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Changing patterns of bladder cancer in the USA: evidence of heterogeneous disease

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Abstract

- To test the hypothesis that bladder cancer is a heterogeneous disease.
- We examined the temporal trends of bladder cancer by histological subtype and by disease stage and grade using the National Cancer Institute's Surveillance, Epidemiology, and End Results data collected in 1973–2007.
- The age-adjusted incidence rates of bladder cancer showed a slight decrease from 1973 to 2007 (annual percentage change [APC] = -0.4 , $P < 0.05$).
- Although the age-adjusted incidence rates of non-papillary transitional cell carcinoma decreased by about 53% from 7.9 per 100 000 in 1973 to 3.7 per 100 000 in 2007 (APC = -2.2 , $P < 0.05$), the age-adjusted incidence rates of papillary transitional cell carcinoma increased by about 56% from 6.8 per 100 000 in 1973 to 10.6 per 100 000 in 2007 (APC = 0.5 , $P < 0.05$).
- Among other rare histological subtypes, except for small cell carcinoma which showed a slightly rising trend, squamous cell carcinoma, adenocarcinoma and others all presented a decreasing trend.
- Similar patterns were found for different stages (localized, regional and distant), but a dramatic increasing trend of grade IV was found between 1998 and 2007 when a corresponding decreasing trend was shown for grades I, II and III.
- The results support the hypothesis that bladder cancer is a heterogeneous disease and taking disease heterogeneity into consideration in future epidemiological studies is essential.

Keywords

bladder cancer; transitional cell carcinoma; papillary transitional cell carcinoma; non-papillary transitional cell carcinoma; incidence; mortality

Introduction

Bladder cancer is the fifth most common cancer in the USA with an expected 70 530 individuals who will be diagnosed with it and 14 680 deaths in 2010 [1]. Cigarette smoking

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and occupational exposure to arylamines are two well established risk factors for bladder cancer and are considered to account for more than half of all cases in the USA [2]. As a major contributor, the trend of cigarette smoking in the USA has been declining steadily since 1973 [3,4]. The first recognized human bladder carcinogens, arylamines, have been under strict government control during the past 50 years [5]. Given the decreasing exposure to these well documented risk factors and lack of concrete evidence of increasing exposure to other potential risk factors, we would expect a decreasing trend of bladder cancer in the US population. However, the reduction of incidence trends of bladder cancer is not as compelling as for other tobacco-related cancers (i.e. lung and oral cavity–pharynx cancers) [6], suggesting that other potential risk factors may also play an important role in the aetiology of bladder cancer.

Arsenic in highly exposed populations is an established risk factor for bladder cancer [7–10]; however, the role of exposure to lower levels of arsenic in the general population remains controversial [11–13]. Other potential risk factors such as hair dye use, individual fluid intake and dietary factors have been inconsistently linked to the risk of bladder cancer [14–16]. Although different genetic susceptibilities in different populations may explain some of the controversial findings from epidemiological studies, disease heterogeneity may also contribute to the inconsistent findings since epidemiological studies often treat bladder cancer as a single disease.

To fully understand the patterns of incidence trends across various stages, grades and histological subtypes of bladder cancer, which have shown different clinical presentations in terms of recurrence and progression, we analysed the temporal trends using the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) data collected between 1973 and 2007.

Patients and Methods

SEER data collection began in the early 1970s with nine population-based registries (Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco–Oakland, Seattle–Puget Sound and Utah), which account for about 10% of the US population. Although SEER expanded in 1992 and 2001 to include eight additional registries (Los Angeles, San Jose–Monterey, Rural Georgia, the Alaska Native, Greater California, Kentucky, Louisiana and New Jersey), this report focuses on the original nine registries for data completeness.

The incidence and mortality rates of bladder cancer for each year from 1973 to 2007 were calculated using SEER*Stat (6.6.2). All rates were age adjusted to the 2000 US population. The annual percentage change (APC) was calculated by using weighted least squares regression of natural logarithms of age-adjusted incidence rates. The 95% CI (Tiwari method) was calculated from the fitted regression, assuming a constant rate of change by calendar year [1].

