

Bladder cancer trends in Latvia during 1990–2017: incidence, mortality, and survival rates

Ērika Bitiņa-Barlote^{1,2}, Juris Plonis^{1,2}, Vinita Cauce³, Egils Vjaters^{1,2}, Jānis Gardovskis¹, Edvīns Miklaševičs¹, Miki Nakazawa-Miklaševiča¹

¹Rīga Stradiņš University, Institute of Oncology, Riga, Latvia

²Center of Urology, Pauls Stradiņš Clinical University Hospital, Riga, Latvia

³Rīga Stradiņš University, Statistics Unit, Riga, Latvia

Citation: Bitiņa-Barlote Ē, Plonis J, Cauce V, et al. Bladder cancer trends in Latvia during 1990–2017: incidence, mortality, and survival rates. Cent European J Urol. 2021; 74: 14-23

Article history

Submitted: Sept. 18, 2020

Accepted: Jan. 18, 2021

Published online: Feb. 18, 2021

Corresponding author

Ērika Bitiņa-Barlote
ORCID: <https://orcid.org/0000-0001-7859-3940>
Pauls Stradiņš Clinical University Hospital
Center of Urology
13 Pilsonu St.
LV-1002 Riga, Latvia
phone: +371 200 92 515
erika.bitina@gmail.com

Introduction The aim of this article was to evaluate bladder cancer (BC) incidence, mortality and survival trends in Latvia over the past 28 years.

Material and methods Our study included patients diagnosed with BC between 1990 and 2017. The data were obtained from the national population-based cancer registry. Joinpoint regression analysis was used to identify points where a significant change in incidence and mortality trends occurred, accordingly with the patient's gender and age. Relative survival (RS) was estimated by Ederer I and II methods.

Results Altogether, 9589 patients with initial BC diagnosis were included in the study. The age-standardised (ASR) incidence rates (per 100,000) increased from 6.8 in 1990 to 12.5 in 2014 followed by a statistically insignificant decrease continuing up to 2017. The ASR BC mortality rates (per 100,000) also rose from 3.9 in 1990 to 4.4 in 2017. However, there was a decline in BC mortality trends in the age-group 40–59 with annual percentage change (APC)-1.1%. RS rates increased from 55.0 % in 1990–2000 to 59.0% in years 2013–2017.

Conclusions This study revealed that the incidence and mortality rates have been gradually increasing over the past 28 years. The exception being cancer-specific mortality in the age group 40–59, which tends to decrease. Although the 5-year RS rates improved over the reviewed period, there is still plenty of room for improvement.

Key Words: urinary bladder <> cancer <> incidence <> survival <> mortality

INTRODUCTION

Bladder cancer (BC) is the most common malignancy of the urinary system. According to the Global Cancer Observatory (GCO) data, it is the tenth most common cancer worldwide. During the year 2018, the incidence of BC increased to 549,393 cases annually, and estimated number of prevalent cases (5-year) of BC have risen to 1,648,482 worldwide [1]. BC predominantly affects males with an average male to female ratio of 4:1 [2] and is the sixth most common cancer in men globally [1]. This could be partly explained by the fact that men are exposed

more to smoking and occupational exposure, which are the main well-known environmental risk factors for BC [3, 4]. It is thus ranked in 13th place for cancer mortality rate [1].

Greater incidence and cancer mortality rates are found in countries with a high human development index (HDI). The highest rates are in counties of Eastern Asia, North America and Western Europe, particularly in the United States of America, China, Japan and Germany [5]. BC is an age-related disease that typically occurs in the older population, with a median age of 72 and 73 years in white men and women, and 69 and 73 years for black men and

women at the time of diagnosis, respectively [6]. In addition, the overall increase of life expectancy is the current demographic trend in many Western European countries [7]. Although life expectancy in Latvia increased by almost 20 years between 1924 and 2018, it is still very low compared to the rest of Europe. In 2018, the life expectancy of men in Latvia was the lowest in the European Union [8]. There is a tendency for incidence to increase with age. The highest number of newly diagnosed BC cases occurred in individuals over the age of 70 years compared to those aged 60–69 years in 2013, 56.5% (226,612) and 24.0%, respectively [9]. Current smokers are associated with younger age of onset compared to non-smokers [10]. The predominant histologic type of BC is urothelial carcinoma, accounting for approximately 90% of BC cases. Although, in countries with common schistosomiasis infections, squamous cell BC is more prevalent [11]. There are articles on BC incidence and mortality in Europe and worldwide, some mentioning Latvia [2, 5]. However, there is still no comprehensive analysis of the epidemiological trends and long-term survival rates of BC in Latvia. According to the latest GCO data, Latvia has one of the highest mortality rates in Europe and worldwide [1].

This study includes the first comprehensive 28-year analysis of BC incidence, mortality and relative survival (RS) rates in Latvia.

MATERIAL AND METHODS

A retrospective cohort study was performed. Data relating to all patients diagnosed with BC according to an International Classification of Diseases (ICD-10, C67) between January 1, 1990, and De-

cember 31, 2017 were provided by the Centre for Disease Prevention and Control of Latvia (CDPCL). Since 1963, a population-based cancer registration has been established in Latvia, covering the entire country. In 2012, CDPCL inherited the Latvian Cancer Registry (LCR) database, which was officially established in 1993. Now LCR is part of the Register of Patients with Particular Diseases. The register records almost 100% of all diagnosed cases of cancer [12]. The CDPCL collects and regularly updates all the information related to cancer from all over Latvia, with a population of almost two million people.

