Clinics in Oncology

Review Article
Published: 19 Oct, 2016

A Contemporary Review of Risk Factors for Bladder Cancer

*Lokeshwar SD[1], Klaassen Z[2] and Terris MK[2]**

[1]Miller School of Medicine, University of Miami, USA

[2]Department of Urology, Augusta University, USA

Abstract

Increased risk of bladder cancer has historically been associated with smoking and environmental exposure, however other factors have recently been investigated. The role of marijuana and bladder cancer risk requires further validation, although there appears to be an inverse relationship perhaps associated with decreased tobacco smoking. A correlation between obesity and increased risk of bladder cancer has yet to be established, however the pro-inflammatory affect of obesity and the operative challenges associated with obese patients suggest a potential relationship. African Americans race is associated with a higher likelihood of mortality and recurrence after bladder cancer diagnosis, likely secondary to poorer socioeconomic status and lack of access to healthcare. Although men are more likely to present with bladder cancer, the mortality rates in women are higher due to delayed diagnosis. Finally, radiation exposure from treatment of previous primary malignancies increases bladder cancer risk, as does environmental contaminants such as arsenic. Health care providers should ultimately seek to alleviate preventable disparities associated with increased risk of bladder cancer, as well as be aware of less common, high-risk patient populations when evaluating and educating patients and their families.

Keywords: Bladder cancer; Mortality; Lymphadenectomy

Introduction

In 2015, there were more than 76,000 new cases of bladder cancer and 16,300 bladder cancer related deaths [1]. However, in the United States, bladder cancer incidence and mortality has declined over the past decade [1]. This trend is likely secondary to reduced smoking rates among the American population: from 20.9% of adults in 2004 to 16.8% in 2014 [2]. Tobacco smoking is arguably the most established risk factor for bladder cancer [3], and recently the intensity of smoking has been implicated in bladder cancer pathophysiology [4]. Heavy smokers are more likely to present with high-grade muscle invasive disease compared to patients who were light smokers or nonsmokers [4]. Furthermore, long-term heavy smokers also have worse prognosis after radical cystectomy [5]. In addition to tobacco smoking, recent cohort and case-control studies have suggested other important risk factors for developing bladder cancer. The purpose of this review is to assess the literature and highlight these additional, contemporary risk factors.

Marijuana

With the recent advocating for legalization of marijuana in certain US states, side effects and implications of cannabis use has garnered public interest, including a potential role in bladder cancer risk. In 2006, prior to marijuana legalization, we suggested that marijuana smoking may increase the risk of bladder cancer [6]. In this case-control study, 88.5% of patients with bladder cancer had a history of habitual marijuana use compared to only 69.2% of age-matched controls. Subsequently, a study of 84,000 Californian men aged 45-69 were followed for 11 years to determine their risk of bladder cancer [7]. Cannabis consumption was associated with a 45% decrease in bladder cancer incidence (HR, 0.55; 95% CI, 0.31-1.00) indicating cannabis use may be protective for risk of bladder cancer. Research on this topic is limited and currently hypothesis generating. Perhaps marijuana smoking is associated with decreased tobacco smoking, thus resulting in decreased risk for bladder cancer. Further investigation is necessary to establish a possible causal relationship between cannabis use and bladder cancer risk.

Obesity

Obesity and lack of physical activity among Western populations has recently emerged as a

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Correspondence:
Martha K. Terris, Department of Urology, Medical College of Georgia–Augusta University, 1120 15th Street, Augusta, GA 30912, USA, Tel: 706-721-2519; Fax: 706-721-2548; E-mail: mterris@augusta.edu

Received Date: *24 Aug 2016*
Accepted Date: *26 Sep 2016*
Published Date: *19 Oct 2016*

Citation:
Lokeshwar SD, Klaassen Z, Terris MK. A Contemporary Review of Risk Factors for Bladder Cancer. Clin Oncol. 2016; 1: 1121.

potential risk factor for bladder cancer. A recent review article analyzed 31 studies evaluating the relationship between obesity and bladder cancer [8]. Among these studies, ten suggested a positive association between obesity and increased bladder cancer risk, while three found a negative association between physical activity and bladder cancer risk [8]. A report from earlier this year assessed the role of BMI on oncological outcomes in patients treated with radical cystectomies for muscle invasive disease [9]. BMI 30 kg/m^2 correlated with both elevated risk of disease recurrence (HR 1.58; 95% CI 1.06-2.34, p=0.02) and cancer-specific mortality (HR 1.58; 95% CI 1.01-2.48; p=0.04). Although a causal association of obesity and increased risk of bladder cancer has yet to be established, the pro-inflammatory affect of obesity and the operative challenges associated with obese patients suggest a potential relationship [9]. As the global obesity pandemic continues to transpire, the role of obesity and sedentary lifestyles on bladder cancer incidence and long-term outcomes will be an important area of research.