Results

A total of 127 614 first primary bladder cancer cases (ICD-O-3: C670–C679), including 95 045 men, 32 569 women, 117 210 whites, 5450 blacks and 4954 other ethnic groups, were reported to the nine SEER registries between 1 January 1973 and 31 December 2007. Of those, 82 749 (64.8%) were papillary transitional cell carcinoma (PTCC) (ICD-O-3: 8050, 8121 and 8130–8131) [17]; 36 953 (29.0%) were non-papillary transitional cell carcinoma (NPTCC) (ICD-O-3: 8120 and 8122); 1970 (1.5%) were squamous cell carcinoma (ICD-O-3: 8051, 8052, 8070–8072, 8074 and 8076); 1496 (1.2%) were adenocarcinoma (ICD-

O-3: 8140, 8141, 8144, 8255, 8260, 8310, 8320, 8323, 8440, 8470, 8472, 8480, 8481, 8490 and 8570); 236 (0.2%) were small cell carcinoma (ICD-O-3: 8041, 8042); and 4210 (3.3%) were others (ICD-O-3: 8000, 8001, 8002, 8004, 8010, 8012, 8020–8022, 8030, 8032, 8033, 8044, 8046, 8082, 8083, 8230, 8262, 8560, 8700, 8720, 8933, 8935, 8940, 8950, 8951, 9064, 9100 and 9364).

The overall age-adjusted incidence rates of bladder cancer decreased by about 9% from 16.7 per 100 000 in 1973 to 15.2 per 100 000 in 2007 with an APC of -0.4 (95% CI -0.5 , -0.3 ; Fig. 1A), while the age-adjusted mortality rates decreased by about 31% from 6.1 per 100 000 in 1973 to 4.2 per 100 000 in 2007 with an APC of -1.1 (95% CI -1.3 , -0.9). Although both incidence and mortality showed decreasing trends overall, there was difference between the two trends. The incidence trend was increasing from the beginning and reached its highest rate of 18.3 per 100 000 in 1987, after which the trend started decreasing. However, the mortality trend was decreasing from the beginning until about 1987 and then the trend remained stable. Similar patterns were shown for both men (Fig. 1B) and women (Fig. 1C) and for different racial groups (Fig. 1D), although the rates were less stable for blacks and other racial groups because of the small numbers.

Then we examined incidence trends by histological subtypes (Fig. 2). While the rates of NPTCC decreased about 53% from 7.9 per 100 000 in 1973 to 3.7 per 100 000 in 2007 (APC = -2.2 , 95% CI -2.0 , -2.4), the age-adjusted incidence rates of PTCC increased about 56% from 6.8 per 100 000 in 1973 to 10.6 per 100 000 in 2007 (APC = 0.5 , 95% CI 0.2 , 0.8 ; Fig. 2A). Among other rare histological subtypes (Fig. 2B), squamous cell carcinoma (APC = -3.4 , 95% CI -3.8 , -3.0), adenocarcinoma (APC = -1.9 , 95% CI -2.5 , -1.2) and others (APC = -2.0 , 95% CI -2.4 , -1.6) presented decreasing trends, but small cell carcinoma showed increasing trends starting from 1986 with an APC of 4.3 (95% CI 2.5 , 6.2). Similar patterns were observed for both men and women, for all ethnic groups (white, black and others) and for different stages (localized, regional and distant; data not shown).

