



Essentials of bladder cancer worldwide: incidence, mortality rate and risk factors

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Abstract

Bladder cancer (BC) is the sixth most common cancer in the world. An increase in the incidence and recurrence of BC has led to massive pressure on health care systems. Studies have shown that the geographical and ethical distributions of BC are variable in different parts of the world. However, most studies have focused more on clinical challenges and treatment strategies in BC management. Due to the limited number of studies conducted on the incidence rate, mortality and risk factors of BC worldwide, it is necessary to carry out studies in these areas. Therefore, the aim of this study was to determine the global incidence rate, mortality rate and risk factors for BC.

Keywords

Bladder cancer, Incidence, Mortality, Patient, Risk Factor, World

Introduction

BC is the 6th most common cancer in the world, the 7th most common cancer in men, and the 17th most common cancer in women (Burger et al., 2013). The increase in the incidence rate of BC and its recurrent nature have led to massive pressures on health care systems (Sievert et al., 2009). The American Cancer Society in 2017 estimated there to be 79,030 new cases of BC and 16,870 deaths from it in the United States ([Internet], 2017). The rate of BC diagnosis in men is 4 times greater than in women and the 5-year survival rate varies from 40-80% (Ranasinghe et al., 2012). Nevertheless, during the last two decades, BC rates have been steady in men while there has been a 0.2% annual increase in women ([Internet], 2017).

Research findings have shown that the geographical and racial distributions of BC varies in different parts of the world; for instance, it is more dominant in American countries than in Asian countries (Colombel et al., 2008). Significant geographical changes in the incidence rates of BC indicates that various factors influence the increase of BC. However, most studies in this field have focused more on clinical challenges and treatment strategies in BC management (Feifer et al., 2011; Simone and Gallucci, 2012; Sylvester, 2011). Due to the limited number of studies conducted on the incidence, mortality and risk factors of BC worldwide, it is necessary to conduct studies in these areas. Therefore, the purpose of this study was to evaluate the incidence, mortality rate and risk factors of BC worldwide.

Methods

This review study was conducted on all studies published in English and before January 2017. The following databases were searched: PubMed, Embase, Scopus, and Science Direct. The search strategy included key words of "bladder cancer", "epidemiology", "incidence", "mortality", "risk factors", and "world". The search strategy was tailored due to the requirements of each database. An advanced search was also carried out in cancer-related websites to access specific information for each country.

Results

The incidence and mortality rates of BC in the world

The incidence of BC varies considerably according to the geographical area, with the highest age-standardized incidence rate of 17.5 cases in Belgium (Jemal et al., 2010), 16.6 in Lebanon (Shamseddine et al., 2014), 15.8 in Malta (Torre et al., 2015), 15.2 in Turkey (Antoni et al., 2017), and 14.4 in Denmark (Ferlay et al., 2013), per 100,000 people. Also, the 5 countries with the highest standardized

incidence rate in males were: Belgium- with 31 (Jemal et al., 2010), Lebanon- with 29.1 (Shamseddine et al., 2014), Turkey- with 28.7 (Antoni et al., 2017), Armenia- with 27.3 (Mahdavifar et al., 2016), and Malta- with 26.9 (Torre et al., 2015) cases, per 100,000 people. Also, the 5 countries with the highest age-standardized incidence rate of BC in women were: Hungary- with 7.4, Denmark- with 7 (Ferlay et al., 2013), Norway- with 6.4 (Jemal et al., 2011), Belgium- with 6.2 (Jemal et al., 2010), and Malta- with 6.2 (Torre et al., 2015) cases, per 100,000 people. The rate of BC in males is 4 times higher than in females (Kirkali et al., 2005).

The standardized mortality rate of BC varies from 2-10 for every 100,000 per year in men and 0.5-4 for every 100,000 per year in women (Mahdavifar et al., 2016). BC in women is not among the ten most common cancers. Therefore, it is expected that for 2016, the mortality rate of BC in men would be higher than in women; indeed, reports indicated 11,820 cases in men and 4,570 cases in women (Scosyrev et al., 2009). The comparative higher rate of BC in men versus women could be due to differences in smoking habits and occupation (which are two common risk factors for BC) (Freedman et al., 2011). However, over the past two decades BC rates have been steady in men, but have risen by 0.2% in women (Burger et al., 2013).

