

Research Report

25-Year Trends in Stage-Specific Incidence Rates for Bladder Cancer in a Large Statewide Registry

Justin Loloia^a, Yu-Kuan Lin^a, Fabian Camacho^b, Eugene Lengerich^b and Jay D. Raman^{a,*}

^a*Division of Urology, Penn State Health Milton S. Hershey Medical Center, Hershey, PA, USA*

^b*Department of Public Health Sciences, Penn State Health Milton S. Hershey Medical Center, Hershey, PA, USA*

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Abstract.

BACKGROUND: Bladder cancer (BC) is a common genitourinary malignancy with over 80,000 new cases diagnosed annually and over 17,000 associated deaths.

OBJECTIVE: We review 25-years of BC incidence (1993-2017) within the state of Pennsylvania to better define incidence, geographic distribution, and trends over time.

METHODS: The Pennsylvania Cancer Registry was reviewed for statewide and component county age-adjusted BC incidence rates and stage distribution. Choropleth maps plotting statewide and county-specific incidence rates across time were created using the GeoDa statistical package.

RESULTS: 93,476 cases of BC were recorded in Pennsylvania from 1993 to 2017. Age-adjusted annual rates of BC over the study interval were stable at 24.5 patients per 100,000 (range, 22.7–25.6). However, annual rates of distant disease increased from 0.5 to 1.1 patients per 100,000 ($p < 0.001$) with an average percent change increase of 6.6% over the study interval. The annual percent distribution of distant disease doubled from 2.3% to 5.1% ($p < 0.001$) with a greater increase in women compared to men. Choropleth maps highlighted growing “hot spots” of bladder cancer incidence in the northwestern, northeastern, and southeastern portions of the state.

CONCLUSIONS: While BC incidence in the state of Pennsylvania has remained relatively stable over the past 25 years, a concerning increase in distant disease was observed. Geospatial investigation implicates higher risk regions. Further studies are necessary to delineate the underlying etiologies for these observations.

Keywords: Urothelial cancer, state, trend, bladder, stage

INTRODUCTION

Urothelial carcinomas originate from the epithelial lining of the urinary tract including the bladder and upper urinary tract [1]. The incidence of

bladder cancer (BC) continues to rise within the United States, increasing from approximately 50,000 new cases diagnosed annually during the 1990s to greater than 80,000 new cases in 2020 [2]. Among American men, it is the fourth most common cancer and the seventh leading cause of cancer-related mortality [2]. With similar trends outside of the United States [3], it is apparent that BC is a significant public health concern.

*Correspondence to: Jay D. Raman, M.D., F.A.C.S., Penn State Health Milton S. Hershey Medical Center, Division of Urology, 500 University Drive, BMR Building c4830B, Hershey, PA 17033-0850, USA. Tel.: +1 717 531 6979; Fax: +1 717 531 4475; E-mail: jraman@pennstatehealth.psu.edu.

Cigarette smoking and occupational exposure to aryl amines are well-established risk factors for BC. Smoking, in particular, is a reported causal factor in approximately half of all bladder cancer cases [3]. Despite observing a decrease in the prevalence of cigarette smoking since 1998 [4] and stricter government regulations on the use of aryl amines, there has not been a reduction in the incidence of BC. In fact, there has been a paradoxical increase in its overall incidence. Although this could reflect the lag time between exposure and the development of the disease, these observations also suggest the impact of other potential carcinogenic exposures and risk factors including (but not limited to) arsenic, hair dye, dietary, and environmental factors [5, 6].

In Pennsylvania, the incidence rate for BC is the eighth highest in the United States with 22.7 cases per 100,000 per year [7]. The need for relatively intensive and lifelong surveillance coupled with expenses associated with treatment has resulted in bladder cancer incurring the highest per-patient costs (from diagnosis to death) of all cancers [8–10]. Thus, in addition to the impact on psychological health and well-being, there is a major economic burden placed on the patient, family, and society overall [11].

Previously published population-based registry studies have suggested an increase in the absolute and relative percentages of newly diagnosed BC cases [12, 13]. In this context, we review data from a large statewide cancer registry over a contemporary 25-year interval to determine incidence rates and trends for BC, stage distribution of these cancers, as well as specific geographic “hot spots” harboring higher rates of disease.