Then we analysed the trends by grade. A dramatic increase in the incidence rates of grade IV were found between 1998 and 2007 when decreasing trends were observed for grades I, II and III (Figs 2C, 2D). For PTCC (Fig. 2C), grade I (APC = -2.0 , 95% CI -3.3 , -0.7), grade II (APC = -3.6 , 95% CI -4.3 , -3.0) and grade III (APC = -5.8 , 95% CI -7.5 , -4.1) showed decreasing trends from 1998 to 2007, while grade IV presented a dramatic increase in the age-adjusted incidence rate (APC = 12.1 , 95% CI 9.7 , 14.7). The shift from low grade to high grade was similar for NPTCC (Fig. 2D), (APC = -5.3 , 95% CI -9.0 , -1.5 for grade I; APC = -6.2 , 95% CI -7.6 , -4.7 for grade II; APC = -5.4 , 95% CI -6.6 , -4.3 for grade III; and APC = 6.7 , 95% CI 4.8 , 8.5 for grade IV). Similar patterns were also shown for men and women, for different racial groups and for different stages (data not shown).

Discussion

The observed dramatic increase in grade IV bladder cancer between 1998 and 2007 is probably due to the change in the grading system. In 1998, the WHO and the International Society of Urological Pathology (ISUP) proposed WHO/ISUP 1998 to replace numerous earlier grading systems [18]. The new WHO/ISUP 1998 tends to upgrade bladder cancer cases compared with earlier grading systems [19]. Although it is unclear whether the increase is entirely or partially due to the changing grading system, given the fact that high grade tumours tend to grow quickly and have worst prognosis, a large proportion of patients diagnosed with high grade diseases is of great concern in both the clinical setting and public health. The observed decreasing incidence and stable mortality after 1987 also supported the fact that there was no reduction of more aggressive bladder cancer cases.

Emerging evidence from both clinical observations and findings of molecular distinctions between various types of bladder cancer indicates that separate pathways may be involved in bladder carcinogenesis and may account for the development of different forms of bladder cancer [20]. The observed striking differences in the temporal trends between PTCC and NPTCC suggest that they may be two disease entities and may have different aetiological profiles. However, no epidemiological studies have investigated risk factors separately for PTCC and NPTCC. Recent survival analysis showed that survival rates are substantially higher for PTCC compared with NPTCC [17].

We recognize that disease misclassification is possible due to the lack of central pathology review for all cases in the SEER. However, such misclassification is likely to be non-differential.

In summary, our study provides the first evidence of striking differences in temporal trends between PTCC and NPTCC. The observed results suggest that bladder cancer is a heterogeneous disease and may involve different pathogeneses. Investigation of aetiological profiles by disease subtypes in future epidemiological studies is essential. In addition, large proportions of high grade bladder cancer diagnosed initially indicate that efforts are urgently needed to develop innovative diagnostic tools for early detection of bladder cancer.

Acknowledgments

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References

1. Altekruse, SF.; Kosary, CL.; Krapcho, M., et al., editors. SEER Cancer Statistics Review, 1975–2007. Bethesda, MD: National Cancer Institute; Available at http://seer.cancer.gov/csr/1975_2007/, based on November 2009 SEER data submission, posted to the SEER website 2010
2. Jones PA, Ross RK. Prevention of bladder cancer. *N Engl J Med.* 1999; 340:1424–6. [PubMed: 10228196]
3. Centers for Disease Control and Prevention. State-specific prevalence and trends in adult cigarette smoking – United States, 1998–2007. *MMWR Morb Mortal Wkly Rep.* 2009; 58:221–6. [PubMed: 19282813]
4. Garfinkel L. Trends in cigarette smoking in the United States. *Prev Med.* 1997; 26:447–50. [PubMed: 9245664]
5. Yu MC, Skipper PL, Tannenbaum SR, Chan KK, Ross RK. Arylamine exposures and bladder cancer risk. *Mutat Res.* 2002; 506–7:21–8.
6. Polednak AP. Trends in incidence rates of tobacco-related cancer, selected areas, SEER Program, United States, 1992–2004. *Prev Chronic Dis.* 2009; 6:A16. [PubMed: 19080022]
7. Bates MN, Rey OA, Biggs ML, et al. Case-control study of bladder cancer and exposure to arsenic in Argentina. *Am J Epidemiol.* 2004; 159:381–9. [PubMed: 14769642]
8. Chen Y, Ahsan H. Cancer burden from arsenic in drinking water in Bangladesh. *Am J Public Health.* 2004; 94:741–4. [PubMed: 15117692]
9. Hopenhayn-Rich C, Biggs ML, Fuchs A, et al. Bladder cancer mortality associated with arsenic in drinking water in Argentina. *Epidemiology.* 1996; 7:117–24. [PubMed: 8834549]
10. Smith AH, Lingas EO, Rahman M. Contamination of drinking-water by arsenic in Bangladesh: a public health emergency. *Bull World Health Organ.* 2000; 78:1093–1103. [PubMed: 11019458]
11. Bates MN, Smith AH, Cantor KP. Case-control study of bladder cancer and arsenic in drinking water. *Am J Epidemiol.* 1995; 141:523–30. [PubMed: 7900719]
12. Michaud DS, Wright ME, Cantor KP, Taylor PR, Virtamo J, Albanes D. Arsenic concentrations in prediagnostic toenails and the risk of bladder cancer in a cohort study of male smokers. *Am J Epidemiol.* 2004; 160:853–9. [PubMed: 15496537]