Studies have shown that with increasing number of deliveries, the incidence of BC decreases. Also, BC rates in women who have had a single delivery are lower than those who have not yet given birth; pregnancy-induced hormonal changes seem to act as a protective factor in women (Dietrich et al., 2011). Indeed, the findings of an animal study showed that rats treated with androgen hormones were more likely to have bladder tumors than rats treated with estrogen hormones (Reid et al., 1984). This finding, therefore, suggests that some androgenic hormones stimulate oncogenesis while estrogen hormones are protective (Davis-Dao et al., 2011). Furthermore, BC rarely occurs at the ages of 40-50; the average age of BC diagnosis is 69 in men and 71 in women (Letašiová et al., 2012).

The incidence of BC has recently decreased in some countries, which may be due to differences in recording or reporting low-grade tumors (Jemal et al., 2010) and the reduction of exposure to risk factors (mainly due to reduced smoking and improved occupational health) (Bosetti et al., 2011). However, there is no similar trend of BC incidence. For instance, the age-standardized rate of BC has declined in the United Kingdom while at the same time it has remained constant in America among white Americans (Burger et al., 2013). BC is the 4th most common cancer in men in the United States (Koay et al., 2011). The incidence of BC in white men is twice that of black men. However, the prognosis of BC in black patients is worse than white patients (Yee et al., 2011). The highest standardized mortality rates were 6.6 in Turkey (Antoni et al., 2017), 6.5 in Egypt (Chavan et al., 2014), 6.3 in Iraq (Mahdavifar et al., 2016), 6.3 in Lebanon (Mahdavifar et al., 2016), and 5.2 in Mali (Chavan et al., 2014), per 100,000 people. The 5 countries with the highest standardized mortality rates in

males were: Turkey- with 12.8 (Torre et al., 2015), Iraq- with 11.4 (Mahdavifar et al., 2016), Armenia- with 1.3 (Pakzad et al., 2015), Egypt- with 11.1 (Chavan et al., 2014), and Lebanon- with 11 cases (Mahdavifar et al., 2016), per 100,000 people. The 5 countries with the highest standardized mortality rates among women were: Mali- with 4.4 (Chavan et al., 2014), Malawi- with 4.4 (Antoni et al., 2017), Malta- with 4.3 (Jemal et al., 2010), French Polynesia- with 2.9 (Mahdavifar et al., 2016), and Iraq- with 2.9 (Mahdavifar et al., 2016), per 100,000 people (Mahdavifar et al., 2016).

BC risk factors

1-Smoking

Tobacco use is one of the primary and common risk factors of BC in the world, especially in the United States, and it has also become a concern in developing countries (Letašiová et al., 2012). Other BC risk factors include use of pipe and secondhand smoke. The findings of a meta-analysis study showed that the risk of developing BC in smokers was 3 times higher than non-smokers. Findings from studies have shown that there is a direct correlation between the number of cigarettes, the duration, and severity of smoking with the risk of BC in both sexes ([Internet], 2017; Escudero et al., 2011; Freedman et al., 2011). A study by Zeegers et al. which assessed the etiological fraction of smoking showed that cigarette consumption is responsible for 23% of BC cases in women and 50% of cases in men (Zeegers et al., 2004). The precise mechanism of BC induction by the use of cigarettes is not known but it seems that the risk of BC is related to some of the chemicals found in cigarettes, such as naphthylamine-2, aminobiphenyl-4 and polycyclic aromatic hydrocarbons (Baris et al., 2009). Tobacco flares, including nitrosamine, polycyclic aromatic hydrocarbons, 2-naphthylamine and other aromatic amines, all playing a role as direct mutagenic agents in BC formation and in the release of at least 69 carcinogens (Kiriluk et al., 2012). Notably, the main pathways for inducing cancer in smokers are through the formation of adduct DNA and via genetic damage, which cause changes in specific cellular pathways and consequently uncontrolled cell growth and inhibition of tumor growth inhibitory mechanisms (Alberg and Hébert, 2009).

2-Occupational factors

2-1. Aromatic amines

The most important risk factor for developing BC after smoking is exposure to aromatic amines, which include 2-naphthylamine, 4-aminophenyl, and benzidine (García-Pérez et al., 2009). These compounds are found in dyes, chemical compounds, rubber, hair coloring dyes, cigarette smoke, plastics, vehicle smoke, paint products, and fungicides (Letašiová et al., 2012). Findings of occupational cohort studies have indicated an increased risk of non-smoking BC in individuals exposed to aromatic amines, including people working in

different industries such as rubber and leather producers, weavers, colored product workers, and printing companies (Carreón et al., 2010; Pira et al., 2010). Recently, due to increased awareness by individuals about safety principles, the extent and pattern of exposure to occupational hazards have improved (Kogevinas M, 2014).