A total number of 13,158 patient records were received from the CDPCL. There were 3569 (27.1%) doubly registered (duplicate registration) records, therefore 9589 (72.9%) patients with ICD-10 topographical code C67 of all ages were included for further analysis. Patients younger than 40 years were excluded from the age-specific incidence, mortality, and survival trend analysis as a statistically insignificant group. Therefore, the following age groups were formed: 40–59, 60–79, 80+. Patients, who were registered by death certificate only, or post mortem, were excluded from survival analysis. The following primary tumour stages were included in the stage-specific incidence and survival trend analysis: T1, T2, T3 and T4.

Cancer-specific incidence and mortality rates of the Latvian population were calculated as cases per 100,000 people using the data obtained from the Central Statistical Bureau of Latvia updated 2018 [13]. Then, cancer rates were age-adjusted to the World Health Organization standard population in 2000 [14]. To calculate the RS rate, a life expectancy table for the Latvian population was downloaded from Human Mortality Database [15].

Table 1. Bladder cancer patients' cohort characteristics (N = 9589)

	Total 1990–2017		Time period					
	N	%	1990–2000		2001–2012		2013–2017	
			N	%	N	%	N	%
Gender								
Male	7188	75.0	2277	75.7	3233	74.7	1678	74.5
Female	2401	25.0	729	24.3	1098	25.3	574	25.5
Age group								
0–19	14	0.2	9	0.3	3	0.1	2	0.1
20–39	121	1.3	38	1.3	54	1.2	29	1.3
40–59	1711	17.8	589	19.6	796	18.4	326	14.5
60–79	6085	63.4	1919	63.8	2754	63.6	1412	62.7
80+	1658	17.3	451	15.0	724	16.7	483	21.4
T stage								
1	2858	29.8	422	14.0	1412	32.6	1024	45.5
2	2063	21.5	797	26.5	833	19.2	433	19.2
3	1526	15.9	675	22.5	630	14.5	221	9.8
4	546	5.7	177	5.9	249	5.8	120	5.3
Unknown	2596	27.1	935	31.1	1207	27.9	454	20.2

Statistical methods

Computer package SPSS (version 22.0, 2013, USA: IBM Corp) was applied for all data analyses. Performing descriptive analysis, categorical variables as the frequency was reported as absolute numbers and percentages. Continuous variables were reported as the mean and standard deviation.

The Joinpoint Regression Analysis programme (version 4.6.0.0, April 16, 2018, USA), available through the Surveillance Research Program of the US National Cancer Institute, was used to examine trends in age-standardised (ASR) incidence and mortality rates of BC patients based on age and gender groups. The Monte Carlo Permutation method was used to select the number of joinpoints. The number between 0 and 4 was supplied. A significance level of 0.05 was used for the permutation test with 4499 randomly permuted datasets [16]. APC was also calculated for each separate linear segment to define time trends in BC incidence and mortality. A significant increase or decrease of a trend was defined as the slope of the curve being statistically significant ($p < 0.05$).

The R statistical programme (version 4.0.3, October 2020, R Foundation for Statistical Computing, Austria) with the package 'relnsurv', was used for the calculation of RS. For the survival analysis, a cohort of BC patients with ≥ 5 -year follow-up was selected.

Patients were followed up from the date of diagnosis until death, censoring, or December 31, 2017. Patients were stratified into three time periods: 1990–2000, 2001–2012 and 2013–2017. The 5-year RS for 1990–2012 data were calculated by cohort analysis (Ederer I method). The expected 5-year RS rates for 2013–2017 data were calculated using period analysis (Ederer II method).

Ethics approval

The study was approved by the Ethics Committee for Clinical Research at Development Society of Pauls Stradins Clinical University Hospital. Patient consent was not required, because this study used regularly collected anonymous electronic data.

RESULTS

Overall, 9589 patients with newly diagnosed BC were identified between 1990 and 2017. Patients' cohort characteristics are represented in Table 1. The average age was 68.8 years (SD 11.5), 67.8 (SD 11.3) years for males and 72.0 (SD 11.7) years for females. A total of 7182 BC patients died over the period under review and 67% ($n = 4790$) of them had BC-related deaths. Mean age of death was 72.8 years (SD 10.4).

Table 2. Bladder cancer incidence and mortality trends in Latvia 1990–2017 (Joinpoint analysis: age-standardised (ASR), by gender, age and stage groups)

	Trend 1		Trend 2		AAPC (95% CI) 1990–2017
	Years	APC (95% CI)	Years	APC (95% CI)	
Incidence	1990–2014	2.6* (2.2 to 3.0)	2014–2017	-3.6 (-11.8 to -5.3)	1.9* (0.9 to 2.9)
Gender					
Male	1990–2017	2.1* (2.5 to 10.1)			2.1* (2.5 to 10.1)
Female	1990–2017	2.7* (2.0 to 3.5)			2.7* (2.0 to 3.5)
Age group, years					
40–59	1990–2017	1.7* (0.8 to 2.5)			1.7* (0.8 to 2.5)
60–79	1990–2017	2.5* (2.1 to 2.8)			2.5* (2.1 to 2.8)
80+	1990–2017	2.6* (2.0 to 3.1)			2.6* (2.0 to 3.1)
T stage					
1	1990–2013	9.7* (8.5 to 10.9)	2013–2017	-1.3 (-10 to 8.2)	8.0* (6.9 to 9.7)
2	1990–2017	0.4 (-0.3 to 1.1)			0.4 (-0.3 to 1.1)
3	1990–1995	6.9 (-1.4 to 15.9)	1995–2017	-2.3* (-3.2 to -1.5)	-0.7 (-2.2 to 0.9)
4	1990–2017	1.3* (0.2 to 2.5)			1.3* (0.2 to 2.5)
Mortality	1990–2017	0.5* (0.1 to 0.9)			0.5* (0.1 to 0.9)
Gender					
Male	1990–2017	0.5* (0.1 to 1.0)			0.5* (0.1 to 1.0)
Female	1990–2017	0.2 (-0.8 to 1.3)			0.2 (-0.8 to 1.3)
Age group, years					
40–59	1990–2017	-1.1* (-2.2 to -0.1)			-1.1* (-2.2 to -0.1)
60–79		0.7* (0.2 to 1.3)			0.7* (0.2 to 1.3)
80+		1.9* (1.2 to 2.5)			1.9* (1.2 to 2.5)

