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Demographic differences in cervical cancer survival in Lithuania

Research Article

Karolis Ulinskas*, Birute Aleknaviciene, Giedre Smailyte

Cancer Control and Prevention Centre,
Institute of Oncology Vilnius University
LT-08660, Vilnius, Lithuania

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Abstract: Background. The aim of this study was to evaluate changes in the survival of cervical cancer patients during 15 years period and to analyze differences in survival. Materials and Methods. Cervical cancer cases (ICD-10 codes C53.0, C53.1, C53.8 and C53.9) were selectedfrom Lithuanian cancer registry. Five-year relative survival estimates were computed with the Ederer II method and a Cox proportional hazards model applied using STATA software. Results. Five year relative survival in 19901994 was 46.91%, in 1995-1999 - 51.52% and in 2000-2004 - 55.29%. Worse 5-year relative survival estimated for patients with older age. Survival by the stage was higher in early stages in all the periods. The highest survival was found in larger towns, and the lowest, in villages. Place of residence itself had increased the risk of death for women from villages (hazard ratio 1.37). The earlier periods had an increased incidence of death. Tumor stage IV was the leading risk factor (hazard ratio 23.14). After multivariate adjustment risk of death was larger in village residents. Conclusions. The study identified survival differences by age and place of residence. The cervical cancer prevention should be made available and accessible for all women in the country through equal distribution of well-organized screening program.

Keywords: *Cervical cancer • Relative survival*

1. Introduction

The burden of cervical cancer varies considerably in the European Union. Recent analysis in the countries with the highest cervical cancer incidence and mortality revealed rising trends of incidence and mortality in Lithuania, as in other most affected EU member states [1].

Survival information has long been recognized as an important indicator for monitoring the success of cancer-controlled activities [2]. The average European 5-year age-standardized relative survival among cervical cancer patients diagnosed from 1990 to 1994 was 63%, whereas 53% for Estonia [3]. The trend of the 5-year survival revealed a slow but steady increase of about 2% per year among cancer patients diagnosed in the period of 1983-1994 in Europe [4]. No improvement was noted in the areas where survival was the lowest (Central/Eastern Europe and UK). According to EUROCARE-4, overall cervical cancer 5-year relative survival in Europe was 66.6%, in Iceland – 76.7%, in UK – around 65%. The lowest 5-year relative survival was found in Lithuanian's neighborhood Poland – 53.3% [5]. A more recent period-based analysis, over the years 2000–2004, showed lowest survival rates for Lithuania (52%) and Poland (53%) without significant improvement [6].

The aim of this study was to evaluate changes in the survival rates of cervical cancer patients over 15-year period and to analyze differences in survival according to age, stage at diagnosis and place of residence.

2. Materials and methods

The Lithuanian Cancer Registry is a population-based registry covering the entire population. The collected data met the quality and completeness criteria for

* E-mail: karolis.ulinskas@vuoi.lt

inclusion in the "Cancer Incidence in Five Continents" edited by the International Agency for Research on Cancer [7,8]. Basic data, like demographics, the anatomical site and the pathology of cancer were recorded.

The study analyzed data from Lithuanian cancer registry. All newly diagnosed cervical cancer cases (ICD-10 codes C53.0, C53.1, C53.8, and C53.9) between 1st January, 1990 and 31st December, 2004 were selected. Cases identified by death certificates only were excluded. Only primary site invasive cervical cancer cases were included in this analysis. Survival analyses was based on the cohort of the remaining 6680 cervical cancer patients followed up until 31st December, 2009. The end-point of each analysis was: the date of death, the censored date of last follow-up or termination of the study. Chi-square test was used to compare distribution of the demographic and clinical variables between groups.

Survival was expressed as a relative survival rate, which is the ratio between observed survival and expected survival. Expected survival rates were estimated according to the Ederer II method using Lithuanian population life tables. Calculations were carried out using the STATA algorithm written by Paul Dickman [9].

Relative survival rates were computed for 3 different periods of time when cervical cancer was diagnosed (1990-1994, 1995-1999 and 2000-2004), by age (15-34, 35-49, 50-64, 65-74, 75 and older), stage at diagnosis (I, II, III, IV, unknown) and place of residence (big town, medium or small town, village).