Race

Bladder cancer has traditionally been associated with Caucasian patients, however recent data has emerged suggesting increased trends in African Americans and Hispanic populations [10]. Although the raw number of new bladder cancer cases is still highest in Caucasians, mortality rates for bladder cancer are higher among non-white patients [10]. Many reports have hypothesized possible explanations for these racial discrepancies. Utilizing state inpatient databases for New York, Florida and Maryland, Barocas et al. [11] found that African Americans were more often treated by lower volume surgeons and hospitals, had lower receipt of pelvic lymphadenectomy and continent diversion, and had higher rates of complications compared to Caucasian patients. A SEER-Medicare study of 74,000 bladder cancer patients, found that African American race imparted a greater risk of disease progression and mortality [12]. To assess for race specific outcomes, the University of Alabama followed patients from 2001-2012 that underwent radical cystectomy and reported that race was independently associated with tumor recurrence (HR, 3.1; 95% CI, 1.2-7.4) [13]. Additionally, in a recent SEER study performed by our group, patients with metastatic disease at diagnosis were more commonly female, African American, and unmarried compared to patients with non-metastatic disease at diagnosis [14]. The importance of equal access care for improving outcomes in African American patients has also been evaluated by the Department of Defense, where universal healthcare is provided irrespective of racial background. In this setting, there was comparable overall survival between Caucasian and African American bladder cancer patients (HR: 0.96, 95% CI: 0.76-1.22) [15], suggesting that access to care may be more important than disease biology. These findings highlight the importance of healthcare access (specifically hospitals and providers equipped for evaluating and treating bladder cancer patients), patient education and administrative support for patients of lower socioeconomic status.

Gender

Although men have a higher incidence of bladder cancer (3:1), women have a higher mortality rate relative to disease incidence [1]. Rather than a more aggressive disease entity, research has suggested that these discrepancies may be secondary to delayed diagnosis. Among patients presenting with hematuria, the time from the hematuria evaluation to bladder cancer diagnosis was 85.4 days in women, compared to 73.6 days in men (p <0.001) [16]. Exceptionally long delays in diagnosis (>6 months) were also higher in women compared to men. Furthermore, a study published this year found that women are less likely to be treated with systemic chemotherapy for advanced bladder cancer than men (45% *vs.* 52%; adjusted relative risk 0.91, 95% CI 0.88-0.94) [17]. Additionally, women also experienced delays in systemic chemotherapy administration (9.8 months *vs.* men 8.0 months; p <0.001) [17]. Similar to US data [14], an Austrian Cancer Registry study evaluating 27,773 patients found that women more frequently have advanced stage disease at diagnosis [18]. In a study evaluating 27,912 patients in Europe and North America, survival rates after radical cystectomy were lower in women compared to men (pooled HR 1.20, 95%CI 1.09-1.32) [19].

Whether females have more aggressive disease or primarily suffer from delayed diagnosis and more advanced presentation remains to be fully elucidated. However, when presenting with irritative voiding symptoms with bladder cancer risk factors, women are generally treated for voiding complaints and alleged UTIs (i.e. antibiotics) without more in depth investigation [17]. Educating primary health care providers to the significance of these presenting symptoms, specifically in women with long-term tobacco smoking and/or environmental risk factors, will lead to early diagnosis/appropriate urologic referral and may alleviate these seemingly correctable gender disparities.

Radiation exposure

The most common radiation exposure leading to increased risk of bladder cancer is pelvic radiotherapy for a prior malignancy, including prostate, uterine, cervical and rectal cancer. In a retrospective cohort study of 56,681 patients with primary uterine cancer, the prevalence of subsequent bladder cancer for patients treated with radiation therapy was 0.93% versus 0.48% in those who did not receive radiation therapy [20]. Furthermore, the prevalence of fatal bladder cancer in the radiation therapy cohort was 0.25% compared to 0.09% in patients without radiation therapy [20]. Patients with localized prostate cancer treated with adjuvant radiation therapy after radical prostatectomy are 1.7 times more likely to develop bladder cancer compared to those undergoing radical prostatectomy [21]. Adjuvant radiation therapy also increases bladder cancer mortality (HR=1.28 P=0.05) [21], perhaps secondary to these patients more commonly presenting with locally advanced tumors [22]. Finally, a study from Taiwan highlighted the increased risk of secondary bladder cancer diagnosis after cervical cancer radiation, reporting a standardized incidence ratio of 2.26 [23]. While primary or adjuvant radiation therapy may be clinically indicated for patients with pelvic malignancies, health care providers should be aware of the increased risk of bladder cancer in this patient population.

Industrial & environmental exposure

The long-term carcinogenic effects of industrial and environmental exposure are currently being elucidated. A French cohort of 2,897 uranium processing workers with at least 6 months of chemical exposure was studied for bladder cancer incidence [24]. Interestingly, exposure to aromatic solvents was associated with developing bladder cancer after adjusting for other chemical exposure (HR 6.53, 95% CI 1.14-37.41). Tetrachloroethylene exposure (used during dry-cleaning) has a relative risk of 1.50 for bladder cancer when adjusted for smoking [25]. In study of New York state rubber manufacturing workers, o-toluidine exposure was associated with a relative risk of 6.13 for bladder cancer compared to the general population [26]. Recent studies have highlighted environmental bladder cancer risk factors, particularly in water and food supplies. A hospital-based case-

control study from Spain reported that drinking water with nitrates for >20 years at high nitrate levels (>9.5 mg/L) was associated with a 1.4x increased risk for bladder cancer [27]. Results from World Health Organization (WHO) food consumption data have also implicated arsenic as a risk factor for bladder cancer, suggesting that inorganic arsenic in food may account for 9,129 to 119,176 additional cases of bladder cancer each year [28]. Occupational risk factors may account for ~10% of bladder cancer risk factors [29], highlighting the need for clinicians to be aware of these unique at-risk patient populations.

Conclusion

Tobacco smoking is the most well-known and publicized risk factor for bladder cancer, however a number of other important risk factors exist. In addition to prior radiation, industrial and environmental risk factors, certain gender and racial disparities in diagnosis and treatment are prevalent. Health care providers should seek to alleviate preventable disparities, as well as be aware of less common, high-risk patient populations when evaluating and educating patients and their families.

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