Published in final edited form as:

Cancer Epidemiol. 2016 October ; 44: 154–160. doi:10.1016/j.canep.2016.08.014.

Temporal Changes in the Cervical Cancer Burden in Bulgaria: Implications for Eastern European Countries Going Through Transition

Kaeli K. Samson, M.A., M.P.H.¹, Gleb Haynatzki, Ph.D., D.Sc.¹, Amr S. Soliman, M.D., Ph.D.¹, and Zdravka Valerianova, M.D., Ph.D.²

¹College of Public Health, University of Nebraska Medical Center, Omaha, Nebraska, USA

²Bulgarian National Cancer Registry, National Oncological Hospital, Sofia, Bulgaria

Abstract

Introduction—In most developed countries, incidence of cervical cancer declined likely due to well-established cervical cancer screening programs. However, such decline has not been identified in Eastern Europe, where such programs are not well established.

Methods—This study utilized data of the Bulgarian Cancer Registry for the period 1993–2013. Age-standardized incidence and mortality trends were analyzed using Joinpoint regression. Maps were created to illustrate spatial distributions of rates.

Results—The northern region of Bulgaria showed a larger cervical cancer burden than the southern region and rural women tended to be diagnosed at older ages ($p < .0001$) and later stages ($p < .0001$) than urban women. The distribution of disease stages changed over the 21 years, with most common stages of diagnosis being stage II in 1993 (39.2%) to stage I in 2013 (44.7%; $p < .0001$). While age-standardized mortality slightly increased over the 21 years (from 4.8 to 5.2 per 100,000; $p = .009$), age-standardized incidence increased from 14.0 to 21.4 per 100,000 up until 2006 ($p < .001$), after which it plateaued.

Conclusions—The lack of a similar plateau in mortality may be because the second most prevalent stage of diagnosis in recent years was stage III, indicating diagnosis at advanced symptomatic stages. Cervical cancer incidence is expected to continue to decrease if screening programs are strengthened and human papillomavirus vaccines are widely utilized. As Bulgaria has shared cervical cancer trends with other Eastern European countries in the past, it may be beneficial to develop future prevention interventions based on a regional, rather than a country-specific level.

Correspondence to: Prof. Zdravka Valerianova, Bulgarian National Cancer Registry, National Oncological Hospital, 6 Plovdivsko Pole Str., 1756, Sofia, Bulgaria, Tel.: +359 28076335, zvalerianova@sbaloncology.bg.

Conflict of Interest Statement: The authors have declared no conflicts of interest.

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Keywords

Cervical Cancer; Spatial Distribution; Temporal Trends; Cancer Registry; Bulgaria; Eastern Europe

1. Introduction

In 2012, cervical cancer had the third highest age-standardized incidence rate for cancers affecting women worldwide, and ranked within the top five cancers affecting women for mortality [1]. Cervical cancer is unique in that its risk factors are well established and it is considered highly preventable through vaccination and early detection by screening. The vast majority of cervical cancers is linked to infection with human papilloma virus (HPV) [2,3]. Primary risk factors for cervical cancer include those related to HPV infection, such as early age of sexual activity and having a large number of sexual partners [2]. Fortunately, the development of cervical cancer is slow, leaving ample time to be able to detect and treat in its early stages [4].

Despite the opportunity for early detection, some countries struggle with increased cervical cancer incidence and mortality rates. Bulgaria, which joined the European Union in 2007, has double the cervical cancer incidence and mortality than that of the United States or the European Union as a whole [1]. This unfortunate disparity has been exacerbated in recent decades; since 1980 to 2005, age-standardized mortality for cervical cancer has been slightly increasing in Bulgaria, while sharply decreasing in the majority of European Union countries [5]. Similar patterns are also seen in cervical cancer incidence from 1995 to 2005 [6]. Trends in incidence and mortality similar to what has been observed in Bulgaria have also been identified in other Eastern European countries [7].