PATIENTS AND METHODS

BC incidence rates between 1993 and 2017 were extracted from the Pennsylvania Cancer Registry available through the Enterprise Data Dissemination Informatics Exchange (EDDIE; <https://www.health.pa.gov/topics/HealthStatistics/EDDIE/Pages/EDDIE.aspx>; referenced 7/3/20). The study was IRB exempt as the data were obtained from the database. No informed consent was obtained as this is available data.

Age-adjusted BC incidence rates were calculated annually for the entire state of Pennsylvania as well as component counties. The Joinpoint Regression Program (Version 4.8.0.1) examined trends of gender, race, and stage. Joinpoint Regression model uses a

Table 1
Pathologic and Demographic data for Bladder Cancer from the Pennsylvania Cancer Registry 1993 – 2017 (25 years)

Variables	Number of Cases (Percent)
TOTAL CASES	93476
AGE	
0–49	4134 (4.4%)
50+	89342 (95.6%)
GENDER	
Female	24080 (25.8%)
Male	69396 (74.2%)
RACE	
White	88443 (94.6%)
Black	3822 (4.1%)
SEER STAGE	
<i>In Situ</i>	39555 (42.3%)
Local	39524 (42.3%)
Regional	6676 (7.1%)
Distant	3414 (3.7%)
Unstaged	4266 (4.6%)

linear approach that fits incidence rate data for multiple years and allows adjustments for various factors such as age, race and gender while standardizing the incidence rates with the standard population. It therefore allows for a trend analysis and focus on relative percentage changes.

Stage distribution across the cohort was reported according to the SEER Summary Staging system (*in situ*, local, regional, and distant) as recorded within the PA Cancer Registry. The TNM system is not used within this dataset. The classification was based on the stage of incident cancer at diagnosis as opposed to disease progression from earlier stage disease. The GeoDa spatial statistical package created Choropleth maps plotting incidence rates across time and counties. Localization to counties was based upon zip code of patients as opposed to sites where treatment was rendered. Rates were tailored towards local area means using a spatial Empirical Bayes smoothing technique. Empirical Bayes Smoothing uses the population in a region as a measure of the confidence in the data, with higher populations in a given area lending a higher confidence to the estimated number of events in that location. Statistical significance was set at a p value of <0.05 .

RESULTS

From 1993 to 2017, a total of 93,476 cases of BC were recorded in the Pennsylvania Cancer Registry. Table 1 illustrates pathologic and demographic data for the cohort. Over 95% of patients were older than 50 years of age, over 90% were white, while

122 approximately 75% were male. Stage distribution
 123 included *in situ* in 42.3%, local in 42.3%, regional
 124 in 7.1%, distant in 3.7%, and unstaged in 4.6%.

125 Age-adjusted rates of BC over the study interval
 126 were stable at 24.5 patients per 100,000 (range,
 127 22.7–25.6) (Fig. 1). Similarly, when considering gender,
 128 overall rates for men (43.4 per 100,000 [range,
 129 39.6–46.7] and women (11.1 per 100,000 [range
 130 10.1–12.0]) did not demonstrate significant changes
 131 between 1993 and 2017 (Fig. 2). A similar observa-
 132 tion was noted with different racial groups, with white
 133 (25.3 per 100,000 [range, 23.7–26.6]) and black (14.1
 134 per 100,000 [range, 12.2–16.5]) patients showing sta-
 135 ble rates over the 25 years of study (Fig. 3).

136 Although the overall age-adjusted rates of blad-
 137 der cancer remained stable, interesting observations
 138 were noted when considering the stage distribution of
 139 newly diagnosed bladder cancer. Specifically, a sig-
 140 nificant increase with respect to *in situ* (APC 9.5%,
 141 $p < 0.001$) as well as distant disease (APC 6.6%,
 142 $p < 0.001$) over the 25-years was observed and these
 143 increases persisted across almost every 5-year inter-
 144 val evaluated (Table 2). Furthermore, the percent
 145 distribution of distant disease doubled from 2.3% to
 146 5.1% ($p < 0.001$) with a greater increase in women
 147 than men over this time interval (Fig. 4).

