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Original Article

Risk Factors for Bladder Cancer: Results of a Survey of Hospital Patients

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Abstract

Introduction: Several risk factors have been identified in the occurrence of bladder cancer. These include genetic and hereditary factors, smoking and tobacco use, increased body mass index, occupational exposure to certain chemicals and dyes, medical conditions such as chronic cystitis and infectious diseases such as schistosomiasis. This study aimed to evaluate risk factors in patients with bladder cancer. **Materials and Methods:** All patients presenting to the uro-oncology department of the hospital with imaging and histology confirmed bladder cancer were included in the study. Age- and gender-matched patients presenting to the department of urology with benign disorders were prospectively included as controls. All the study subjects and the controls completed a self-administered structured questionnaire. **Results:** Seventy-two (67.3%) of the participants with bladder cancer were males. The mean age of participants with bladder cancer was 59.24 ± 16.28 years. Most participants with bladder cancer worked as farmers (35.5%) or industrial workers (24.3%). Recent history of recurrent urinary tract infections was seen in 85 (79.4%) of the participants with bladder cancer and 32 (30.8%) of controls. Diabetes mellitus was more common among participants with bladder cancer. A significant number of participants with bladder cancer used tobacco and smoked compared to controls. **Conclusions:** This study highlights numerous potential biological and epidemiological factors that may act as a risk factors for bladder cancer. These factors could explain the gender differences observed in the incidence of bladder cancer. In addition, the study indicates the intense risk of tobacco products and smoking on the incidence of bladder cancer.

Key words: Alcohol, bladder cancer, epidemiology, gender, genetics, occupation, risk factors, tobacco smoking

Introduction

The bladder is an organ that remains in constant contact with the environment and is, therefore, sensitive to the effects of environmental carcinogens and inflammation.[1] Tobacco smoking and occupational hazards account for the two most frequent routes of environmental exposure. Tobacco smoke is full of aromatic amines. These amines, when hydroxylated, lead to DNA adduction and damage.[1]

Several risk factors have been identified for the occurrence of bladder cancer. These include genetic risk factors, hereditary factors, smoking and tobacco use, increased body mass index, occupational exposure to certain chemicals and dyes, medical conditions such as chronic cystitis and infectious diseases such as schistosomiasis. Indirect medical causes of bladder cancer are typically unintended side effects of treatment with certain drugs such as anti-diabetic drug pioglitazone, radiation, chemotherapy agents such as cyclophosphamide and environmental pollution through exposure to arsenic in drinking water.[1]

Bladder cancer is a global disease, with a worldwide incidence of 540,000 new cases and 188,000 deaths in 2015.[1] Internationally, the incidence of bladder cancer varies about 10-fold. The disease is reported most often in Europe and North America and least often in several areas of Asia.[2] Epidemiologic data clearly show that bladder cancer is much more common among men, Caucasians, and the elderly.[3] In most high-income countries, men have at least a 3 times greater risk than women.[4]

This study aimed to review the current state of knowledge regarding Bladder cancer risk factors, including factors related to occupation, diet, fluid intake, tobacco and smoking habits and concurrent medical conditions.

Materials and Methods

The research was carried out at the Department of Urology of Doctor Prabhakar Kore Hospital and Medical Research Centre in Belagavi between September 2019 and May 2022. This prospective study was taken up after obtaining ethical clearance from the Institutional Review Board (KAHER/EC/20-21/001/05). All patients presenting to the uro-oncology outpatient department, the hospital admitted patients with signs or symptoms suggestive of bladder cancer and patients followed up for a history of treated bladder cancer were included in the study as cases. Age- and gender-matched patients presenting to the department of urology with symptoms and diagnosis of benign prostatic hyperplasia, urinary stones, urinary tract infection and voiding dysfunction were prospectively included as controls.

All the study subjects and the controls completed a self-administered structured questionnaire (*available on request from the corresponding author*). Trained interviewers monitored the process. The questionnaire collected information on sociodemographic factors, lifestyle habits and diet 2 years before diagnosis, anthropometric measurements, problem-oriented medical history and family history of cancer. Two-specific sections investigated lifetime occupational exposure and exposure to chemicals known (or suspected) to be related to bladder cancer, including the use of hair dyes. Information on smoking included lifetime status (i.e., never, former, or current smoker), the daily number of cigarettes/beedis and grams of tobacco chewed, age at starting, duration of the habit and age at stopping for former smokers.

Odds ratios (ORs) and the corresponding 95% confidence intervals (CIs) were calculated using unconditional logistic regression models. ORs for status, intensity and duration of years were adjusted [Figure 1].

Results

The study included 107 participants with imaging and histopathology confirmed bladder cancer and 104

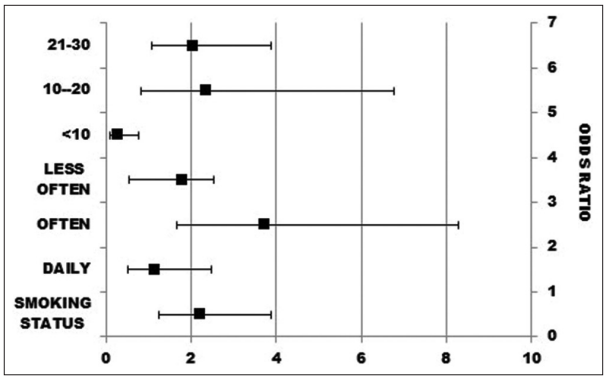

Figure 1: Shows Odds ratios (ORs) and corresponding 95% confidence interval (CI) for smoking status, daily exposure, and duration of years.