The primary reason suspected for the increased cervical cancer burden in Eastern European countries is due to cohort-specific risks, likely due to changes in sexual behaviors over time which has put younger generations at higher risk for exposure to HPV [6]. Interestingly, the same cohort-specific risks are seen in the other parts of Europe that show declines in cervical cancer incidence; Vaccarella and colleagues hypothesized that these countries are able to counteract the effects of cohort-specific risks with well-organized cervical cancer screening programs [6]. Population-based cervical cancer screenings were conducted using pap smears in Bulgaria beginning in the 1970's and continued until the mid to late 1980's, prior to the country's political transition [8]. Since that time, cervical cancer screening has been opportunistic [9].

This study utilized the existing population-based cancer incidence and mortality data on cervical cancer in Bulgaria to examine the patterns and trends in cervical cancer incidence, mortality, and spatial distribution from 1993–2013.

2. Methods

2.1 Data source and Inclusion Criteria

Data used in this study was retrieved from the population-based Bulgarian National Cancer Registry (BNCR) in Sofia. The BNCR utilizes primarily active (although some passive) collection on all incident cases, which are initially collected in one of 13 regional cancer registries, before being sent to the national registry where data are examined for accuracy and completeness [10]. The registry collects basic demographics on all registered cancer or carcinoma in situ patients, details regarding their diagnosis, as well as treatment. In addition, death records, population, and mortality data from the Civil Registration System (GRAO) and the National Statistical Institute (NSI) are utilized within the BNCR to regularly update and complete the registry information.

For this study, all known cervical cancer cases (stages I–IV or unknown, excluding carcinoma in situ; ICD-O codes C53.0, C53.1, C53.8, and C53.9) from the time period of 1993 to 2013 were retrieved from the database, excluding identifiers, for analysis. Note that these cases do not include possible cervical cancer cases that may be classified as C55 or uterine cancers of unspecified origin. Previous research assessing the quality of the data from this registry found that the completeness of the data for cancers related to female genital organs during the period of 2006 – 2010 was at least 95% [11].

2.2 Data Analysis

Basic descriptive statistics were performed. Crude rates were calculated by dividing the number of cases by the population at risk (in this case, females only). The calculation for age-standardized rates (ASR) utilized the world reference population from Segi (1960) [12], and were calculated using the BNCR's software (CancerRegBG, 2011). Standard errors for the ASRs were calculated as described by Boyle and Parkin [13]. Spatial distribution maps of averages of annual incidence and mortality ASRs within specified time periods were created using ArcGIS software (version 10.3.1; Redlands, CA). To assess large regional differences, the country was divided into north and south by grouping the 14 northern most districts and the 14 southern most districts. Mann-Whitney U tests were used to determine if there were significant differences in ASRs between the north and the south for each of the time periods. The p-values for these tests were multiplied by four to adjust for the testing of multiple time periods.

SAS software (version 9.3; Cary, NC) was utilized to analyze changes in the distribution of stage of diagnosis over time. Stages were originally sub-divided within each stage (e.g. Ib2, IIa, etc.) in the registry data, but were coded by their stage (i.e. I, II, III, IV, and unknown) for analysis; lower stages indicated earlier detection of cancer. Urban and rural classifications were assigned to the city of residence of cervical cancer patients by the cancer registry, based on the city's population size; cities less than 3500 were classified as rural, and cities greater than 3500 were classified as urban. T-tests were used to compare ages of diagnosis between urban and rural women, using the Satterthwaite method if variances were unequal. A Wilcoxon two-sample test was used to compare stages of diagnosis between urban and rural women. A chi-square test was used to determine if the overall distribution of

the stages at the beginning and the end of the study period were significantly different, as well as to determine if the stage distribution in 2013 significantly differed between urban and rural populations. Joinpoint regression software (National Cancer Institute; Bethesda, MD) was utilized to detect significant changes in the trend of incidence and mortality ASR over the time period analyzed. Graphs were created in MS Excel (Redmond, WA).

3. Results

A total of 21,737 women in Bulgaria were diagnosed with cervical cancer between 1993 and 2013 (see Table 1 for demographics). The average age of diagnosis of patients was 52.2 years ($SD = 13.8$). The majority of women lived in urban areas (75.8%), as opposed to rural areas (24.2%; $\chi^2 = 5775.7$, $p < .0001$). The overall distribution of the study population by stage of diagnosis is as follows: stage I (35.4%), stage II (28.5%), stage III (25.7%), stage IV (4.5%), and unknown (5.9%).