Occupational exposure to aromatic amines occurs mainly through skin contact (García-Pérez et al., 2009) and are correlated with increased risk for BC. Findings of two cohort studies showed that the risk of BC increased in individuals exposed to 1-naphthylamine, 2-naphthylamine, benzidine, and 4-aminobiphenyl over a period of 60 years (Case and Hosker, 1954; Melick et al., 1955). Findings from a case-control study by Samniac et al. showed that the risk of BC in men employed in the printing industry as machine operators (case group) was significantly higher than that for the control group (Colt et al., 2010). Also, Case et al. found that the BC risk in British staff exposed to 2-naphthylamine was 200 times higher than other staff (Case and Hosker, 1954). Moreover, the findings of a cohort study performed on 11,000 cases of rubber industry workers also showed that the standardized mortality ratio (SMR) of BC in maintenance, transportation, and general staff increased in this industry (159, 95% CI 92-279). A study in 171 workers in the rubber industry showed that 19 cases of BC were diagnosed in the workers (Golka et al., 2004). In fact, 4-aminobiphenyl (aromatic amine) is as a carcinogen of smoke tobacco which is used in the rubber industry too and benzidine (in dyed products used in the rubber industry) is the most important carcinogenic aromatic amine associated with bladder damage. Moreover, the results of a cohort study of 784 workers in China showed that the risk of BC in these individuals increased 35-fold (Gago-Dominguez et al., 2001). Those individuals, especially barbers, who are exposed to hair dye and cosmetics are more prone to have BC (Letašiová et al., 2012). As the findings of the Golka study showed, the risk of BC has increased (Odds Ratio (OR): 1.9; 95% CI: 1.1-3.3) in people who regularly use hair colors at least once a month for 1 year or more (Golka et al., 2004). Also, for people who regularly use hair color at least once a month for 15 years or more, the risk of BC is 3.33 times higher than other people (95% CI: 1.3-4.8) (Golka et al., 2004).

2-2. 4,4'-Methylene-bis(2-chloroaniline) (MBOCA)

One of the chemicals used as a therapeutic agent in polyurethane products is 4,4'-methylene-bis(2-chloroaniline) (MBOCA). The highest risk of exposure to MBOCA is in workers who absorb MBOCA vapor or dusts through the skin, or inhale MBOC dusts (Chen et al., 2014). Findings from studies have shown that moderate and chronic exposure to MBOCA can cause bladder tumors (Chen et al., 2014; Kiriluk et al., 2012; Lin et al., 2013).

3-Genetic susceptibility

People with family members having BC are at greater risk for BC since BC risk is twice as high in first degree relatives than in other patients (Burger et al., 2013).

One of the reasons for this correlation is that family members are exposed to the same risk factors (such as those who are exposed to tobacco smoke). Among the risk factors of BC risk factors, hereditary genetic changes (such as changes in acetylator N-acetyltransferase 2 (NAT2) and glutathione S-transferase mu1 (GSTM1)-null genotypes) make it difficult to decompose some of the toxins in the body and thus lead to BC (Kiemeny et al., 2010; Volanis et al., 2010).

4-Nutritional factors

Lack of adequate fluid intake, especially water, increases the risk of BC. Bladder vacancy seems to cause chemical accumulation due to delay in the removal of bladder waste, leading to increased risk of BC. In other words, increasing the amount of fluid intake (e.g. by diluting the urine) and increasing the micturition will reduce exposure of the urothelial tissue to carcinogens (Ros et al., 2011). Vitamin D is one of the complementary ingredients which may reduce cancer incidence. The findings of a prospective study on male smokers showed that BC risk has a significant relationship with vitamin D deficiency (Garland et al., 1985). The findings of several case-control studies also showed that the risk of BC in subjects receiving vitamin D and those exposed to ultraviolet B (UVB) was significantly lower than in control group (Brinkman et al., 2010; Chen et al., 2010; Mohr et al., 2010).

Overall, despite all the supporting evidence, there is a need for more clinical trials to confirm the role of vitamin D in reducing BC incidence. Taking nutritional supplements containing aristolochic acid (from the Aristolochia family) is also associated with an increased risk of BC (Chen et al., 2013). Aristolochic acid contains wild ginger, which is one of the main causes of kidney damage and urinary tract cancer (Chen et al., 2012). Despite its prohibition, it is still used in China as an herbal remedy for weight loss, rheumatism, and diminishment of menstrual disorders (Clyne, 2013).