APC – annual percent change; AAPC – average annual percent change; ASR – age standardised rate per 100,000; * $p < 0.05$

The overall ASR incidence rates (per 100,000) of BC have increased gradually from 6.8 in 1990 to 10.8 in 2017, from 15.1 to 21.5 in males and 1.9 to 3.9 in females. There was one joinpoint observed indicating 1 period with a statistically significant APC: 2.6% from 1990 to 2014 followed by a statistically insignificant reduction (Table 2). Joinpoint analysis showed a significantly increased ASR incidence rate in both genders (Table 2, Figure 1). As far as BC incidence rates by age groups are concerned, APC

for all age groups remained stable during the entire review period. The greatest APC of 2.6% was registered in the >80 years group (Table 2, Figure 2). Concerning BC incidence rates by T stage, the largest APC occurred in the T1 stage group with APC 8.0% during the whole period, and one joinpoint was observed in 2013. Meanwhile, only the T3 stage BC incidence rates significantly decreased with APC -2.3% between 1995 and 2017 (Table 2, Figure 3).

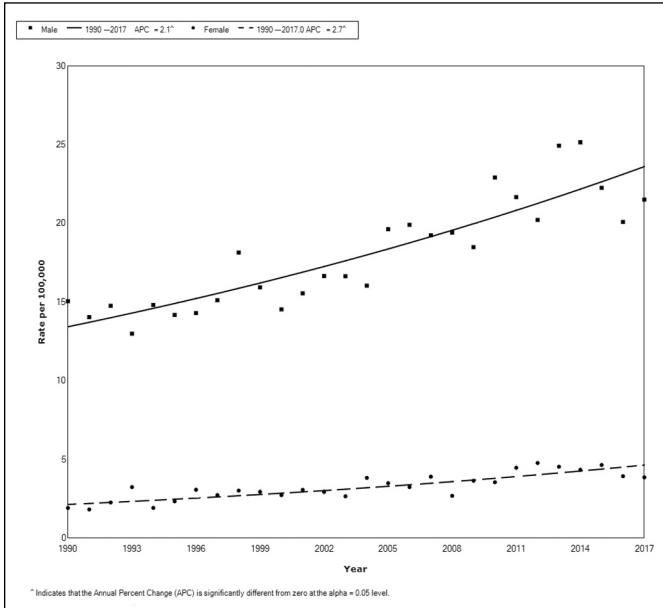


Figure 1. Gender-specific bladder cancer incidence trends using Joinpoint analysis.

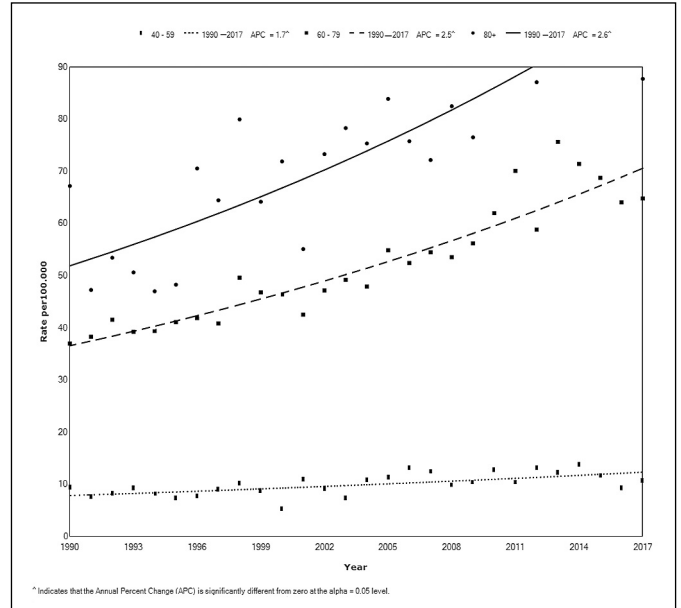


Figure 2. Age-specific bladder cancer incidence trends using Joinpoint analysis.

