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Review Article

Urinary bladder cancer and its associated factors – An epidemiological overview

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ABSTRACT

As per the GLOBOCAN 2018, bladder cancer was estimated to have 549,000 new cases and 200,000 deaths per year and was ranked 10th among all cancers in the world; it contributed 3.4% to the total cancer burden worldwide. In India, there were 18,921 new cases and 10,231 deaths with an incidence rate (per 10^5) of 2.4 and 0.7 in males and females, respectively, and mortality rates (per 10^5) as 1.3 and 0.3 in males and females, respectively; it is ranked 17th in incidence and 19th in mortality. The aim of the study is to report incidence rates, mortality rates, and risk factors for bladder cancer with special emphasis to Indian data. It is hypothesized that bladder cancer is likely to increase due to changing lifestyle and environmental factors that would directly impact on the disease burden. This review study on bladder cancer (ICD: C67) is based on various reports and studies published. Incidence and mortality rates are obtained from GLOBOCAN-2018, Cancer Incidence in Five Continents (CI5-XI), and Indian Council of Medical Research publication on Indian Cancer Registry database. There are case–control studies reported in literature that elucidates on risk factors that include age, gender, tobacco consumption, arsenic and nitrate in drinking water, exposure to potential carcinogens at workplace, and family history. Urinary bladder cancer has a wide spectrum of severity from the indolent low grade non-muscle invasive disease to muscle invasive disease which has poor outcomes despite treatment. There seems to be an increasing trend of this cancer in the developing countries, including India. More studies are required to be undertaken to understand this disease, with the underlining importance of public awareness. The review aims to provide some leads to formulate policies for cancer control strategies based on past findings from the literature.

Keywords: Bladder cancer, Epidemiology review, Incidence, India, Risk factors

INTRODUCTION

The global burden of cancer is estimated to have increased many folds with 18.1 million new cases of cancer and around 9.6 million deaths in 2018.[1] In the world, it is estimated that one in every five men and one in every six women will develop cancer during their lifetime. The 5-year prevalence is estimated to be 43.8 million, worldwide. Bladder cancer is ranked 10th in incidence in the world. In India, it is ranked 17th in incidence and 19th in mortality, with a varying incidence across Indian population. There are marked geographical variations in incidence of bladder cancer across the globe.[2] Similarly, there was significant variation in incidence rates of different regions in India.[3,4] Highest rates are seen in Delhi in both males and females.[3]

The primary objective of the study was to report the incidence and mortality rate of bladder cancer, in the world and in India, and conduct review of various studies published on associated factors for bladder cancer. Based on published reports and the trend observed in bladder cancer incidence, it is hypothesized that bladder cancer is likely to show an increase in number of cases due to several factors, including aging, population growth, and socioeconomic development; in emerging economies, with a westernization of lifestyle, a shift is observed from cancers related to infections and poverty, to cancers related to lifestyle.[5,6]

This study on bladder cancer (ICD: C67) being a review article, the primary source of information is from the published reports of International Agency for Research publication, GLOBOCAN-2018,[1] and Cancer Incidence in Five Continents (CI5- XI),[2] and Indian Council of Medical Research publication as NCDIR (2016)[3] and NCRP (2013).[4] Inference on associated factors was obtained from various scientific publications reported in PUBMED and SCIENCE DIRECT databases. The survival statistics is from published reports.[7]

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RESULTS

Bladder cancer

Incidence and mortality

As per the GLOBOCAN (2018) estimate, there are 18.1 million new cancer cases in the world. Death due to bladder cancer is one of the leading causes of cancer mortality in developed countries and accounts for 3.4% of worldwide cancer burden.[1] It is seen from the table that with reference to the year 2018, there will be 79.6% increase in India and 80.3% increase in the world in the number of bladder cancer cases by the year 2040 [Table 1].