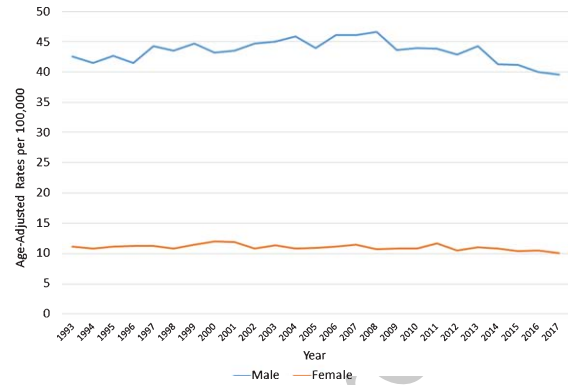


Fig. 2. Age-Adjusted Rates of Bladder Cancer per 100,000 population by gender, 1993–2017.

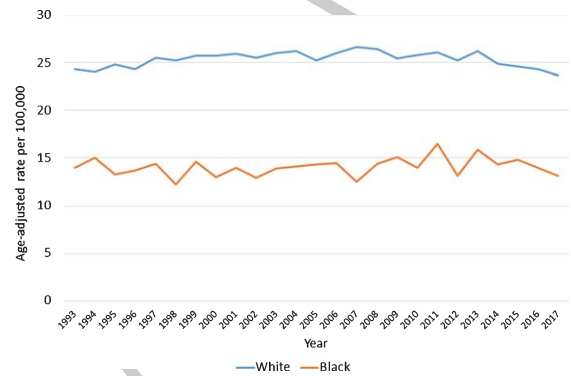


Fig. 3. Age-Adjusted Rates of Bladder Cancer per 100,000 population by race, 1993–2017.

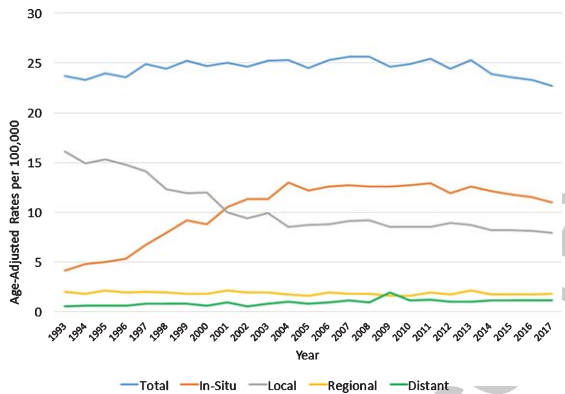


Fig. 1. Age-Adjusted Rates of Bladder Cancer per 100,000 population, 1993–2017.

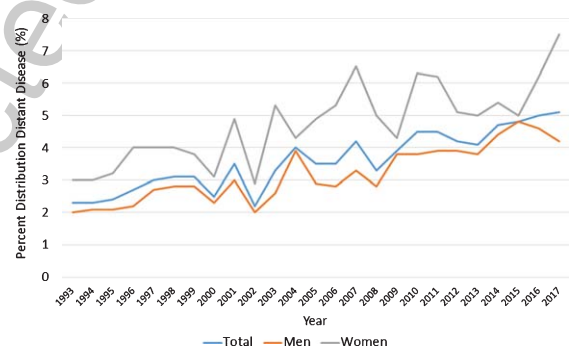


Fig. 4. Annual Percent Distribution of Distant Bladder Cancer, 1993–2017.