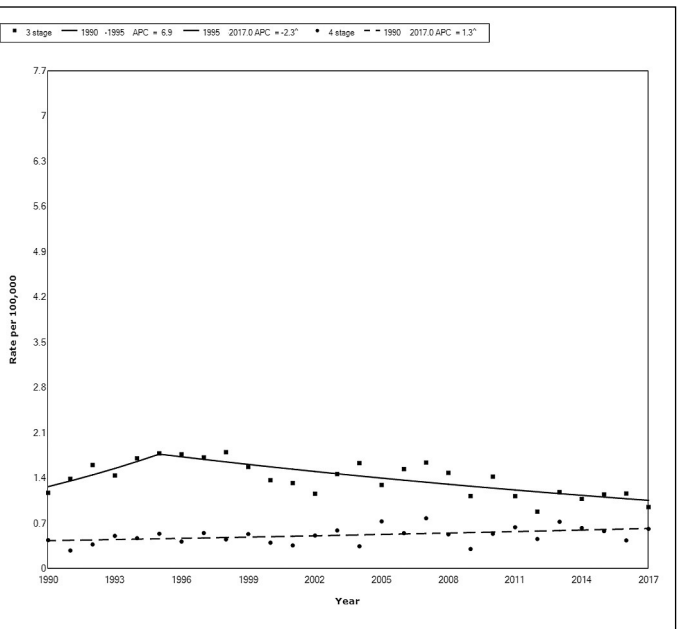
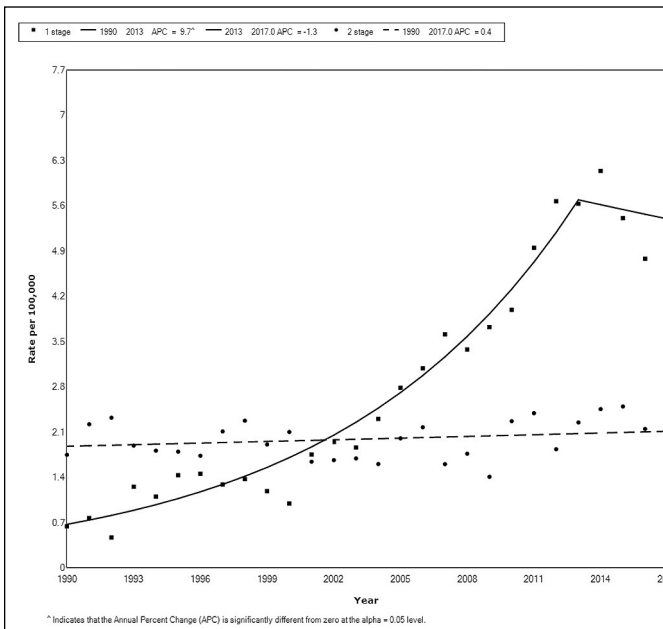


Figure 3. Stage-specific bladder cancer incidence trends using Joinpoint analysis.

Cancer-specific age-standardised BC mortality rates (per 100,000) rose from 3.9 (males 8.5, females 1.3) in 1990 to 4.4 (males 9.7, females 1.2) in 2017 (Figure 4). Overall cancer-specific age-standardised BC mortality rates slightly increased with APC 0.5% and statistically significantly decreased in the 40–59 years group at an APC of -1.1% from 1990 to 2017. However, BC mortality rates significantly increased in the age group >80 years (APC 1.9%, 95% CI 1.2 to 2.5) (Table 2, Figure 5).

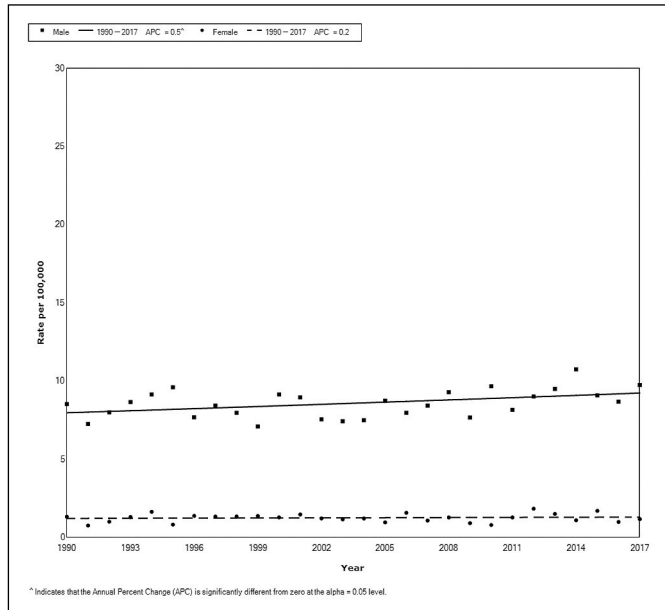


Figure 4. Gender-specific bladder cancer mortality trends using Joinpoint analysis.

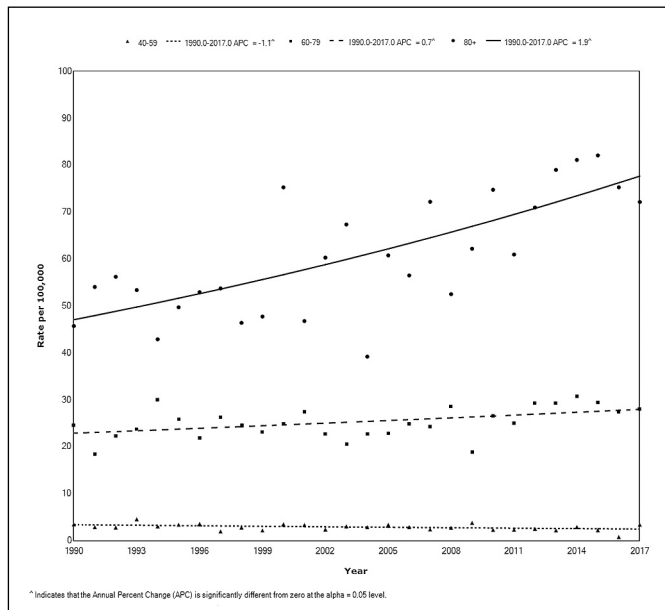


Figure 5. Age-specific bladder cancer mortality trends using Joinpoint analysis.