Table 1: Age and gender distribution of patients with bladder cancer

Variables	Bladder cancer (%)			Controls n (%)			*P*-value
Males	72			68			0.001
Females	35			36			
Age (years)	**Males**	**Females**	**Total**	**Males**	**Females**	**Total**	
<30	3	2	5 (4.7%)	4	2	6 (5.8%)	0.001
31–60	32	17	49 (45.8%)	29	17	46 (44.2%)	
>70	37	16	53 (49.5%)	35	17	52 (50%)	

participants were age and gender-matched controls. Seventy-two (67.3%) participants with bladder cancer were males, and the remaining 35 (32.7%) were females. The cancer was significantly more common among males ($P < 0.001$) when compared to females [Table 1]. The mean age of participants with bladder cancer was 59.24 ± 16.28 years (males 59.53 ± 16.16 and females 58.66 ± 16.75). About 50% of the participants with bladder cancer were >70 years old. Most of the participants with bladder cancer worked as farmers (35.5%) or industrial workers (24.3%) [Table 2]. Most of the industry workers worked in chemical industry plants dealing with oils, rubber, paints and heavy metal chemicals.

Most participants in the bladder cancer group (89.7%) and controls (91.3%) were married. Recent history of recurrent urinary tract infections was noted in 85 (79.4%) of participants with bladder cancer and in 32 (30.8%) participants from the control group. Diabetes Mellitus was more common among participants with bladder cancer and a significantly high number of participants with bladder cancer gave a history of cancer (including bladder cancer) in the family. About 45% of the participants with bladder cancer gave an account of ingesting red meat [Table 3]. A significant number of participants with bladder cancer used tobacco and smoked compared to controls. Moreover, the number of participants continuing to use tobacco products, including cigarettes, even after diagnosis was significantly more [Table 4].

Discussion

Bladder cancer is a common urological cancer and ranks as the seventh most common cancer

Table 2: Occupation of the patients with bladder cancer

Occupation	Bladder Cancer		Controls		*P*-value
	n	%	*n*	%	
Farming	38	35.5	32	30.8	0.83
Menial worker	8	7.5	13	12.5	0.75
Industry worker	26	24.3	15	14.4	<.05*
White-collared job	9	8.4	14	13.5	0.36
Business	13	12.1	5	4.8	<.05*
Homemaker	13	12.1	25	24.0	0.09
Total	107	100.00	104	100.00	

* means statistically significant.

Table 3: Association of various factors with bladder cancer

Variable	Bladder cancer		Controls		Odds ratio
	n	%	*n*	%	
Married	96	89.7	95	91.3	0.826
Recent h/o recurrent UTI	85	79.4	72	69.2	1.7172
Family h/o cancer	11	10.3	2	1.9	5.843
Diabetes mellitus	31	29.0	12	11.5	3.127
Fluid intake (1Lt/day)	25	23.4	21	20.2	0.666
Non-vegetarian diet	86	84.1	75	72.1	2.0471
Pure vegetarian diet	21	15.9	29	27.8	1.458
Red meat consumption	41	45.6	25	29.1	2.265
Alcohol consumption	35	32.7	18	17.3	1.622

Table 4: Use of tobacco products and smoking in patients with bladder cancer

Variables	Bladder cancer		Controls		*P*-value
Tobacco users	60	56.1	40	38.4	<.01*
Smoking	51	47.7	32	30.8	<.01*

among men.[5] Bladder cancer is considerably more common in men than in women (the worldwide ratio is about 3.5:1), which has been regarded as a possible indication of an occupational origin.[6] Bladder cancer has been associated with occupational exposure to industrial carcinogens.[7] As early as the late 19th century, it has been reported that unusual incidences of bladder cancer exist in the industry.[8] Case and Hosker[9] reported an exceptionally high incidence of bladder cancer in the British rubber industry. Several other agents or occupations were later shown to be associated with an increased risk of bladder cancer. Exposure to polycyclic aromatic hydrocarbons in the aluminium, coal tar and coal gasification industries was also reported to be an increased risk.[7]

Painters were reported to be at high risk for developing bladder cancer.[10-13] Several epidemiological studies reported relative risks (RRs) between 1.2 and 1.5 among painters for bladder cancer.[7] Some studies have also reported on the increased risks of bladder cancer with increasing duration of exposure to paint components.[14,15] Several epidemiological studies have also reported an increased incidence of bladder cancer among lorry drivers, taxi drivers and bus drivers.[16-18] The RRs for bladder cancer in studies of these occupational groups varied from 1.3 to 2.2. Most studies found positive trends with the duration of exposure.[7] The most likely causal agent is the constituents of the diesel exhaust emissions. However, these associations have not always been confirmed and are still debated.