Additionally, the type of ingredients in drinking water, such as arsenic and disinfectants, can affect BC risk. Among the potential sources of arsenic, we can point to water, cigarette, air pollution, glass products, and insecticides (Kiriluk et al., 2012). Arsenic in drinking water is a risk factor for BC in many parts of the world (Naranmandura et al., 2011). The chances of exposure to arsenic depends on the living conditions, such as whether they receive their drinking water from public and sanitary systems; this possibility is low in accordance with the standards defined by arsenic (Fernández et al., 2012). The findings from a case-control study in Main-New Hampshire-Vermont showed that there is a link between low to moderate levels of arsenic in drinking water and the risk of BC; the daily BC rate in these individuals is 20% higher than the United States population ([Internet], 2017). Another source of arsenic is arsenic-based pesticides widely used on products (e.g. apples, tomatoes, and cornelian cherries) between the 1920s and 1950s (Jomova et al., 2011; Letašiová et al., 2012).

The concentration of arsenic in groundwater and soil surface is high in countries such as China, Hungary, India, and Hungary (Peralta-Videa et al., 2009). Studies show that long-term consumption of water containing high levels of arsenic (greater than 0.2 mg/L) is associated with BC, while concentrations less than 0.1 do not show a clear correlation (Meliker et al., 2010; Steinmaus et al., 2003). Findings of a study in Bangladesh showed that mortality risks doubled after consumption of arsenic-contaminated water (Burger et al., 2013). In a recent Chilean analysis, it was found that after 20 years of discontinuation of arsenic-contaminated water use, mortality rates were significantly higher in contaminated areas (Hazard Ratio (HR): 3.6; 95% CI: 3-4.7) (Fernández et al., 2012). The mechanism of BC induction through arsenic is uncertain, but it seems that arsenic increases the risk of BC through indirect inhibition of sulfhydryl-containing enzymes, interference with cytotoxic metabolism, genotoxicity, and inhibition of enzymes that play an antioxidant role (Tapio and Grosche, 2006). Importantly, p53 protein plays a role in the development of BC. Indeed, findings from a study in Taiwan showed that individuals exposed to arsenic have a gene mutation in the p53 gene in codon175 and a transition occurring in 9 and 10 section (Letašiová et al., 2012).

Other potential carcinogens include nitrite and nitrate. Human contact with nitrite and nitrate is mainly due to food intake; nitrates are found especially in vegetables, processed meat, and contaminated water. The findings of studies on the relationship between excessive consumption of nitrate and BC induction are unclear (Chiu et al., 2007; Ward et al., 2003; Zeegers et al., 2006). A study in Slovakia showed that no correlation was found between nitrate and kidney cancer or bladder cancer (Gulis et al., 2002). However, a study on more than 40,000 women in Iowa showed that there is a positive correlation between high concentration of nitrates in drinking water and the risk of developing BC in these areas (W., 2001). Other cohort study findings on 21,977 old women in Iowa, who used a high concentration of nitrate water for more than 10 years, showed that the incidence of BC in them was 2.8 times greater than in other women (Weyer et al., 2001). Other studies indicate that nitrosamines may act as a carcinogens since they are a byproduct of urinary tract infection (and nitrite-producing organisms); however, there is not enough evidence to support this study (Botelho et al., 2011). Therefore, given the controversial findings in this regard, further studies are needed to confirm the effect of nitrates on increasing BC incidence.

5-Age, sex, ethnicity, race, and socio-economic status

In terms of age, BC risk increases in the elderly; in fact, 90% of BC cases occur in people over the age of 55 while the average age for BC diagnosis is 73 (Kiriluk et al., 2012). In terms of sex, the incidence of BC in men is higher than in women; some studies have reported the incidence in men to be 4 times higher. However, mortality rates in women are higher than in men (Ranasinghe et al., 2012). It seems that one main reason for the lower incidence of BC in women is the lower prevalence of smoking and lower occupational risk in women (Burger

et al., 2013). The reasons for the higher mortality rate in women, however, remains unclear.

The risk of BC is two times higher in Whites than in African Americans. In the United States, the age-standardized rates for African Americans are 13 per 100,000 and for Whites are 22 per 100,000 (Yee et al., 2011). BC rates are lower in Asian Americans, Indian Americans, and Spaniards than other races. The causes of these differences are not well-defined (Scosyrev et al., 2009). Additionally, the findings from the Datta study showed that there is a significant relationship between marital status and survival rate of BC, independent of other factors like race, socioeconomic status, diseases or aggressive treatments; indeed, survival rates in married men are higher than in unmarried ones (Datta et al., 2009). Findings of the Koroukian study showed that there is a relationship between low socio-economic status and the unsustainable survival of BC (Koroukian et al., 2010). It seems that lack of access to healthcare and health services, as well as the increased risk of smoking in groups with a low socioeconomic status, account for the connection.

