Cancer Epidemiology 44 (2016) 154–160

Contents lists available at ScienceDirect

Cancer Epidemiology

The International Journal of Cancer Epidemiology, Detection, and Prevention

journal homepage: www.cancerepidemiology.net

Temporal changes in the cervical cancer burden in Bulgaria: Implications for eastern european countries going through transition

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ARTICLE INFO

Article history:
Received 21 May 2016
Received in revised form 20 July 2016
Accepted 22 August 2016
Available online 3 September 2016

Keywords:
Cervical cancer
Spatial distribution
Temporal trends
Cancer registry
Bulgaria
Eastern europe

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 ($p < 0.0001$) and later stages ($p < 0.0001$) 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%; $p < 0.0001$). While age-standardized mortality slightly increased over the 21 years (from 4.8 to 5.2 per 100,000; $p = 0.009$), age-standardized incidence increased from 14.0 to 21.4 per 100,000 up until 2006 ($p < 0.001$), 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.

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 1980–2005, 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

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http://dx.doi.org/10.1016/j.canep.2016.08.014
1877-7821/

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		5265		24.22	
Number of Women Diagnosed over Study Period by District					
District				Average Female Population	
Number	Name	N	%	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
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	Targovishte	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	

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 1970s and continued until the mid to late 1980s, 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 to 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 1993–2013 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