A bladder cancer diagnosis is 3–4 times more common in men than women. Numerous explanations for this gender discrepancy in incidence have been offered, including disparate exposures to bladder cancer risk factors and the potential for sex steroid hormone regulation.[19] Women diagnosed with bladder cancer are more likely to have locally advanced tumours at the time of diagnosis.[20] Moreover, the female gender has been reported – albeit not uniformly – to be associated with higher risks of disease recurrence, progression and mortality after the treatment.[21-25] Dobruch *et al*.[19] reported that the gender difference in bladder cancer incidence was independent of differences in exposure risk, including smoking status. Potential molecular mechanisms included the disparate metabolism of carcinogens by hepatic enzymes between men and women, resulting in differential exposure of the urothelium to carcinogens. In addition, the sex steroid hormone pathway activity also played a role in bladder cancer development, demonstrating that both androgens and oestrogens have biological effects on bladder cancer *in vitro* and *in vivo*. Importantly, gender differences do exist in the timeliness and completeness of haematuria evaluation, with women experiencing a significantly more delay in urologic referral and less frequently undergoing guideline-concordant imaging. Correspondingly, women had more advanced tumours at the time of bladder cancer diagnosis. Interestingly, higher cancer-specific mortality was noted among women even after adjusting for tumour stage and treatment modality. Our study also shows that the incidence of bladder cancer is 2–3 times more common in men than in women.

Contemporary studies have underscored the importance of loss of heterozygosity on chromosomal arms 9p and 9q and inactivation of the p16 tumour suppressor gene as potential initiating events in the development of bladder cancer in adults.[26-28] The mutation of important cell cycle regulators, such as the p53 tumour suppressor gene on chromosomal arm 17p, has been tentatively associated with disease progression and a poor prognosis after surgical therapy for invasive tumours in adults.[29,30]

No association between alcohol and bladder cancer was found in a multicentric U.S. study of 2982 cases and a comparable number of controls.[31] On the contrary, a meta-analysis gave an overall RR for current drinkers versus non-drinkers of 1.3, a borderline significant.[32] Similarly, Pelucchi *et al*.[33] reported in a large case–control study on the issue for a population with frequent and heavy alcohol consumption revealed no consistent association between alcohol consumption and bladder cancer risk, the RRs being below unity also for six or more drinks of alcoholic beverages per day.

Tobacco smoking is a significant risk factor for bladder cancer,[34] responsible for about half the cases in both men and women.[34] The risk is generally threefold to fivefold higher in heavy smokers compared with never smokers, with a clear dose-response relationship for intensity.[35] A plateau in risk at approximately 20 cigarettes/day has also been reported in a pooled analysis of 11 case–control studies.[36] Furthermore, smoking duration has a high RR. The risk is fivefold higher in long-lasting smokers than in never smokers.[35,37,38] Although most studies focused on smoking intensity rather than duration,[35] the pooled analysis results suggested that smoking duration is the overriding factor in determining the risk of bladder cancer.[36]

Tobacco smoking has been consistently associated with bladder cancer invasiveness and grading.[39-42] These tumour characteristics strongly correlate with the papillary feature, which is crucial in the TNM classification to classify non-invasive bladder cancers into Ta or Tis. Polesei *et al*.[43] evaluated the impact of tobacco smoking on specific histological subtypes of transitional cell carcinoma of the bladder (TCC). Compared to never smokers, TCC risk was 3-fold higher in former smokers (95% CI 2.07–4.18) and more than 6-fold higher in current smokers (95% CI 4.54–9.85). TCC risk steadily increased with increasing intensity (OR for C25 cigarettes/day 8.75; 95% CI 3.40–22.55) and duration of smoking (OR for C50 years 5.46; 95% CI 2.60–11.49). No heterogeneity emerged between papillary and non-papillary TCCs for smoking intensity and duration. Still, the risk for those who had smoked for C50 years was twice for non-papillary TCC (OR 10.88) compared with papillary one (OR 4.76). The risk for a 10-year increase in duration among current smokers grew across intensity strata (P = 0.046). Conversely, the risk for a 5-cigarette/day increase in smoking intensity was relatively steady across duration strata (P = 0.18). The authors concluded that the duration of smoking outweighed the intensity in determining TCC risk, with little differences across histological subtypes. Elimination of tobacco smoking could prevent about 65% of bladder TCC.

Conclusion

In conclusion, according to the findings of this study, bladder cancer is associated with several risk factors, one of which is gender. The link between gender and bladder cancer is complicated and it is most likely influenced by various biological and epidemiological characteristics. Numerous factors, including the importance of the steroid hormone pathway, gender differences in chemical exposure, metabolic enzyme activity, disparities in dietary factors and India's consumption of alcohol and tobacco products, may explain these demographic trends. Tobacco use, cigarette smoking and industrial chemicals are the leading risk factors for bladder cancer.

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Author Contributions

Conceived and designed the analysis: SR, RBN and SCG, Collected the data: SR and SRB, Contributed data or analysis tools: SR, SRB and SCG, Performed the analysis: SR and SRB and Wrote the paper: SR, RBN and SCG.