The 5-year RS has improved by comparing the beginning (1990–2000) with the end of the study period (2001–2012) and (2013–2017) (55.0% vs. 61.9% vs. 59.0%; $p = 0.006$) (Figure 6). Although women have higher 5-year RS rates than men, they are not statistically significant. For women, 5-year RS has increased over 28 years, while it remains fluctuating for men (Figure 7). Analysing survival by age groups, younger patients have a better survival compared to older ones (Figure 8). The 5-year RS in the T2 and T3 stage groups has significantly deteriorated compared to 1990–2000 and 2001–20012 and 2013–2017 (Figure 9).

DISCUSSION

BC is one of the most common cancers worldwide. Many epidemiological data concerning bladder tumours in different countries exists, however, such a study has not been previously conducted in Latvia. Furthermore, in 1991 Latvia regained its independence and started to follow European Urology Association guidelines.

The global burden of urologic cancers has increased globally during the past decades. According to Dy et al., ASR incidence rates during the past decades have decreased by 24.7%, however, new BC diagnoses have risen 1.5-fold. These changes were attributed to population growth (35.0%) and redistribution in age structure (42.1%) [9]. In 2018, epidemiological data for 39 countries was analysed by Wong et al., and increased incidence rates of BC in recent 10 years was observed in 7 countries (six of which were European) in both genders [5]. The current study showed that ASR BC incidence rate has increased from 6.8 in 1990 to 10.8 in 2017, with an APC of 2.6% from 1990 until 2014, with following

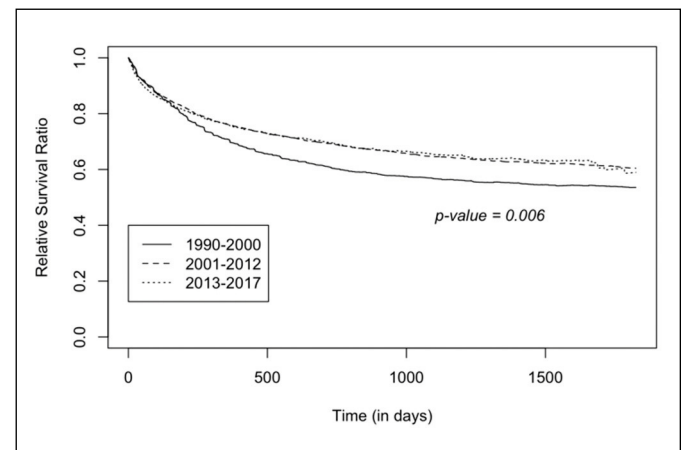


Figure 6. Bladder cancer relative survival during three time periods.