Place of residence was classified by the number on inhabitants as follows. Residence residing in highly populated towns were defined to include those living in urban areas with populations more than 100,000 and possessing an average income per household per month with 846EUR (Vilnius, Kaunas, Klaipeda, Siauliai, Panevezys). Medium and small-sized towns were defined as urban areas with populations of at least 500 people and possessing an average income per household per month with 608EUR and villages where settlements with populations less than 500 and an average income per household per month of 550EUR [10].

A Cox proportional hazards model was then used to assess the impact of covariates on survival and estimate adjusted relative risks and 95% confidence intervals (CIs). Regression included age, stage at diagnosis, place of residence and period of diagnosis. P values of less than 0.05 were considered statistically significant. All data were analyzed using STATA version 11 (StataCorp. 2009. Stata Statistical Software: Release 11.0. College Station, TX, USA).

Table1. Demographic and clinical characteristics of women diagnosed between 1 January 1990 and 31 December 2004 with cervical cancer (n =6680).

Characteristics	Total N (%)	Large town N (%)	Middle and small town N (%)	Village N (%)	p value
Stage					<0.001
I	1334 (20.0)	710 (25.7)	283 (19.3)	341 (13.9)	
II	2141 (32.1)	876 (31.7)	532 (36.2)	733 (30.0)	
III	2138 (32.0)	747 (27.0)	474 (32.2)	917 (37.5)	
IV	591 (8.8)	195 (7.1)	121 (8.2)	275 (11.2)	
Unknown	476 (7.1)	237 (8.6)	60 (4.1)	179 (7.3)	
Age group					<0.001
15–34	578 (8.7)	253 (9.2)	137 (9.3)	188 (7.7)	
35–49	2190 (32.8)	914 (33.1)	544 (37.0)	732 (29.9)	
50–64	2074 (31.0)	870 (31.5)	445 (30.3)	759 (31.0)	
65–74	1136 (17.0)	452 (16.3)	229 (15.6)	455 (18.6)	
75+	702 (10.5)	276 (10.0)	115 (7.8)	311 (12.7)	
Period of diagnosis					0.501
1990–1994	1934 (29.0)	818 (29.6)	419 (28.5)	697 (28.5)	
1995–1999	2224 (33.3)	889 (32.2)	492 (33.5)	843 (34.5)	
2000–2004	2522 (37.8)	1058 (38.3)	559 (38.0)	905 (37.0)	

3. Results

Data analysis included 6680 cervical cancer cases. The mean age at diagnosis was similar for the periods (55.89±14.41 in 1990-1994, 54.49±15.04 in 1995–1999 and 53.00±15.02 in 2000-2004).

Table 1 demonstrates the characteristic of cervical cancer patients included in the analysis by place of residence. There are statistically significant differences between groups in distribution of the cancer cases by stage of disease and age (P<0.05). The difference between periods of time when cervical cancer is diagnosed does not have statistical significance (p= 0.501).

Five year relative survival for women with cervical cancer diagnosis was highest in the period 2000-2004 compared to the 1990-1994 and 1995-1999 periods (Table 2). Five year relative survival in the period 1990-1994 was 46.91%, in the period 1995-1999–51.52% and in the period 2000-2004 – 55.29%.

Worse 5-year relative survival was estimated for patients with older age at cervical cancer diagnosis. Highest survival rates were within 15-34 years age group–in all periods they were between 59% and 66%.

Survival, considering the cervical cancer stage at diagnosis, was higher in early stages. In stage IV survival was significantly lower in all the periods. In the period 2000-2004 highest 5-year relative survival was observed in stage I–89.85%. In the periods 1990–1994 and 1995-1999 five year relative survival rates where above 86% for patients with stage I of the disease.

Women who lived in villages showed lower five year relative survival rate compared to women from biggest and medium towns in all periods under study. Moreover, the differences in survival by place of residence were increasing. The highest five year relative survival was found for those living in big towns (64.12%) and medium towns in the period 2000-2004. Five year survival rates within villages' residents were lowest and there were no differences between periods 1990–1994 and 2000-2004 (five years survival rates – 45.24% and 44.85% respectively).