In 1993, women diagnosed at early stages tended to be younger than those diagnosed in later stages; by 2013, that trend was less clear, with women being diagnosed at stages II, III, and IV at similar ages (see Table 2). In 1993, the majority of women had their cervical cancer diagnosed at stage II, followed by stage I. Around the year 2000, the number of women diagnosed at stages I, II, and III were very similar. In 2013, the majority of women had their cervical cancer diagnosed at stage I, followed by stage III. The distribution of stages of diagnosis in 1993 and 2013 were significantly different ($\chi^2(4) = 97.2$, $p < .0001$; see Figure 1).

Spatial distributions of annual average ASRs for cervical cancer incidence and mortality for the time periods of 1993–1997, 1998–2002, 2003–2007, and 2008–2013 are presented in Figure 2. Cervical cancer incidence and mortality increased over the study period. Furthermore, northern districts tended to have higher ASRs than southern districts (see asterisks in Figure 2 for time periods with significant regional differences, where adjusted p -values were less than 0.05). Those who lived in urban areas were more likely to be diagnosed at a younger age ($Mean = 51.7$ years, $SD = 13.5$) than those in rural areas ($Mean = 53.6$, $SD = 14.8$ years; $t(8266.3) = 8.47$, $p < .0001$; see Table 2). Similarly, those who lived in urban areas were more likely to be diagnosed at an earlier stage ($Median = 2$, $Mean = 1.95$) than those in rural areas ($Median = 2$, $Mean = 2.13$; $z = 11.9$, $p < .0001$, see Figure 1). The stage distribution in 2013 significantly differed between urban and rural cervical cancer patients ($\chi^2(4) = 16.12$; $p = 0.003$).

The trend in cervical cancer incidence and mortality ASRs from 1993 to 2013 are shown in Figure 3. With cervical cancer incidence, there was a significant increase from 14.0 to 21.4 per 100,000 (a change of approximately 3.0% per year; $p < .001$) up until 2006, the time at which there was a significant change in the slope of the trend, after which the incidence was no longer increasing (but was not significantly decreasing; $p = .050$). During the same time period, there was a slight, significant increase in cervical cancer mortality from 4.8 to 5.2 per 100,000 (a change of approximately 0.7% per year; $p = 0.009$). Age-specific crude rates for incidence and mortality for every five years during the period 1993 – 2013 are displayed

in Figure 4. Crude rates for urban and rural populations over the study period are displayed in Figure 5.

4. Discussion

Overall, cervical cancer incidence and mortality in Bulgaria was higher in 2013 than it was in 1993, and the cancer burden was highest in the northern half of the country. Women from rural areas tended to be diagnosed at an older age and later stage, relative to women from urban areas. While crude incidence rates for rural women were consistently lower than for urban women, crude mortality rates were not. The distribution of stages of diagnosis in the country had shifted over this period; while the most common stage of diagnosis in 1993 was Stage II, it was Stage I by 2013. Finally, cervical cancer incidence increased until 2006, after which it plateaued, while mortality has been slowly increasing over the same time period.

Previous research suggested that the reduced rates of cervical cancer in southern Bulgaria might be due to a larger proportion of Muslim populations in that area and their associated customs related to sexual behaviors, such as less promiscuity [14]. Data from the 2011 Bulgarian census indicates that the Turkish population within in Bulgaria, which makes up 8.8% of the country's population, has the largest number of people identifying as Muslim [15]. While Kardzhali, the district with the highest Turkish population located in the southern part of the country, has one of the lowest levels of cervical cancer incidence, the next four districts with the highest Turkish populations (Razgrad, Targovishte, Shumen, Silistra) have relatively high levels of cervical cancer, indicating that religious affiliation may not play a strong role in the spatial distribution of the cervical cancer burden in Bulgaria.