Regional variations in incidence rates

Bladder cancer incidence rates were more common in men, 4-fold, than in women worldwide. It is seen from Table 2 that the incidence rates, both sexes, were highest in South Europe (male – 26.5 and female – 5.5), followed by West Europe (male – 22.5 and female – 5.1), and lowest in South America (7.0) among males and in East Asia (1.9) among females;[2] similarly, the mortality rates for men are highest in North Africa (7.5), followed by West Asia (6.5), and lowest in South America (2.5), while in women, highest rates are in North Africa (1.7) and North Europe (1.4) and lowest in East Asia (0.77).[2]

Variations of bladder cancer rates in countries across the world

Assessing the burden of bladder cancer worldwide is highly reliant on the data availability of cancer registries, thus all the registries play an important role in the studies related to bladder cancer.[8] Incidence and mortality rates show a significant variation in males and females. The rates are higher in men than women which justify the male preponderance of bladder cancer. Table 3 represents ASR of bladder cancer in males and females across countries for both incidence and mortality. The incidence rates for men are highest in Greece (40.4) followed by Lebanon (40) and Denmark (29.3). The highest mortality rate among men is in Lebanon, West Asia (15.3 per 100,000) followed by Albania (8.9) and Greece (7.8). In females, Lebanon showed highest incidence (9.4) as well as mortality rates and (3.7). Italy showed the lowest incidence (6.0) and mortality rates (1.0).[1]

Comparisons of incidence rates between selected registries across the world

Incidence of bladder cancer varies across the world as shown in male and female. It is interesting to see the comparative incidence rates among international registries.[2] For some selected countries [Figure 1], it is seen that rates are highest in Connecticut, USA, among males (25.4), whereas among females, rates are highest in Scotland (7.6); in India, rates are highest in Delhi, among urban registries.[2]

Table 1: Number of bladder cancer cases and age-standardized rates per 105 – world.

All cancers	
Number of new cases	18.1 million
Number of deaths	9.6 million
Bladder cancer	
Number of new cases	549,393
Number of deaths	200,000
Incidence rates (ASR)	
Both sexes	5.7
Males	9.6
Females	2.4
Mortality rates (ASR)	
Both sexes	1.9
Bladder cancer projection	
Year 2018 World/India	549,393/18,926
Year 2040 World/India	990,724 / 33,996

*Source: GLOBOCAN (2018).[1] ASR: Age-standardized rate

Table 2: Age-standardized rates per 10^5 in world regions.

World regions	Age-standardized rates per 100,000			
	Incidence rates		Mortality rates	
	Male	Female	Male	Female
South Europe	26.5	5.5	6.0	1.1
West Europe	22.5	5.1	5.2	1.3
North America	19.7	5.1	3.6	1.1
West Asia	16.4	2.8	6.5	1.2
Central, East Europe	16.1	3.2	6.0	0.92
North Africa	14.3	3.2	7.5	1.7
North Europe	13.9	4.2	4.2	1.4
Australia, New Zealand	8.8	2.2	3.4	1.1
East Asia	7.3	1.9	2.6	0.77
South America	7.0	23.0	2.5	0.85

*Source: GLOBOCAN, 2018[1]

Population-based cancer registry (PBCR) – India

Population registries are basis for obtaining cancer incidence, mortality, and in India, there are 30 PBCR. It is shown from Figure 2, that among males, Delhi had the highest incidence rates (7.4), followed by Thiruvananthapuram (4.9) and Kolkata (4.0), and lowest rate was in Dibrugarh (1.1); however, among females, the rate was highest in Delhi (1.7) followed by Mumbai (1.1) and Mizoram (1.1), respectively, and lowest in Barshi (0.2).[9]

Time trends across the globe and in India

Global trends

The trend over a period of 15 years (1998–2012) indicated that in males, bladder cancer incidence, in selected registries [Figure 3], showed a significant decline in rates in the UK, France, and Japan, and not in India, China, the USA, and Brazil.[2] Similarly,

among females, the trend shows that there is minimal decline in incidence rates [Figure 4], in all the countries, except in Japan where there is a marginal increase in incidence over the years.[2]

Time trends in Indian PBCR

It is interesting to see the trends of incidence rates of bladder cancer between 1989 and 2014 in major Indian registries [Figure 5]. It is evident that Delhi showed a substantial increase in rates over the years (5.2 in 1989–7.4 in 2014), whereas Mumbai showed a stable increase from 3.5 in 1989 to 4.1 in 2014 in Mumbai but Chennai showed a decline from 3.4 in 1989 to 3.0 in 2014; however, the rates in Bangalore show initially an increase, a plateau and eventually minimal change in incidence rates from 2.3 in 1989 to 2.4 in 2014.[10,11]

Hospital-based cancer registries (HBCR) – India

The frequencies of bladder cancer in different hospital registries across India are shown in Figure 6.[12] It is seen that among males, Mumbai recorded the highest number of cases (498) followed by Chandigarh (318) and Thiruvananthapuram (231), and among females, the highest was in Mumbai (80) followed by Chandigarh (58) and Thiruvananthapuram (26), indicating a male preponderance.