13. Mink PJ, Alexander DD, Barraj LM, Kelsh MA, Tsuji JS. Low-level arsenic exposure in drinking water and bladder cancer: a review and meta-analysis. *Regul Toxicol Pharmacol.* 2008; 52:299–310. [PubMed: 18783726]
14. Takkouche B, Etminan M, Montes-Martinez A. Personal use of hair dyes and risk of cancer: a meta-analysis. *JAMA.* 2005; 293:2516–25. [PubMed: 15914752]
15. Pelucchi C, La Vecchia C. Alcohol, coffee, and bladder cancer risk: a review of epidemiological studies. *Eur J Cancer Prev.* 2009; 18:62–8. [PubMed: 19077567]
16. Silberstein JL, Parsons JK. Evidence-based principles of bladder cancer and diet. *Urology.* 2010; 75:340–6. [PubMed: 19819528]
17. Ries, LAG.; Young, JL.; Keel, GE.; Eisner, MP.; Lin, YD.; Horner, MJ., editors. SEER Survival Monograph: Cancer Survival Among Adults: US SEER Program, 1988-2001, Patient and Tumor Characteristics. Bethesda, MD: National Cancer Institute; 2007. SEER Program, NIH Pub. No. 07-6215
18. Epstein JI, Amin MB, Reuter VR, Mostofi FK. The World Health Organization/International Society of Urological Pathology consensus classification of urothelial (transitional cell) neoplasms of the urinary bladder. Bladder Consensus Conference Committee. *Am J Surg Pathol.* 1998; 22:1435–48. [PubMed: 9850170]
19. Miyamoto H, Miller JS, Fajardo DA, Lee TK, Netto GJ, Epstein JI. Non-invasive papillary urothelial neoplasms: the 2004 WHO/ISUP classification system. *Pathol Int.* 2010; 60:1–8. [PubMed: 20055945]
20. Droller MJ. Bladder cancer: state-of-the-art care. *CA Cancer J Clin.* 1998; 48:269–84. [PubMed: 9742894]

Abbreviations

SEER	Surveillance, Epidemiology, and End Results
APC	annual percentage change
PTCC	papillary transitional cell carcinoma
NPTCC	non-papillary transitional cell carcinoma

Fig. 1.

Age-adjusted incidence and mortality rates of bladder cancer in the USA by gender and race, nine SEER registries, 1973–2007 (**A**); in men (**B**); in women (**C**); by racial groups (**D**).

Fig. 2. Age-adjusted incidence rates of bladder cancer by histological subtypes in the USA, nine SEER registries, 1973–2007. Age-adjusted incidence rates of PTCC and NPTCC (**A**), of squamous cell carcinoma, adenocarcinoma, small cell carcinoma and others (**B**), of PTCC by histological grade (**C**), of NPTCC by histological grade (**D**).