The urban/rural classifications may influence the spatial distribution of the cervical cancer burden in Bulgaria more so than religious affiliation. As mentioned previously, women who live in rural areas tend to have their cervical cancer diagnosed at a later age and stage. Moreover, the gap between being diagnosed at stage I versus stage III was smaller for rural women than it was for urban women. This may indicate that women living in urban areas may have better access to or awareness of cervical cancer screening programs or specialized services, and thus can be diagnosed at earlier stages compared to those living in rural areas. Previous research has shown that women in rural areas in South Africa are less aware of clinical testing for cervical cancer than those in urban areas [16].

The distribution of the stages of cervical cancer diagnosis has changed significantly over the years. While in 1993 the most common stage of diagnosis was stage II, in 2013 it was stage I. This is beneficial as Bulgarian women who are diagnosed at stage I have half the risk of death within five years after diagnosis than those who were diagnosed at stage II [17]. In recent years, the second most common stage of diagnosis is stage III; Bulgarian women diagnosed at this stage have over five times the risk of death as those who are diagnosed at stage I [17]. This pattern may be indicative of two underlying populations of women; those who get screened regularly and are diagnosed at an early stage, and those who are not regularly screened and are diagnosed after they become symptomatic. Age and cohort may be a factor in these two potential underlying populations. As seen in the age specific rates,

incidence has been decreasing in recent years for those being diagnosed in their 30's, and increasing for those being diagnosed in their 50's.

The recent plateau observed in the cervical cancer incidence in Bulgaria may be due to increased utilization of cervical cancer screening programs, as access to screening has been strongly associated with lower incidence [6]. Bulgaria used to have a nationwide, population-based cervical screening program in the 1970's, but this program did not continue after the country underwent political transition in the late 1980's [8]; currently, cervical cancer screening is opportunistic and requires personal initiative [8,9]. In the early 2000's, the Bulgarian National Health Fund began to cover the cost of cervical cancer screenings, which may have increased the use of screening, leading to earlier detection of cancer [9]. If this was indeed the case, it may be expected that incidence rates initially increase, due to increased cervical cancer detection in women who were never diagnosed, followed by a reduction due to increased detection occurring prior to stage I (i.e. cervical intra-epithelial lesions).

In addition to increased early detection, other factors may have influenced the change in the trend for cervical cancer incidence. Vassilev postulated that the increase in promotion of condom use surrounding the human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) crisis in the mid-1990's might account for decreases in cervical cancer infection almost a decade later, given cervical cancer's relatively long incubation time [18]. Reduced HPV infections has been associated with increased condom use [19]. While HIV rates have been increasing in Bulgaria in recent years, those rates have remained much lower than the average HIV rates for the European Union, which may be a result of increase condom use in the country [20].

While cervical cancer age-standardized incidence rates in Bulgaria appeared to have plateaued, age-standardized mortality continued to slightly increase. It should be noted that while this increase in mortality is statistically significant, it is quite small, ranging from 4.8 to 5.2 per 100,000 over the 21-year period. The lack of a decline or statistical presence of a plateau in the mortality after cervical cancer incidence plateaued could be reflective of the relatively long survival of women diagnosed with cervical cancer, in that the mortality in a given year is more a reflection of previous years' incidence rates rather than the current year's incidence rate. Furthermore, the continued increase in mortality could be influenced by the potential underlying population that is getting screened when they are symptomatic (as opposed to those who are asymptomatic when they get screened), as suggested by the second most frequent stage of diagnosis in recent years being stage III.

A limitation of this study is that our rates were possibly underestimated, as they did not include possible cervical cancer cases that may have been classified as uterine cancers of unspecified origin. Previous publications have estimated the percentage of uterine cancers of unspecified origin that are likely cervical cancer to correct for this issue [7]. While correcting for this in future studies may yield a better approximation of the cervical cancer burden in Bulgaria, it should be noted that the general trends in age-standardized rates calculated in the current study from years which overlapped with age-standardized rates

calculated by Arbyn and colleagues [7] where they corrected for the potential missing cases do not drastically differ.