Tata Memorial Hospital (TMH)

Trends between 1987 and 2017

Tata memorial hospital is the oldest premier cancer hospital in India and it will be worthwhile to mention the trend of bladder cancer seen over 30-year period. From Figure 7, it is observed that in males, the number of cases increased from 122 in 1987 to 493 in 2012, and in females, from 20 cases in 1987 to 78 cases in 2012, indicating a 4-fold increase in both sexes.[13-21]

Table 3: Age-standardized rates per 10^5 in countries across the world.

World regions	Age-standardized rates per 100,000			
	Incidence rates		Mortality rates	
	Male	Female	Male	Female
Lebanon	40.0	9.4	15.3	3.7
Greece	40.4	4.5	7.8	0.9
Denmark	29.3	7.7	4.9	1.9
Belgium	27.7	6.4	5.4	1.3
Spain	27.5	5.6	6.6	1.1
Italy	27.4	6.0	4.9	1.0
Hungary	26.9	9.1	6.8	2.0
Albania	26.8	6.4	8.9	2.0
Germany	26.4	6.3	4.8	1.4
The Netherlands	25.8	7.9	4.8	1.5

*Source: GLOBOCAN, 2018[1]

Human Development Index (HDI)

Based on the classification of HDI, it was observed that India belonging to the medium HDI, showed the lowest incidence rates (1.5) and China belonging to countries with very high HDI, also showed lowest incidence rates (3.7), as shown in Table 4.[1] Further, it is seen that incidence and mortality rates were highest for very high HDI countries and lowest for low HDI countries. The rates were 10.5 and 2.4 in very high HDI and low HDI countries, respectively, indicating 5-fold difference between them.

Migration effect and Ethnic differences

The incidence rates for bladder cancer among males in the USA, San Francisco Bay Area, Japanese (11.8), San Francisco Bay Area, Chinese (8.6), and San Francisco Bay Area, Filipino (5.1) were different from that observed in the USA host population, San Francisco Whites (19.5), and among females in the USA, this indicated that migration had probably no significant effect on the occurrence of bladder cancer, over the years in both the sexes.

The incidence rate observed among American-White males (20.8), was higher than American-Black males (118), and similarly, American-White female (5.4) rates were higher than American-Black females (3.7), indicating that there was a ethnic differences in occurrence of bladder cancer between the groups.[2]

The continuing difference in the incidence of cancer many generations after migration favors the concept that living in the host country alone is not sufficient for a population to modify the risk of cancer to match the level of the host population. The effect of migration (if present) can be explained by known associated factors of a population along with some environmental factors and genetic susceptibility.

Diagnostic methods, treatment modalities, and survival rates

Diagnosis and treatment

Bladder cancer investigation involves routine investigations such as routine hemogram, biochemistry, urine cytology, imaging, as well as pathology tests. Imaging modalities include

Table 4: Age-standardized rates for bladder cancer by HDI.

HDI	Incidence rates	Mortality rates
Very high HDI	10.5	2.5
High HDI	4.3	1.7
China	3.7	1.6
Low HDI	2.4	1.6
Medium HDI	2.3	1.2
India	1.5	0.82

*Source: GLOBOCAN, 2018.[1] HDI: Human Development Index

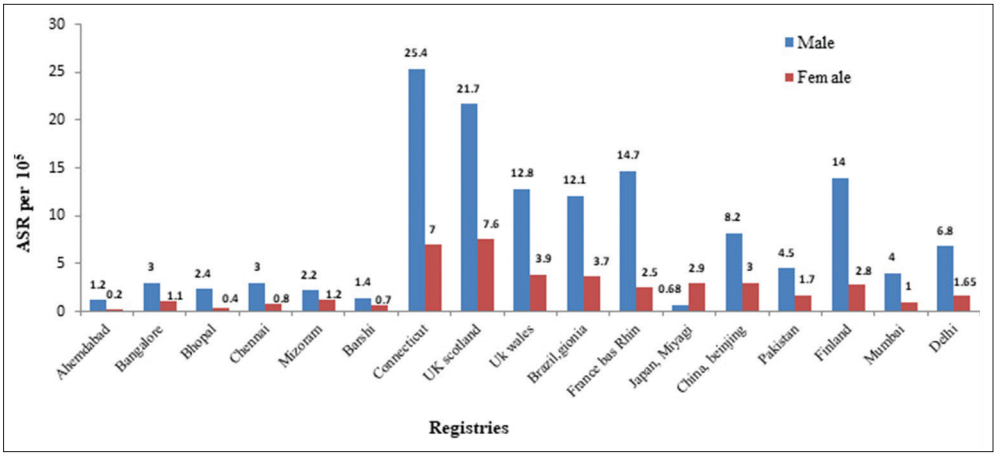

Figure 1: Global comparison of age-standardized incidence rate (ASR) per $10^5$of bladder cancer. *Source: C15-Vol XI.[2]