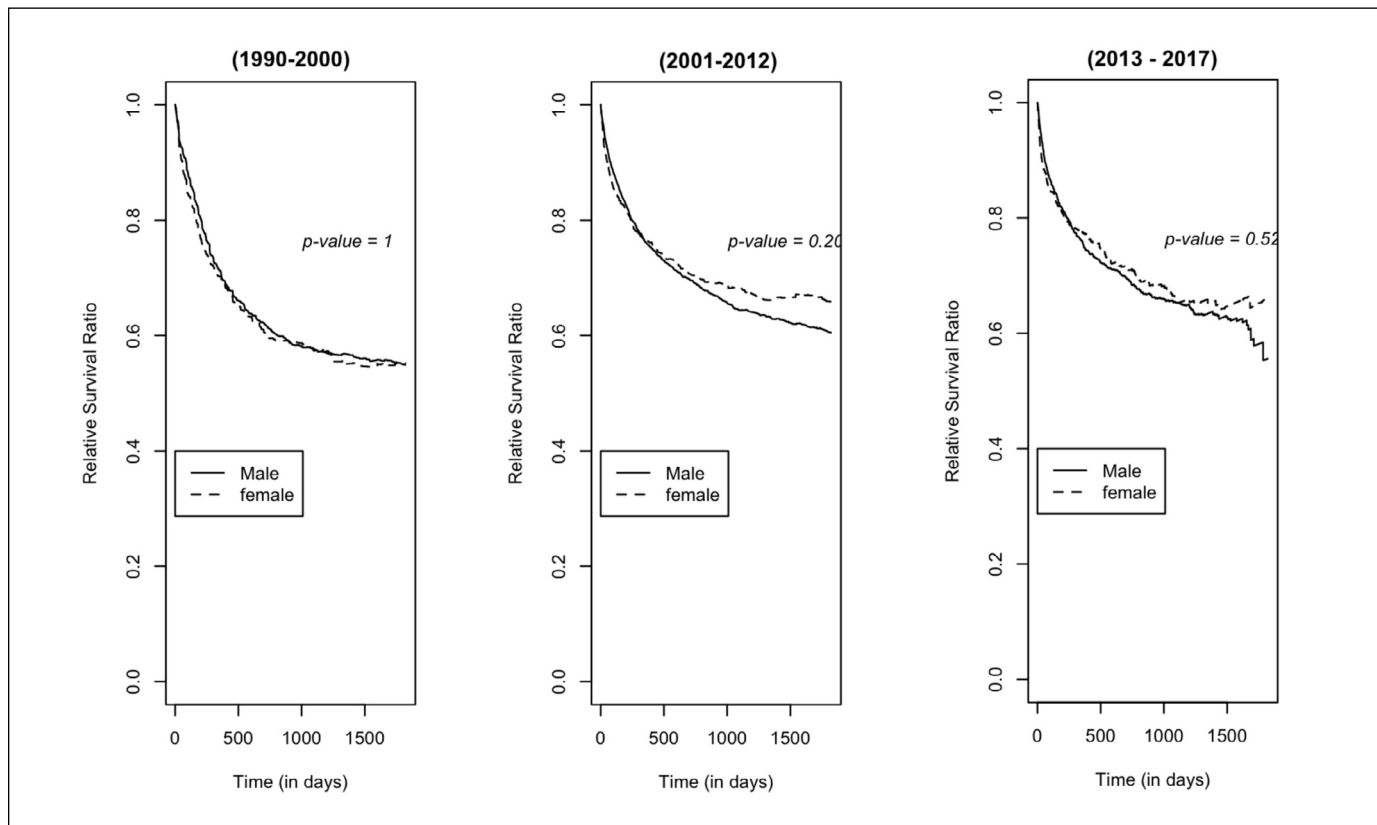


Figure 7. Gender-specific 5-year relative survival of bladder cancer during three time periods.

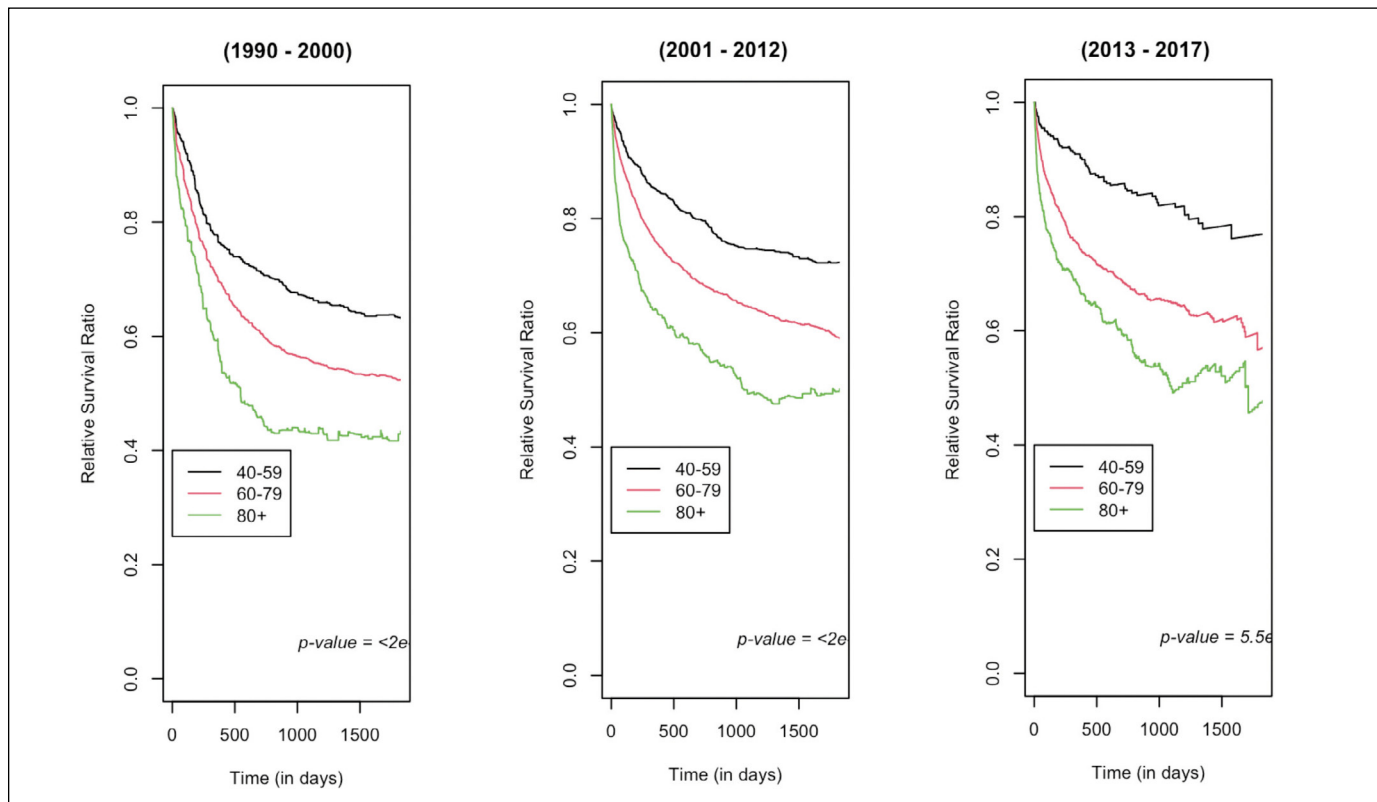


Figure 8. Age-specific 5-year relative survival of bladder cancer during three time periods.