Table 2
 Annual Percentage Change in 5-year increments by Stage

APC (%) 95%CI	Overall 1993–2017	1993–1997	1998–2002	2003–2007	2008–2012	2013–2017
Total	0.8 (0.5, 1.2)	1.8 (1.3, 2.2)	1.0 (0.7, 1.5)	0.7 (0.6, 0.8)	0.6 (0.4, 0.9)	-1.2 (-0.6, -1.9)
<i>In Situ</i>	9.5 (8.4, 10.3)	13.7 (12.2, 14.4)	10.6 (9.9, 11.8)	3.5 (2.9, 3.8)	0.5 (0.4, 0.8)	-1.9 (-2.7, -1.3)
Local	-1.5 (-2.1, -0.8)	-2.4 (-3.3, -1.5)	-5.5 (-4.8, -6.0)	-1.6 (-0.5, -2.2)	0.9 (0.6, 1.6)	-1.1 (-1.6, -0.8)
Regional	0.5 (0.2, 0.9)	1.6 (1.2, 1.9)	1.5 (0.9, 2.1)	1.0 (0.9, 1.4)	1.5 (1.0, 2.3)	-2.1 (-2.9, -1.1)
Distant	6.6 (5.5, 8.0)	9.1 (8.4, 9.9)	-3.1 (-6.4, -1.3)	7.7 (5.1, 8.8)	7.2 (6.1, 8.8)	4.0 (3.1, 5.8)

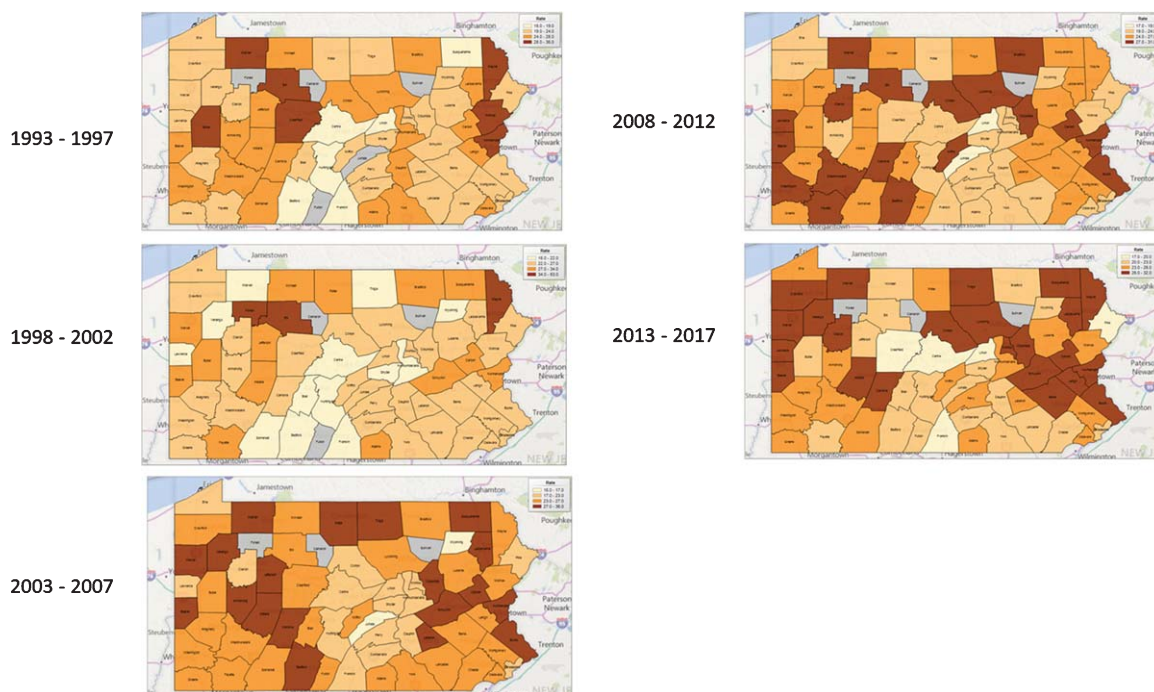


Fig. 5. Age-Adjusted Bladder Cancer Incidence Rates with Spatial Empirical Bayes Smoothing by County in 5-year intervals, 1993–2017.

Choropleth maps highlighted growing “hot spots” of BC incidence in the northwestern, northeastern, and southeastern portions of Pennsylvania (Fig. 5). Subgroup analysis of distant BC cases highlights that these same regions remain “hot spots” for these more aggressive cancers (Fig. 6).

DISCUSSION

The aim of this study was to review contemporary data from a large statewide cancer registry to evaluate the incidence, trends, and geographic distribution of newly diagnosed bladder cancer. We found that, as with other population studies [12, 13], BC was more prevalent in the older, white, and male populations in Pennsylvania. Additionally, the majority of cases (>80%) were localized disease (*in situ*/local disease) with an increasing trend to *in situ* cancers over the time period.