This study is observational in nature, so it is not possible to deduce what factors actually influenced the cervical cancer burden in Bulgaria, but it may provide some evidence for those factors that have been speculated to have influence on the burden. Neither individual-level data on risk factors, such as sexual behaviors or smoking, nor information on ethnicity or religion was collected in the national cancer registry, so it is not possible to analyze these factors at that level. In addition, there was no complete data on carcinoma in situ cases, as many occur at private clinics that do not always report these cases to the Bulgarian National Cancer Registry. Furthermore, data on cervical cancer screenings are not systematically collected, nor are they linked with the cancer registry. These later two pieces of information would be informative regarding early detection of cervical cancer.

Romania is another Eastern European country that ranks with Bulgaria as having the highest cervical cancer rates compared to other European countries [7], and has had similar past trends in cervical cancer incidence and mortality rates as Bulgaria [5–7]. Romania, along with other Eastern European countries, may be interested in what interventions they can implement to slow or stop the increase in cervical cancer incidence, as Bulgaria has recently done. Certainly, having women diagnosed prior to stage I should be a primary goal, which can be achieved through stronger cervical cancer screening programs. However, a focus is also needed on access to and availability of treatment after diagnosis, as Bulgaria has witnessed an unchanging mortality rate. Since Eastern European countries have a similar history when it comes to cervical cancer burden, it may be beneficial to implement future preventative programs at a broader level, encompassing multiple countries.

Future studies should focus on further understanding of the spatial distribution of the cervical cancer burden in Bulgaria to better develop programs and interventions, such as improved access to cervical cancer screenings in regions with the greatest need, while continuing to promote screening practices throughout the country. In addition, it would be important to keep records of these screening practices for future use for associations with incidence and mortality rates. Increasing utilization of cervical cancer screenings is important in the immediate future, as this is an intervention that can have significant effects on the cervical cancer burden in Bulgaria within a few years. It is important to note, however, that significant barriers have been identified in previous literature regarding the ability of the current healthcare system in Bulgaria to sustain a large increase in cervical cancer screening [21].

While early detection is especially beneficial for cervical cancer, given the wide window for detection due to its slow growth, it is also important to consider primary prevention methods such as the HPV vaccination series. Cervical cancer vaccines were approved for use in Bulgaria in 2006–2007 [22] and an immunization program which reimbursed the cost of the vaccines for 12 year old girls was implemented in 2012 [22,23]. Since the most common HPV vaccinations provide immunity against HPV 16 and 18, and 77% of cases analyzed from the country's capital had one of these two strains [24], a widespread HPV vaccination program in Bulgaria may significantly reduce cases of cervical cancer. Benefits from such an

intervention will not be realized for years, or decades, so this strategy is good for long term planning.

Acknowledgments

Funding Support: We would like to thank the staff of the Bulgarian National Cancer Registry for their assistance with the retrieval of the data used for this paper, Yulia Panayotova for her insights on the cervical cancer situation in Bulgaria, as well as Dr. Veenu Minhas from the University of Nebraska Medical Center's College of Public Health for her feedback on the content of this paper. Kaeli Samson was supported, in part, by the Cancer Epidemiology Education in Special Populations (CEESP) Program of the University of Nebraska Medical Center through funding from the National Cancer Institute, USA, [Grant R25 CA112383].

Role of Funding Source: Funding was used for K. Samson's and A. Soliman's travel expenses and compensation.

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Manuscript Highlights

- Down-staging of cervical cancer has occurred over the study period
- Cervical cancer incidence increased prior to 2006, after which is plateaued
- Cervical cancer mortality has slightly increased over the study period
- In recent years, the second most common stage of diagnosis was stage III

Figure 1.

Percentage stage distribution for cervical cancer patients in Bulgaria for the whole population (top), urban population only (middle), and rural population only (bottom), from 1993 to 2013.

Figure 2. Spatial distribution of average annual cervical cancer incidence (left) and mortality (right) ASR (world standard, per 100,000) in Bulgaria for given time periods. Darker regions indicate higher rates. Numbers on map correspond with the numbers of districts in Table 1.

Figure 3.