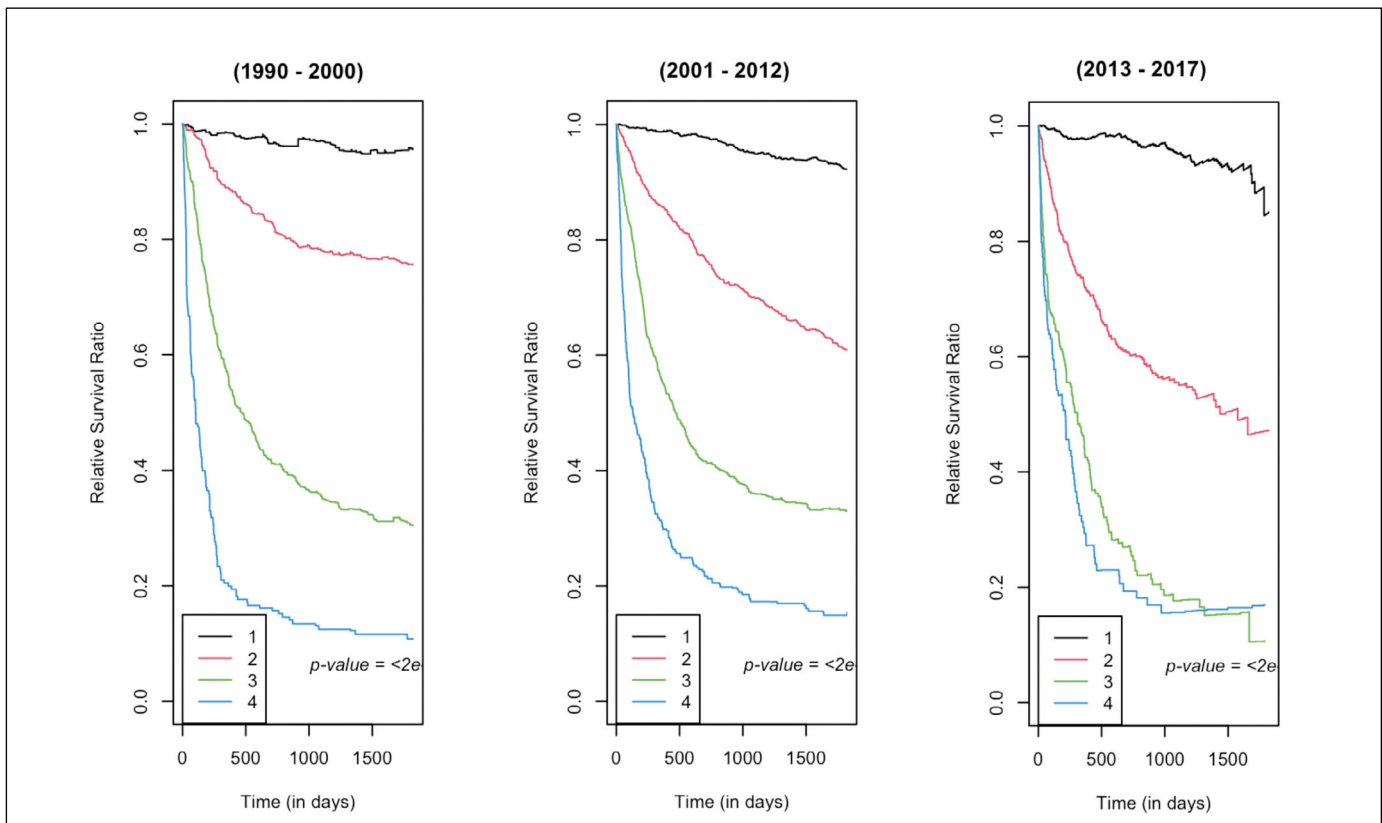


Figure 9. T stage-specific 5-year relative survival of bladder cancer during three time periods.

stabilisation until 2017 (APC = -3.6; $p = 0.4$). But in the Wong et al. study, no statistically significant increase in incidence rate was observed for men in Latvia [5], which previously was described by Antoni et al. [2]. The present study showed similar BC incidence trends with the study by Antoni et al., describing an estimated APC of 2.0% for men and 2.7% for women. However, the analysis revealed that the age-standardised BC incidence rate in 2012 was 20.2 for men and 4.8 for women. That is very different from the data represented using the GLOBOCAN database, which describes BC age-standardised incidence of 15.9 for men and 2.9 for women [2].

Previous studies show that BC incidence is tightly associated with smoking habits [17] and HDI [2, 5], these affirmations can explain the divergence in incidence rates in different populations. According to CDPCL, during the past two decades, cigarette smoking prevalence in Latvia has decreased from 46% in 2008 [18] to 32% in 2017 [19] in the population aged ≥ 15 . This factor interrelates with cancer incidence decline. Although, since 2008, cigarette smoking among women in Latvia has increased from 13% to 20% in 2016 [18, 19] reflecting an increase in cancer incidence among females, which also corresponds with global tendencies [2]. It has been report-

ed that BC incidence positively correlated with HDI [2, 5]; and according to the United Nations Development Programme data, Latvia ranks 41st in the rate with an index 0.847 (world: 0.728) [20]. According to previous reports risk factors such as smoking, obesity, excessive alcohol and meat consumption [21] are more prevalent in developed countries [22]. This explains incidence correlation with HDI. Furthermore, the rise of incidence might be related to better diagnostic accuracy of new available approaches and more widespread performance of urine cytology, cystoscopy and computed tomography (CT) scans. Fluctuations have been observed in a number of unknown cancer T stages with a tendency to decrease in the course of time. The percentage of missing values has gone down from 44.2% in 1990 to 17.8% in 2017. This could be explained by the improvement of cancer registry, data input, widespread use and improvement of diagnostic modalities. Nevertheless, there are still missing data.