BC incidence in Pennsylvania has remained relatively stable at a rate of 24.5 patients per 100,000 over the past 25 years. While male gender and Caucasian race both had higher rates of incident bladder cancers, the trends when stratified by gender and race did not change over time.

Importantly, we observed a shift in the stage specific, age-, race- and gender adjusted incidence rates

of *in situ* and distant disease in Pennsylvania over the last 25 years. The rate of *in situ* disease increased steadily at an annual percentage change of 9.5%. For distant BC cases, the annual percentage increase was 6.6% over the last 25 years. These findings from the Pennsylvania Cancer Registry are consistent with other large hospital-based registry study [13] and population based data [12].

Generally, BC is more commonly diagnosed in the older patient population [14] and approximately 75% of BC patients in the PA Cancer Registry were older than 65 years of age. The overall increase in the incidence of *in situ* BC may be reflective of a variety of factors related to awareness of both health care professionals and patients. Indeed, professional guidelines statements from the American Urologic Association including those on microhematuria and bladder cancer provide standardized and evidence based approaches for diagnosis and treatment of this condition [15, 16].

Of concern, however, is the persistent increase in the incidence of distant bladder cancer diagnosed within the state. Analysis over 25-years noted a 6.6% annual percentage increase in distant disease. Furthermore, the percent distribution of distant cancers doubled over this time interval with women experiencing the most significant change (3% in 1993 to

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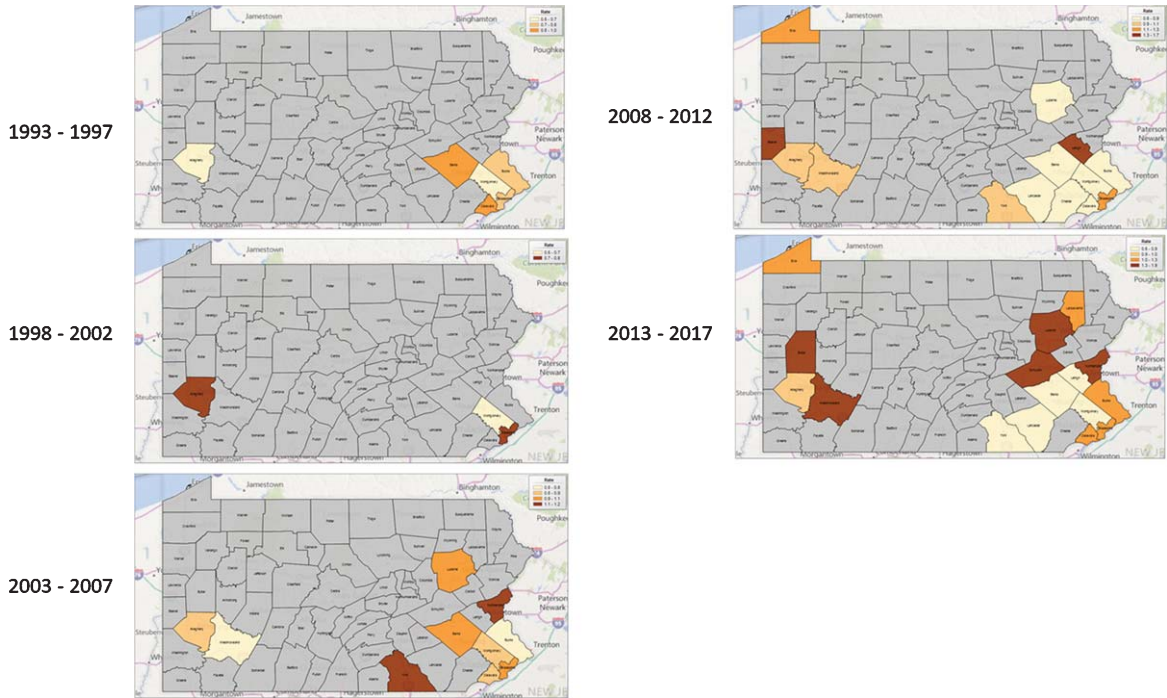


Fig. 6. Age-Adjusted Distant Bladder Cancer Incidence Rates with Spatial Empirical Bayes Smoothing by County in 5-year intervals, 1993–2017.