The impact of demographic and clinical characteristics was assessed by applying a univariate Cox Hazards regression (Table 3). Age at diagnosis, place of residence, the period of diagnosis and stage of disease were significantly associated with survival. Place of residence itself had increased the risk of death for women

Table 2. Five year relative survival of cervical cancer patients by the period of diagnosis.

	1990–1994 N=1934		1995–1999 N=2224		2000–2004 N=2522	
Characteristics	Survival (%)	95% confidence interval	Survival (%)	95% confidence interval	Survival (%)	95% confidence interval
Overall	46.91	44.46–49.33	51.52	49.27–53.74	55.29	53.19–57.35
Stage						
I	86.56	80.98–91.01	86.97	82.76–90.44	89.85	86.94–92.27
II	58.27	54.39–62.01	64.01	60.02–6779	61.93	57.88–65.78
III	23.07	19.23–27.16	34.38	30.94–37.87	35.08	31.64–38.57
IV	1.57	0.31–5.11	5.59	2.86–9.67	4.43	2.18–7.91
Unknown	40.89	33.58–48.20	52.97	40.61–64.43	53.44	42.72–63.30
Age group						
15–34	59.37	50.83–66.94	61.12	53.93–67.54	65.57	59.05–71.33
35–49	46.8	42.41–51.07	56.49	52.72–60.08	60.91	57.62–64.03
50–64	46.05	42.00–50.02	50.88	46.78–54.85	57.56	53.77–61.19
65–74	46.74	40.97–52.42	48.43	42.95–53.80	43.93	37.93–49.88
75+	40.5	30.80–50.90	31.87	24.02–40.50	30.44	23.28–38.34
Place of residence						
Big town	47.12	43.32–50.87	54.99	51.42–58.45	64.12	60.90–67.19
Middle and small town	49.21	44.05–54.21	50.91	46.14–55.53	55.31	50.82–59.62
Village	45.24	41.13–49.31	48.19	44.80–51.83	44.85	41.39–48.26

Table 3. Univariate and multivariate analyses of survival (Cox regression model).

Characteristics	Univariate*			Multivariate†		
	Hazard ratio	95% confidence interval	p value	Hazard ratio	95% confidence interval	p value
Stage (ref:stage I)						
Stage II	3.09	2.71–3.52	<0.001	2.70	2.37–3.08	<0.001
Stage III	6.05	5.33–6.87	<0.001	5.28	4.64–6.01	<0.001
Stage IV	23.14	20.00–26.78	<0.001	18.77	16.17–21.79	<0.001
Unknown	5.32	4.53–6.25	<0.001	4.36	3.70–5.14	<0.001
Period (ref:2000-2004)						
1990–1994	1.33	1.23–1.44	<0.001	1.25	1.15–1.35	<0.001
1995–1999	1.13	1.01–1.22	0.002	0.99	0.91–1.07	0.764
Place of residence (ref: large town)						
Middle and small town	1.11	1.02–1.21	0.017	1.09	0.99–1.18	0.056
Village	1.37	1.27–1.47	<0.001	1.12	1.04–1.20	0.003
Age (ref: 75+)						
15–34	0.23	0.20–0.27	<0.001	0.40	0.34–0.46	<0.001
35–49	0.30	0.27–0.33	<0.001	0.45	0.41–0.50	<0.001
50–64	0.40	0.36–0.44	<0.001	0.53	0.48–0.59	<0.001
65–74	0.57	0.51–0.63	<0.001	0.67	0.60–0.74	<0.001

** Use of Cox regression on single covariate*
† Use of Cox proportional hazards model adjusted for all other factors in the table

from villages (hazard ratio 1.37, p=0.017). In our study, women with cervical cancer diagnosis had increased death risk in the earlier periods (hazard ratio 1.33 for period 1990–1994 and 1.13 for period 1995-1999). The leading risk factor of death with hazard ratio 23.14 (p<0.0001) was tumor stage IV.