6-Medical conditions

One of the causes of BC in developing countries, especially the Middle East, is infection with *Schistosoma haematobium*. A study in Egypt showed that 82% of BC patients carry *S. haematobium* eggs in their bladder. It should be noted that in young people with eggs in their bladders (positive eggs), the tendency to spread the tumor is greater than others (Botelho et al., 2009). In addition to *S. haematobium*, other species (including *S. Mansoni* and *S. Japonicum*) also contribute to the development of schistosomiasis in humans. *Schistosoma* is implanted in the bladder tissue, causing a chronic cyst and eventually BC ([Internet], 2017). Schistosomiasis is predominantly spread in African countries and some Asian countries, such as Iran, Iraq, Syria, Lebanon, Saudi Arabia, southern Portugal, Greece, and India (Mumbai). Infection rates have been reported in some countries, such as Egypt, up to 95%. In this regard, in Egypt, the incidence of BC accounts for 16.2% of all cancers, while in America BC accounts for only 7% of all cancers in men (Kiriluk et al., 2012). One of the other medical causes of BC is infection with the Human Papilloma Virus (HPV). Various studies in different parts of the world indicate the existence of an association between anogenital HPV types 16 and 18 with BC (Husain et al., 2009; Noël et al., 1994) since HPV16 and HPV18 encode E6 and E7 oncoproteins. The E6 and E7 proteins are able to bind to cellular anti-tumor factors, such as p105RB and p53, and finally by inhibiting the function of these proteins they cause permanent cell life (Li et al., 2011). HPV types are classified into 3 classes based on their oncogenic potential: low risk (types 6, 11, 42, 43, 44, 59, 66, 68 and 70), moderate risk (types 30, 31, 33, 34, 35, 39, 40, 49, 51, 52, 53, 57, 58, 63 and 64), and high risk (types 16, 18, 45 and 46). High and moderate risk types with other cofactors are responsible for more than 90% of cases of malignant anogenital tumors (Kiriluk et al., 2012).

The precise mechanism of carcinogenesis due to high-risk infections, especially of HPV16, is not entirely clear. HPV is capable of producing Acuminatum Condyloma (an anogenital ulcer) in the genital and bladder regions. It is a sexually transmitted disease and can be a risk factor for plate changes in the bladder epithelium, resulting in bladder carcinoma (Agliaño et al., 1994; Baithun et al., 1998; Karagas et al., 2005). Findings by Barghi et al. (Barghi et al., 2012) and Youshya et al. (Youshya et al., 2005) have indicated that the prevalence of HPV in BC patients are 35.6% and 34.7%, respectively. Furthermore, a meta-analysis study showed that HPV, especially type 16, may play a role in BC (Li et al., 2011). Radiation-related malignant tumors also usually cause secondary cancers after treatment of primary tumors. Patients undergoing radiation therapy for pelvic malignancies, including prostate, endometrial and cervical cancer, are prone to BC risk (Brown et al., 2010; Burger et al., 2013). Indeed, the standardized BC rate increased in patients with prostate cancer treated with radiation (HR: 1.7; 95% CI: 1.57-1.86) (Abern et al., 2013). Nevertheless, BC associated with radiation therapy has been significantly reduced due to advances in radiation therapy techniques and limiting organs exposed to radiotherapy (Kiriluk et al., 2012).

In spite of the use of alkaline agents, including chemotherapy drugs for the treatment of malignancies and rheumatologic diseases, only oxazaphosphorines are associated with BC and hemorrhagic cystitis. One of the most famous oxazaphosphorine drugs is cyclophosphamide (Cytosan), which is mainly used in lymphoma and leukemia (Emadi et al., 2009; Monach et al., 2010). Taking long-term chemotherapy drugs, such as cyclophosphamide, gives rise to acrolein (a cyclophosphamide metabolite) which stimulates the bladder and increases the risk of BC. Therefore, in order to prevent bladder excitation in these patients, it is recommended that they receive a lot of fluids after taking such drugs (Figueroa et al., 2015; Monach et al., 2010). The infection with BC is higher in patients treated with immunosuppressive drugs than in other patients. In this regard, findings from a retrospective study on 3,000 recipients of kidney transplant showed that the risk of developing BC in these patients increased by 3.3 times due to the use of suppressive drugs (Dietrich et al., 2011). Findings of other studies also showed that the risk of BC in kidney transplant patients is higher than that of end-stage renal disease (ESRD) (Miao et al., 2009; Vajdic et al., 2006). This could be due to long-term use of oral glucocorticoid drugs. Further studies are underway to investigate the mechanism of BC infection by immunosuppressive drugs.