200 7.7% in 2017) of newly diagnosed bladder cancers
 201 (Figure 4). These gender differences are not entirely
 202 surprising and may be explained by prior studies
 203 implicating delays in the evaluation of women with
 204 hematuria while attributing this symptom to infection
 205 or gynecologic causes [17]. The 5-year disease-free
 206 survival rate declines with increasing pathological
 207 stage. For *in situ* and localized disease, the sur-
 208 vival rate is noted to be greater than 85%. However
 209 for distant disease, survival rate historically is poor,
 210 although contemporary systemic therapy regimens
 211 integrating chemotherapy and immunotherapy have
 212 dramatically shifted the landscape of treating such
 213 patients [18]. Indeed, focus should not only be on ear-
 214 lier diagnosis but refined therapy for those present-
 215 ing with advanced stage disease.

216 The Choropleth maps show growing hot spots
 217 of BC in the northwestern, northeastern, and south-
 218 eastern portions of Pennsylvania with commiserate
 219 increase in distant cancers in these same geographic
 220 regions. The classic risk factors for BC are age,
 221 male sex and environmental exposure, in particu-
 222 lar cigarette smoke [19] and occupational exposure
 223 to aromatic amines [20]. On a global level, arsenic
 224 exposure in natural food and water was thought to
 225 cause an increased incidence of bladder, lung and skin

226 cancer. In the northeast portion of Pennsylvania, the
 227 historical high incidence of BC may be attributed to
 228 coal-mining exposure. Intensive coal-mining activi-
 229 ties, along with natural gas extraction, in regions of
 230 the state have been identified as possible sources of
 231 surface water contamination [21, 22]. However, the
 232 direct relationship between these contaminations and
 233 the increased incidence of BC is unclear. The south-
 234 western region, also a growing hotspot for bladder
 235 cancer, has traditionally been involved in the steel
 236 industry. However, it is unclear at this point whether
 237 these trends in BC are attributable to environmen-
 238 tal exposures above or other factors including access
 239 to care. Further epidemiological studies are needed
 240 to better characterize these risk factors to help target
 241 diagnosis and treatment of BC cases.

242 There are several limitations in this study. As with
 243 any registry based observational data, there is the pos-
 244 sibility of misclassification or unmeasured changes in
 245 stage reporting practices over time. There may also be
 246 selection bias base of data collection. Furthermore,
 247 the lack of standardized and centralized pathologic
 248 review precludes a uniform diagnostic assessment of
 249 malignancies both of the diagnosis and of the tumor
 250 stage. Despite these limitations, this work fills an
 251 important gap in the literature regarding the incidence

and geographic distribution of UC disease and the regional conditions that may influence its incidence.

CONCLUSION

BC incidence in the state of Pennsylvania has remained relatively stable over the past 25 years. There was, however, a concerning 6% annual percentage increase in distant disease over the study period. Geospatial investigation implicates growing “hot spots” of BC in the certain portions of the state. The underlying cause for these trends requires further investigation.

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AUTHOR CONTRIBUTIONS

JL: drafting of the manuscript, substantial contributions to the conception or design of the work or the acquisition, analysis, or interpretation of data for the work, drafting the work for important intellectual content; JLA: data collection and analysis and manuscript creation, substantial contributions to the conception or design of the work or the acquisition, analysis, or interpretation of data for the work; AS, CH: statistical analysis and manuscript creation, substantial contributions to the conception or design of the work or the acquisition, analysis, or interpretation of data for the work, drafting the work for important intellectual content; SM, MK: data collection and analysis and manuscript creation, substantial contributions to the conception or design of the work or the acquisition, analysis, or interpretation of data for the work, drafting the work for important intellectual content; JDR: oversight of all aspects of project including construction of protocol, data collection and analysis and manuscript creation, substantial contributions to the conception or design of the work or the acquisition, analysis, or interpretation of data for the work, drafting the work and revising it critically for important intellectual content.

CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

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