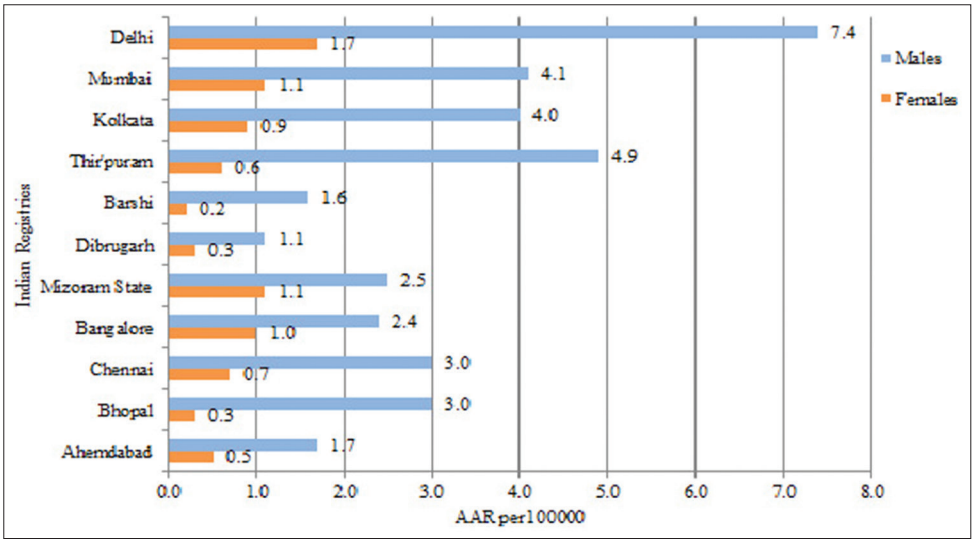

Figure 2: Age-adjusted incidence rate (AAR per 10^5) in Indian PBCRs. *Source: NCDIR.[9]

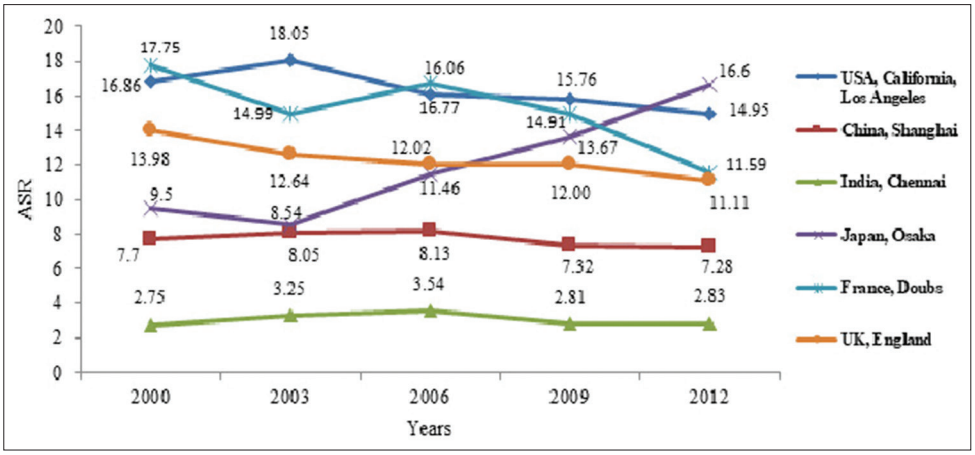

Figure 3: Trends in incidence rates (ASR per 10^5) in selected registries – world (1998–2012) – males. *Source: C15-Vol XI.[2]

computerized tomography, magnetic resonance imaging (MRI), and ultrasonography. Abdominal, transrectal, transvaginal, and transurethral sonography are used specifically to stage bladder cancer. Investigation techniques involve urine tests, cystoscopy,