Results of the multivariable model including the age of diagnosis, tumor stage, period and residency at diagnosis are shown in Table 3. Factors increasing the risk of death for cervical cancer patients in Lithuania were older age, earlier period of diagnosis, late stage of the disease and residence in villages. After multivariate adjustment patients living in villages had worse prognosis than those living in towns.

4. Discussion

Cervical cancers survival has attained little research over the past years. The lack of studies in populations can be associated with the high survival rate of early cervical cancer stage and the decline of cervical cancer incidence. Lithuanian women had cervical cancer mortality among the highest in Europe. Therefore, there is a need to evaluate different risk factors for lower survival and higher mortality in order to identify the high risk groups.

The main etiologic factor for cervical cancer is persistent infection with sexually transmittable high-risk human papillomaviruses [11]. By well-organised screening and treatment of screen-detected high-grade cervical intraepithelial neoplasia (CIN) invasive cancer can be avoided [12]. Therefore, trends in incidence of cervical cancer in Lithuania reflect coverage and quality of screening, as well as changes in exposure to risk factors which are mainly related to sexual habits of successive cohorts.

This study provides the results of population based investigation of relative survival in Lithuania. Use of a population-based cancer registry rather than a clinic or hospital based sample allows a more complete look at all women diagnosed with cervical cancer in the country. Survival of cervical cancer patients in Lithuania increased during the study period. Women diagnosed with cervical cancer in 1990-1994 had almost 10% lower survival rate than women diagnosed in 2000-2004. Despite increasing survival rates, in general, there are substantial differences in cervical cancer survival by age and place of residence.

Survival of cervical cancer patients varies with age. In this study older cervical cancer patients had lower survival rates and no improvement in survival was found for women over 65 years. Advanced age was associated with decreased survival also in other studies [13,14]. However, population based cervical cancer survival analyses were not adjusted for treatment and co morbidities. Advanced age has been described as an important factor in the selection and allocation of treatment [15]. In the EUROCARE study, low survival of elderly patients was attributed to advanced stage at diagnosis, co morbidities, difficult access or lack of availability of appropriate care [16].

There is little known about the relationship between place of residence and survival for cervical cancer. However, mortality rates from cervical cancer have been found to be higher among rural dwellers compared to urban [17,18]. The Australian Institute of Health and Welfare and the Australasian Association of Cancer Registries reported a 7% difference in five-year age-adjusted relative survival proportions for all cancers between remote centers and larger rural and metropolitan centers [19]. In New Zealand people living far from the cancer treatment centers (that provide a full range of multidisciplinary services including medical oncology, radiation oncology and hematology in the largest cities) had poorer survival from cancer than people who lived closer [20,21]. In one study carried out in the US factors influencing cervical cancer was identified from the perspective of key informants who live in Ohio Appalachia. The higher survival was estimated in urban areas. Key informants reported that the residents of a major city (population of 21,796) had a different perspective on access to health care than the residents who lived in the more remote sections of the county. The urban residents had their choice of physicians, a large and respected hospital and paved roads, whereas the rural residents usually had a limited number of physicians and emergency care nearby, with dirt roads being common [22].

Our study found differences in survival of women diagnosed with cervical cancer in Lithuania by place of residence. Women from larger Lithuanian towns where cancer treating centers are located had 20% higher five year relative survival rate than women from villages and almost 10% higher rate than women from small and medium towns. Factors related to the detection and treatment of malignant diseases, such as the availability of screening programs and access to health care facilities, may differ between urban and rural communities. Issues, such as access to care, lack of frequent physician's visits and quality of medical care, have a negative impact on outcomes for women with cervical cancer, particularly in relationship to staging. If better outcomes are to be achieved in Lithuania, then more must be done to reach the community and provide better access to care in rural areas.

5. Conclusion

In spite of the existence of effective screening methods, cervical cancer continues to be a major public health problem in Lithuania. The study identified survival differences by age and place of residence. These findings should now be translated into effective prevention strategies applicable for the whole population with special attention to older women and women living in rural areas. The cervical cancer prevention should be made available and accessible for all women in the country through equal distribution of well-organized screening program.

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