Additionally, the use of anti-diabetic medications, such as pioglitazone (Actos), for a long period of time (more than 1 year) is also associated with an increased risk of BC (HR: 1.4; 95% CI: 1.03-2.0) (90). The findings of a cohort study indicated that the incidence of BC was increased with long-term intake of pioglitazone in diabetic patients (HR: 2.2; 95% CI: 1.3-8.3) (Lewis et al., 2011). Therefore, the Food and Drug Administration has forbidden the use of this drug in diabetic patients with BC, and recommends caution when using this drug in patients who have a history of BC (Levin et al., 2015). There is a need for further

studies to determine the potential impact of taking this drug and BC. Chronic secondary cysts (potentially leading to BC) are associated with the use of persistent catheters, and kidney and bladder stones are also associated with BC (Chow et al., 2010). Although BC levels have been reported to be greater than 10% in paraplegic patients using persistent urine catheters, from the use of alternative bladder evacuation methods the BC rates in these patients have been significantly reduced (Kiriluk et al., 2012; Pannek, 2002). Therefore, considering the presence of BC risk in people with permanent urinary catheters, the use of screening for asymptomatic individuals is recommended.

Indeed, there is a connection between the bladder and the umbilical cord before birth (via the urachus), which accounts for BC in less than 1% of people. When this relationship between the bladder and the umbilical cord persists after birth, the association becomes cancerous (Amin et al., 2014). A cancer originating from the urachus is usually the adenocarcinoma type made up of cancerous cells. More than 30% of bladder adenocarcinomas originate from this section (Jacobs et al., 2010). Another congenital defect that increases the risk of BC is exstrophy. In this anomaly, the bladder is completely out of the lower abdomen and the urethra is completely open. This malformation has a wide range. Its mild form, called epispadias, is the opening of the urethra in the lower portion at the back of the penis (Lee et al., 2014). In more severe forms, a longer opening surrounds the bladder neck and the bladder, and the hip bone is open at the front. These abnormalities are often seen in boys and often accompanied by abnormalities of the reproductive system and the anus. Surgery immediately after birth causes the bladder and abdominal wall to be closed (and repairs the related defects), but those who have not yet had a surgery are at higher risk for urinary tract infections and BC (Giron et al., 2011; Zhang et al., 2013).

Conclusion

The objective of this review is to investigate the incidence and mortality rates of BC in the world and the association between environmental risk factors and BC incidence. The findings of this study showed that BC incidence and mortality differed considerably according to geographic area. One of the main risk factors for BC is smoking. The most important risk factor for developing BC is occupational factors, in particular exposure to aromatic amines after smoking. Another risk factor is genetic susceptibility as BC risk is twice as high in first-degree relatives than other patients. Nutritional factors, such as lack of adequate fluids, vitamin D deficiency, increased arsenic concentrations, and nitrates and disinfectants in drinking water play a significant role in the incidence of BC. There is a need for clinical trials to confirm the role of vitamin D in reducing BC incidence. Further studies are needed to confirm the role of nitrates in the incidence of BC. In terms of age, the risk of BC increases with aging. Among the medically related BC causes are infection with *Schistosoma* and the human papillomavirus. Use of radiation therapy, use of certain medications, persistent

use of urinary catheters, and congenital defects are also associated with BC induction. Further studies are needed to investigate the mechanism of BC occurrence due to immunosuppressive drugs and anti-diabetes medications.

Abbreviations

BC: Bladder Cancer

ESRD: end-stage renal disease

GSTM1: glutathione S-transferase mu1

HPV: Human Papilloma Virus

HR: Hazard Ratio

MBOCA: 4,4'-methylene-bis(2-chloroaniline

NAT2: N-acetyltransferase 2

OR: Odds Ratio

SMR: standardized mortality ratio

UBV: ultraviolet B

Author Contributions

All authors contributed to the design of the research, AAT, FHS, AKR, SH, NNB extracted the data and summarized it. All authors drafted the first version. HSG, AMH and HS edited the first draft. All authors reviewed, commented and approved the final draft.

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