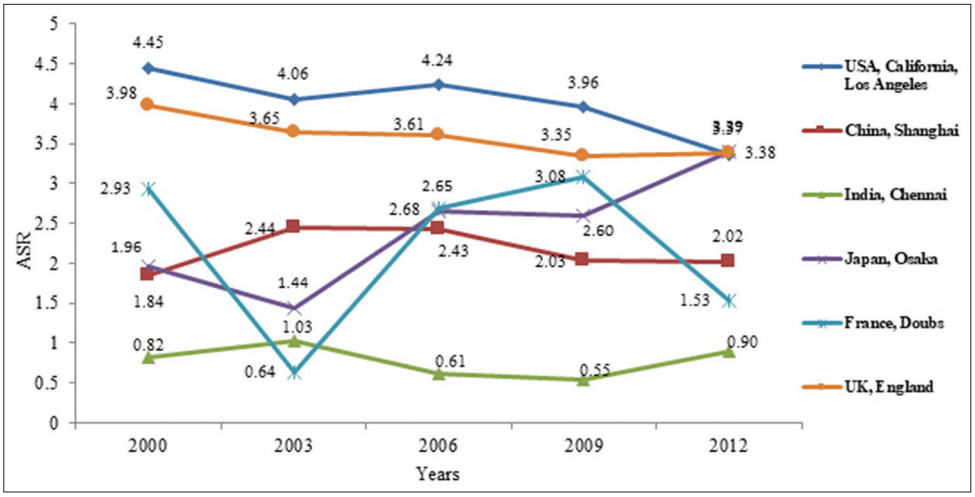

Figure 4: Trends in incidence rate (ASR per 10^5) in selected registries – world (1998–2012) – females. *Source: C15-Vol XI.[2]

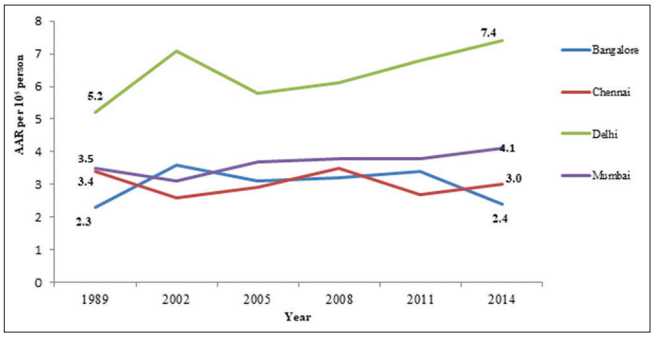

Figure 5: Trends in age-adjusted incidence rate (AAR per 10^5) of bladder cancer in Indian PBCR registries: 1989–2014 – males. *Source: NCDIR.[10,11]

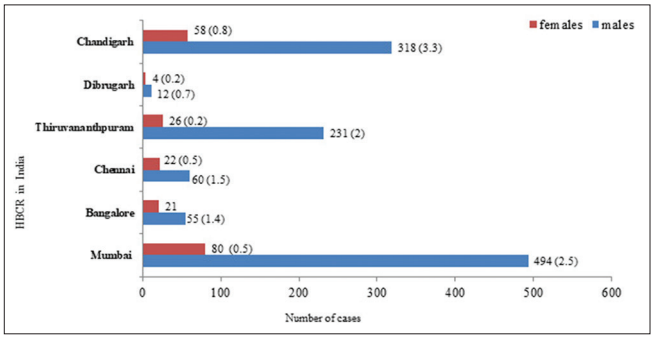

Figure 6: Number of bladder cancer cases by gender in HBCRs in India (2012–2014). *Source: NCDIR[12] numbers in () indicates % of all cancer.

and transurethral resection (TURBT) which are both diagnostic and therapeutic;[22] in one of the earliest studies, MRI had showed 82% sensitivity, 62% specificity, and 73% accuracy.[23]

Treatment for bladder cancer and its management depends on extent of disease and guidelines on treatment (TURBT)are already published and available in literature.[22] Post-TURBT