Antoni et al. data shows that a considerable reduction in mortality rates has been observed in most countries [2]. Although from 1990 until 2017, cancer-specific mortality rates from BC in Latvia significantly increased (APC = 0.5; $p < 0.001$), with an ASR mortality rate of 3.9 in 1990 to 4.4 in 2017. These

findings can be associated with insufficient cancer-preventing measures. Compared to other countries in terms of mortality rates, Latvia ranks 3rd in Europe, with Albania and Poland at the forefront [1]. In contrast, Latvia ranks 1st in male mortality from bladder cancer in Europe [1]. Perhaps such an arrangement in mortality rates can be explained by different prevalence of tobacco smoking [23] and occupational exposure to chemicals in different populations. In the conducted study, there was a trend towards an increase in cancer-specific mortality rates for age groups from 60–79 and >80 years (APC = 0.7 and APC = 1.9; $p < 0.05$), although in younger age group (from 40–59 years) mortality rates have decreased over the time (APC = -1.1; $p < 0.05$). Furthermore, various studies have shown that the cancer mortality rate also has a tendency to increase with age [24]. There are assertions that in younger patients (aged <40 years) urothelial BC tends to be low-grade and therefore commonly has a slow-growing pattern [25, 26]. Furthermore, according to Shariat et al., urothelial BC mortality rate might be higher in the elderly due to administration of less aggressive treatment and avoidance of radical therapy [27, 28]. Low average life expectancy rates in Latvia become another reason for the increased mortality rates [22].

In the current study, increased RS rates have been demonstrated. However, at the beginning of the study (1990–2000), RS rate was 55.0%, which is relatively low compared to other European countries, but eventually RS increased to 59.0% from 2013 to 2017, which is still much lower than the European average rates. According to Cancer Research UK, the ASR 5-year net survival in England and Wales was 60.9% between 1990 and 1991 but fell to 53.7% between 2010 and 2011 [29]. A similar situation with a decline in 5-year RS were observed in Germany [30]. Comparing 5-year survival rates by gender, women have better survival rates (Figure 7); however, this difference is not statistically significant. It could be explained by the fact that women in Latvia have higher average age of life expectancy compared to men. In women's group, RS tends to increase, in contrast to the data from the United Kingdom [29], where survival rates have deteriorated for both genders since 1990. In addition, women's survival rates in the United Kingdom are particularly negative; only 43.9% in the period from 2013 to 2017. On the other hand, the presented survival rates in the current study are quite similar to the estimated RS rate reported in Lithuania: 48.6% in 1995–1999 and 56.4% in 2005–2009 [31].

In the study, 5-year RS rates by tumour T stage have gradually dropped from 1990 till 2017. The apparent decrease in survival rates reflects criteria changes

in TNM classification in 1997 for the diagnosis of muscle-invasive bladder cancer (MIBC) compared with earlier years. However, survival rates are tightly related to a number of factors such as tumour grade, tumour size, treatment and histological variant. The decline in survival could be attributed to the increase in the prevalence of high-grade tumours over time [32], which are associated with a less favourable prognosis due to greater risk of spreading. Also, large tumours are less favourable. Patients with T2 stage, who underwent radical cystectomy (RC) with tumour ≥ 3 cm, have worse cancer-specific survival [33]. Moreover, one of the most important factors in MIBC is presence of nodal involvement. The main determinant of BC patients' survival is rate of utilization of RC in MIBC [34], as well as the type of therapy received. For localised MIBC, the most effective treatment is RC with bilateral pelvic lymph node dissection. In comparison, alternative methods such as chemotherapy and radiation therapy indicate worse outcomes [35]. Processali et al. reported that another factor which impacts oncological outcomes and survival is histological variant of BC [36]. Taking into consideration the above-mentioned, previously observed decrement of 5-year survival rates by T stage could be associated with these factors.

The current study is not devoid from limitations, due to incomplete available data and multiple changes in disease coding throughout the years. The analysis of the survival was performed stratified by T stage, although it would have been more effective to analyse it by individual stage including N and M stages as well as tumour grade, which unfortunately was not available. Furthermore, the LCR inherited the data collected before the restoration of the country's independence, and only since 1992 a personal identification number has been introduced. Also, those who were historically registered with wrong, incomplete identification numbers were removed from the oncology registry during 2015 and 2016. Therefore, it explains the reduced numbers of casualties in Latvia. Also, during the past three decades, LCR has been reformed several times and merged with other registers. Additionally, the financial crisis in 2009 significantly influenced the statistics of newly registered patients. To be more precise, oncology practices were reformed which was followed by a significant reduction in the number of newly discovered BC cases.

This article has exposed epidemiological trends between 1990–2017. Information gathered in this study reflects the most accurate BC incidence, mortality and survival rates in the country. Since this specific issue has not been previously studied in Latvia, future research will help to address and reference current material for epidemiologists, clinicians and

public health managers. Although, further detailed studies are needed, including disease stage, grade, treatment data, income level and social exclusion.

CONCLUSIONS

The increase in BC incidence and mortality rates has been observed during the past 28 years, except cancer-specific mortality in the age group 40–59, which tends to decrease. The 5-year RS in Latvia has improved over time but is still lower than median survival in other European countries. Further

detailed studies are needed to explain differences in epidemiological trends over time and help to introduce new algorithms of BC diagnosis and treatment in Latvia.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

ACKNOWLEDGMENTS

Special thanks should be given to Latvian Centre for Disease Prevention and Control for provided data. This study was supported by Riga Stradiņš University internal grant RSU/PP/2020-07.

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