	58	169
		68.8%	65.2%	68.8%	64.3%	78.8%	56.2%	80.0%	81.7%	73.2%
	village	5	8	5	10	7	9	5	13	62
		31.2%	34.8%	31.2%	35.7%	21.2%	47.4%	20.0%	18.3%	26.8%
	p <sup>1</sup>	0.0021*	0.0392*	0.0021*	0.0373*	0.000*	0.3027	0.000*	0.00*	p <sup>2</sup> =0.18770*
Total <sup>#</sup>	City	111	145	116	116	176	87	122	436	1309
		73.5%	72.1%	68.2%	58.3%	79.3%	50.3%	73.9%	83.8%	72.7%
	village	40	56	54	83	46	86	43	84	492
		26.5%	27.9%	31.8%	41.7%	20.7%	49.7%	26.1%	16.2%	27.3%
	p <sup>1</sup>	0.0000*	0.0000*	0.0000*	0.0014*	0.000*	0.8268	0.0000*	0.0000*	p <sup>2</sup> =0.00000*

† missing data regarding 16 patients' place of residence; 1-Vardar region, 2-Eastern, 3-Southwestern, 4-Southeastern, 5-Pelagonian, 6-Poloshki, 7-Northeastern; 8-Skopje; p<sup>1</sup>= Difference test; p<sup>2</sup>=Pearson Chi-Square test; \*significant for p<0.05

## **Discussion**

This study presents a comprehensive and up-to-date overview of the national cervical cancer rates in the Republic of North Macedonia from 2014 to 2021. It focuses on the geographical (rural/urban) and demographic (age) differences among observed patients. Relevant studies with representative data suggest a general trend of declining cervical cancer incidence and mortality rates in several developed countries worldwide<sup>[14]</sup>. This decline can be primarily attributed to factors like economic growth/development and the widespread adoption of screening programs. Some countries, such as India, Thailand, Brazil and Poland have experienced significant decreases in incidence, likely due to their declining fertility rates, reduced parity across generations, better screening coverage and better access to treatment services, particularly in urban areas<sup>[15,16]</sup>. However, one must take into consideration that data reported from regional registries often tend to cover only a portion of the total population, with generally insufficient coverage in rural areas where women tend to be exposed to a greater danger/risk, and thus might not provide a comprehensive representation of the entire population. Conversely, during the same time period, the incidence rates of cervical cancer saw a marked increase in some countries in Eastern Africa and Eastern Europe<sup>[1]</sup>.

Further analysis has shown that the majority of newly diagnosed cases of cervical cancer (69.4%) occurred in individuals aged 50 or older, whereas the prevalence of women younger than 50 years was significantly lower (30.6%). Taking into account that our results were based on the absolute number of diagnosed cases, more extensive research is needed to show whether our country is really not in line with the majority of contemporary global research, showing an increasing incidence of cervical cancer in all age groups, particularly among individuals younger than 50 years<sup>[7,17]</sup>.

Factors such as changes in sexual behavior, including having one's first sexual encounter at a younger age and having multiple sexual partners, are considered major contributors to this trend. For example, there has been a rising incidence rate of cervical cancer among younger age groups in China over the past two decades. Additionally, environmental pollution, endocrine factors and other influences also have a significant impact on the risk of cervical cancer among the younger population<sup>[18]</sup>.

However, it must be noted that a careful analysis of screening programs among the younger population is of utmost importance in order to conduct a proper interpretation and comparison of the findings from this study with other relevant research in the field<sup>[17]</sup>.

Furthermore, our analysis based on absolute number of cases throughout the eight-year period has indicated a significantly higher occurrence of cervical cancer cases among women living in urban areas, both in the overall sample and for specific years, wherein seven of the eight statistical regions had a notably higher number of newly diagnosed cervical cancer cases in urban settings. Despite previous studies suggesting a higher rate of cervical cancer among women residing in rural environments, the findings of this study may serve to shed light on the impact of healthcare inequality<sup>[19]</sup>. The aforementioned discrepancy can largely be attributed to having a very limited number of healthcare facilities in each region, thus resulting in disparities in access to healthcare, among other various weaknesses in the healthcare system<sup>[2,20,21]</sup>. Moreover, women in rural areas face challenges in accessing information about cervical cancer prevention. Many of these women still hold certain misconceptions, biases and antiquated beliefs regarding regular screenings and checkups, which have unfortunately not been adequately addressed<sup>[22]</sup>. These factors collectively pose a serious obstacle to timely diagnosis and treatment of cervical cancer in rural women. Similar patterns have been noted in rural regions of Mexico, where women's health issues are often associated with factors such as inadequate nutrition, lack of communication or healthcare

access, excessive burdens and frequent pregnancies, along with insufficient prenatal and maternal care<sup>[23,24]</sup>. One noteworthy exception was observed in the Poloshki region in the period of 2015-2021, where a slight increase of newly diagnosed cervical cancer cases among women residing in rural areas was recorded, although this increase was not statistically significant.

The findings of this study highlight the importance of continuous monitoring of cervical cancer at the national level, with particular focus on the most vulnerable regions and population groups. Socioeconomic characteristics play a key role in explaining the disparities in the prevalence of cervical cancer, both within and between countries<sup>[25]</sup>. The thorough analysis of this data provides strong evidence and an impetus for the creation and adoption of improved strategies aimed at prioritizing national efforts and accelerating progress towards the goal of cervical cancer prevention set forth by the WHO. Still, overcoming the pronounced variations in the global and national landscape of cervical cancer incidence remains a challenge for health authorities worldwide, one that must be addressed and improved upon at any given opportunity.

### **Conclusion**

Cervical cancer remains a pressing global issue, affecting over half a million women every year. Thankfully, the majority of cervical cancer cases can be prevented by timely HPV vaccination and screening. However, access to necessary services and information regarding the diagnosis and treatment of cervical cancer is far from equal. Thus, it is of utmost importance that early detection, prevention and treatment initiatives focus on addressing the regional and country-specific disparities and challenges. Furthermore, the development of targeted research and strategies concerning geographic (rural/urban) and demographic (age) characteristics would significantly improve prevention efforts and lead to an increase in timely treatment. By utilizing more precise geographic data, future thorough analyses can better examine the nuances of cervical cancer incidence across rural and urban areas, surpassing what can be achieved using the current rural-urban dichotomy. This approach would provide a better understanding of extant disparities and facilitate the identification of areas and populations that would benefit the most from interventions, such as increasing the HPV vaccination rates and improving access to cervical cancer screening. Future research should delve into the distribution of cancer stages, treatment utilization and survival outcomes, contributing to a fuller comprehension of rural-urban discrepancies and guiding the development of more effective strategies and interventions.

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