Trends in cervical cancer incidence and mortality (ASRs world standard, per 100,000) from 1993 to 2013. Incidence rates (squares) trend lines are depicted with dashed lines; two lines for incidence trend are indicative of a significant change in the trend using Joinpoint regression software. Mortality rates (triangles) trend line is depicted with a solid line.

Figure 4. Crude age-specific incidence (top) and mortality (bottom) rates (per 100,000) for cervical cancer in Bulgaria in five year increments between 1993 and 2013.

Figure 5. Crude incidence (top) and mortality (bottom) rates (per 100,000) for cervical cancer in Bulgaria by urban and rural populations from 1993 to 2013.

Table 1

Demographics of women diagnosed with cervical cancer in Bulgaria from 1993 to 2013.

Total Number					
21,737					
Age of Diagnosis (in Years)					
Mean	S.D.				
52.17	13.84				
Urban/Rural Classification					
N	%				
Urban	16,469 75.78				
Rural	5,265 24.22				
Number of Women Diagnosed over Study Period by District					
District Number	Name	N	%	Average Female Population	
				1993 – 1998	2008 – 2013
1	Blagoevgrad	701	3.22	176,628	165,744
2	Burgas	1201	5.53	221,503	210,870
3	Varna	1220	5.61	229,863	239,938
4	Veliko Tarnovo	956	4.40	161,710	137,759
5	Vidin	407	1.87	75,400	53,483
6	Vratsa	919	4.23	134,570	97,443
7	Gabrovo	403	1.85	81,364	65,049
8	Dobrich	676	3.11	116,131	99,027
9	Kardzhali	234	1.08	107,857	77,630
10	Kyustendil	540	2.48	90,011	71,939
11	Lovech	684	3.15	93,755	74,298
12	Montana	589	2.71	102,998	77,510
13	Pazardzhik	522	2.40	164,000	143,657
14	Pernik	610	2.81	80,915	68,881
15	Pleven	1164	5.35	169,170	142,489

Number of Women Diagnosed over Study Period by District					
District Number	Name	N	%	Average Female Population	
				1993 – 1998	2008 – 2013
16	Plovdiv	1218	5.60	376,241	358,112
17	Razgrad	345	1.59	85,546	65,692
18	Ruse	831	3.82	144,759	124,053
19	Silistra	419	1.93	79,379	62,352
20	Sliven	633	2.91	118,665	102,939
21	Smolyan	199	0.92	79,672	63,046
22	Sofia City	3342	15.40	620,999	667,406
23	Sofia District	823	3.79	141,521	126,923
24	Stara Zagora	1000	4.60	199,858	175,231
25	Tagovishhte	401	1.84	75,417	63,832
26	Haskovo	697	3.21	148,012	128,400
27	Shumen	621	2.86	112,416	95,891
28	Yambol	382	1.76	87,407	68,624
Bulgaria		21,737	100.00	4,275,769	3,831,255

Stage Distribution		
	N	%
I	7685	35.35
II	6191	28.48
III	5585	25.69
IV	984	4.53
Unknown	1292	5.94

Table 2

Average Age of Diagnosis (in years) for All (top), Urban Only (middle) and Rural Only (bottom) Cervical Cancer Patients by Stage for Every Five Years from 1993 – 2013.

All (Urban + Rural)					
Stage	1993	1998	2003	2008	2013
I	44.1	46.2	48	49	51.2
II	51.1	51.2	51.9	53.7	55.4
III	53.9	52.7	55.8	55.8	55.9
IV	57.4	60	56.3	56.1	55.7
Unknown	56.7	63.7	60.6	58	58.1

Urban					
Stage	1993	1998	2003	2008	2013
I	43.7	46	47.6	49.2	51.2
II	50.9	51.2	52.1	53.8	54.6
III	54.2	53	55.3	54.6	55
IV	58.9	59.7	55.8	58	55.1
Unknown	54.6	61.7	59.4	58.9	56.7

Rural					
Stage	1993	1998	2003	2008	2013
I	45.4	47	49.5	48	51.1
II	51.8	51	51.1	53.7	57.5
III	53.1	52	57.1	59.2	58
IV	55.5	60.6	57.8	51	59.9
Unknown	67.6	67.2	62.5	55.5	61