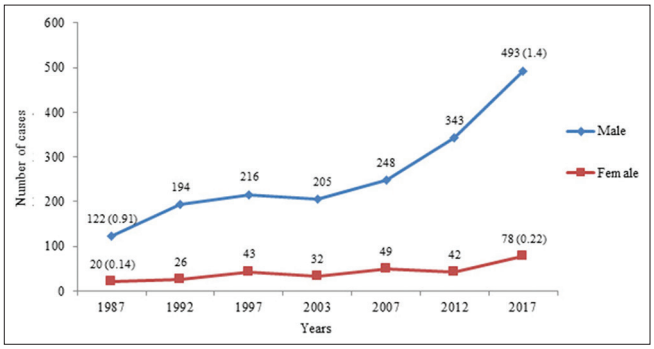

Figure 7: Trends in distribution of bladder cancer in Tata Memorial Hospital: 1987–2017. *Source: HBCR TMH Mumbai;[13-21] figure in () is % of all cancer cases.

adjuvant intravesical therapy is indicated depending on the risk stratification and staging. Intravesical therapy involves chemotherapy and Bacillus Calmette–Guerin. Radiotherapy is also suggested along with chemotherapy. Muscle invasive bladder cancer may require surgical removing the bladder (cystectomy) and lymphadenectomy (lymph node removal) along with urinary diversion.[22]

Cancer survival rates

Survival statistics is often used to infer a patient's prognosis (chance of recovery). However, in cancer usually, a 5-year relative survival rate is considered. The SEER database does not group bladder cancer by AJCC TNM stages (which are used mostly in clinical practices). Instead, it groups cancers into localized, regional, and distant sites; it was reported that patients with localized, *in situ*, regional spread, and distant disease showed 5-year survival of 70%, 96%, 36%, and 5%, respectively;[22] for combined stages, survival was 77%.[22] The 5-year absolute survival in Indian population was lower than other Asian countries as China, Singapore, etc.[24]

Because of variable representation of *in situ* tumors, comparison of survival across countries for bladder cancer is difficult to establish. In Europe, the average 5-year survival rate was 69%, ranging from 79% in Malta and 49% in Scotland.[24] A retrospective audit of all patients registered as urinary bladder cancer in TMH in 2013 was reported recently. The estimated 5-year overall survival and disease-free survival in patients who had RC with PLND were 63% and 57%, respectively (RC – radical cystectomy and PLND – pelvic lymph node dissection).[25] In Europe, the 5-year age-standardized relative survival rate of all bladder cancer was around 70%, the range between individual countries was approximately 60–70%.[26]

Treatment costs

The treatment cost increases because of high rates of recurrence and associated intensive surveillance strategies and expensive treatment cost to improve quality of life and combat with the side effects of cancer directed treatment.[27-29]

Associated factors

Risk factors can be termed as modifiable risk factor, namely, smoking, weight or not-modifiable risk factor, namely, age and family history.

Modifiable risk factors

Tobacco consumption

Tobacco consumption is a significant risk factor for bladder cancer. Many studies have reported on tobacco consumption and risk of bladder cancer. About 50% of cancers are tobacco-related cancers in India.[30] Risk for smokers is 3–4-fold higher compared to non-smokers and is estimated to cause 31% of bladder cancer deaths among men and 16% among women.[31,32] It is reported that 4-aminobiphenyl is the most important carcinogen in cigarette smoke, besides many other carcinogenic substances.[32] Black tobacco (burnt) is considered more carcinogenic because of a greater concentration of nitrosamines, biphenyls, and aryl amines.[33] In a meta-analysis from a large cohort study in the USA, smoking of opium showed an elevated risk and so was cannabis;[34,35] in another cohort study from the USA, the hazard ratio in ex-smokers was 2.22 and 4.06 in current smokers.[36] The excess risk of bladder cancer in males, observed in a study from Spain, attributed to cigarette smoking, rather than occupational/environmental exposures, and risk increased with years of duration and frequency of smoking.[33]

Exposures at workplace

Industrial exposure to aromatic amines and carbon black dust, potential carcinogens, used in the dye industry has been linked to incidence of bladder cancer chemicals like aromatic amines.[37]

It was reported that there was a higher risk for manufacturers of rubber, leather, textiles, steel, metal, paint products and the printing companies,[38] painters, machinists, printers, hairdressers, construction workers and truck drivers,[39] benzamine, used in rubber industry and dye production,[40] hairdressers and barbers, due to the use of dyes[41,42] and exposure to azo dyes.[43] Smoking and workplace exposures can act synergistically to cause bladder cancer. Smokers who work with carcinogens chemicals have a significantly higher risk of bladder cancer. The rise in incidence and mortality among women in East Europe region is due to the prevalence of cigarette smoking, while the decrease in mortality rates in some of the Western countries is attributed to the decreasing prevalence of the use of tobacco.[44]

Arsenic and nitrate in drinking water

It is known that drinking water contains some fraction of arsenic content and poses no threat if it is within the prescribed limits;[45] however, the risk of bladder cancer gets elevated if arsenic concentration exceeds 300–500 μg/L.[46] There is an uncertainty of arsenic content at lower levels.[47,48] A known chemical, nitrate in drinking water showed elevated risk in postmenopausal women.[49]

Less fluid intake

Although the findings of fluid intake and bladder cancer are inconsistent, still a few studies suggest that drinking a lot of fluids, especially water, every day lowers the risk of bladder cancer. Drinking more water helps to dilute urine and reduces the contact time and simultaneously removing excess toxins through urination.[50,51]

Not modifiable risk factors

Age

Although bladder cancer can occur at any age, and many demographic studies have shown that individuals' aged ≥65 years have 11 times higher incidence than those younger than 65 years.[22] Despite this, the treatment decisions may not be solely based on age besides other factors that can affect patient survival outcomes.[52]

Gender

Bladder cancer is more common in men and the possible reason in gender-based disparity in incidence and mortality is the difference in hormonal pathways. The time of diagnosis besides primary care plays an important role in the development of urinary bladder cancer.[53,54]

Infections and chronic bladder irritation

Urinary infections, bladder and kidney stones, longer placement of bladder catheter, and chronic bladder irritation have been linked to bladder cancer. The association of urinary bladder cancer with recurrent urinary tract infection (UTI) reported in a case–control study from the Netherlands, showed an odds ratio of 6.6 in males and 2.7 in females;[55] however, another case–control study did not report any association between UTIs and development of BC[56] though a limited number of episodes of UTI treated with antibiotics were reported to be associated with decreased bladder cancer risk.[55]

Infection with schistosomiasis hematobium

Schistosomiasis (or bilharziasis), a parasitic infection to bladder, in squamous cell cancers is a risk factor since the carcinogen-metabolizing enzymes were increased soon after infection.[57,58] In North Africa, high incidence was attributed to the parasite , while in Egypt and Tanzania, it was reported that control of parasite decreased cases of bladder cancer by improving the sanitization and hygiene, respectively.[59,60]

Genetics and family history

Family history of bladder cancer is considered a higher risk. The cause probably is lower penetrating DNA variants and many such pathways were reported which influences risk through one or more different cancer pathways.[61-63]

High alcohol consumption was shown to be linked to bladder cancer;[64,65] smokers with a higher cumulative arsenic intake had elevated risks of bladder cancer.[66]

Pioglitazone, an antidiabetic agent of the thiazolidinedione class, which is broadly used for glycemic control in patients with type 2 diabetes mellitus, has been reported to increase the risk of bladder cancer as well. The meta-analysis that included 12 studies indicated that pioglitazone was associated with 14% increased risk of bladder cancer.[67]

Protective factors

Studies have shown the possible role of folate in the relationship between arsenic and bladder cancer, among other outcomes.[68] It was reported that arsenic inhibited indirectly sulfhydryl containing enzymes and interfered with cellular metabolism and inhibited enzymes with antioxidant function.[69]

Adherence to a western dietary habits as fried food and red processed meat, though had higher risk, potentially beneficial substances from fruits and vegetables such as antioxidants, phenols, and flavonoids and phytochemicals showed protective effect.[70-72]

Studies have shown prevention of bladder cancer in those who consumed diet rich in plants and rich in isoflavones.[73,74] An Indian cohort study suggested possible use of supplementation as prophylactic agents for prevention and treatment of bladder cancer.[75]

CONCLUSION

Bladder cancer is a highly lethal malignancy and the increasing trends of bladder cancer are alarming, especially in the developing countries including India, and thus, there is a strong need to identify and implement effective prevention and treatment strategies. Bladder cancer, ranked as 10th most common cancer worldwide, accounts to 549,000 new cancer cases annually. Reduction in risk by modifying lifestyle habits, consumption of diet rich in isoflavones, reduced meat eating, control of arsenic content in drinking water, and provide protection for industrial workers and other workers where there is more exposure like dyes will probably help in reducing the burden of bladder cancer. The epidemiological studies are still inadequate with respect to India.

In summary, creating awareness of early signs and symptoms of bladder cancer and subsequently organizing screening camps for the high-risk groups will probably be key for better outcomes in terms of control of bladder cancer.

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Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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