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Seminar article

Bladder cancer risk from occupational and environmental exposures

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Abstract

Approximately 50% of bladder cancer incidence in the United States has been attributed to known carcinogens, mainly from cigarette smoking. Following the identification of this important causative factor, many investigators have attempted to identify other major causes of bladder cancer in the environment. Genetic and epigenetic alterations related to carcinogenesis in the bladder have been linked to environmental and occupational factors unrelated to cigarette smoking and may account for a significant portion of bladder cancer cases in non-smokers. The interaction between genetics and exposures may modulate bladder cancer risk and influence the differing incidence, progression, and mortality of this disease in different genders and races. Comparative molecular studies are underway to measure the relative effects of environment and inheritance to account for observed differences in the epidemiology of bladder cancer. The use of geospatial tools and population-based data will offer further insight into the environmentally-linked causes of bladder cancer.

Keywords: bladder cancer; environment; risk factors; etiology; epidemiology

Introduction

In 2011, it is estimated that 69,250 individuals living in the U.S. will develop bladder cancer, and 14,990 will die of the disease [1]. In developed countries, approximately 90% of bladder cancers are urothelial cancers, with the remainder consisting typically of squamous cell carcinoma and adenocarcinoma [2]. The development of these malignancies has long been connected with exposure to environmental carcinogens. In 1895, Ludwig Rehn, a German physician, first noted that a significant number of dye workers developed bladder cancer theorizing that aniline was the responsible agent [3]. In prior observational studies, a directly inherited link to bladder cancer had also been proposed [4–6]. However, many of these studies failed to adequately account for the effects of smoking and other possible environmental exposures. Moreover, multiple large scale epidemiologic investigations have found no association between bladder cancer incidence within first degree relatives and argue strongly against a straightforward genetic mechanism [7–9]. Currently, many believe that the environment plays a primary role in the development of bladder cancer, while inherited factors alter the phenotype and clinical presentation of the disease [10,11].

In spite of the numerous clinical observations, epidemiologic investigations, and experimental animal studies that have elucidated environmental carcinogens responsible for bladder cancer, many cases still appear to be sporadic with patients having no known risk factors. Identification of causative agents can be problematic as exposures may occur by inhalation, ingestion, and skin contact both in occupational and non-occupational settings. Discovering new risk factors and confirming suspicions are difficult as there is typically a long latency period from time to exposure to the development of cancer and environmental carcinogens may occur together, limiting the ability to identify the risk posed by each individual exposure. Determining the level of risk associated with each carcinogen is further complicated as both the amount and duration of exposure affect the potential to develop cancer in the future. A summary of environmental factors associated with bladder cancer can be found in Table 1. This article will review current knowledge of these factors and discuss the role of novel technologies in identifying new environmental risk factors that may be responsible for the development of bladder cancer.

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Table 1
Environmental factors and their association with bladder cancer

Causative	Indeterminate	No association
Cigarette smoking [14–16]	Second-hand smoke [23,26–28]	Aniline [40,43,46,52]
Cigar/pipe smoking [24,25]	Chlorinated water [137–140]	Artificial sweeteners [131,132]
1-Naphthylamine, 2-naphthylamine, benzidine, 4-aminobiphenyl, ortho-toluidine and chloroaniline [43–46]	Halogentated hydrocarbons [74,83,84]	Analgesics excluding phenacetin [122–124]
High arsenic levels (drinking water concentration > 0.2 mg/l) [64,70]	Low arsenic levels (drinking water concentration < 0.1 mg/l) [68,69,71]	
Polyaromatic hydrocarbons [75–77]	HPV [103,104]	
Ionizing radiation [85,87]	Pioglitazone [125,126]	
Schistosoma haematobium [92,95]	Nitrates and nitrites [134–136]	
Chronic inflammation [97,98]	Vitamin D deficiency [143–145]	
Immunosuppression [105,106,108]		
Oxazophosphorines [109,110,115]		
Phenacetin [117,120]		
Aristolochia fangchi [127,128]		

For all environmental risk factors, ability to cause bladder cancer is dependent on level and duration of exposure. Associations based on level of scientific evidence found on literature review, see select references.

Tobacco smoke

To date, cigarette smoking has proven to be the most important risk factor in the development of bladder cancer, specifically urothelial cell cancer (UCC). The incidence of UCC has been shown to be approximately 4 times higher in smokers compared with non-smokers [12]. It is also estimated that 50% of all bladder cancers in men and 30% in women are due in part to cigarette smoking [13]. The first study to find a connection between smoking and bladder cancer was based on murine models in the 1950s [14]. While the strong association between smoking and UCC may seem obvious now, a definitive connection was not immediately established in early retrospective and prospective analyses [15]. Over the subsequent years, numerous studies have confirmed a correlation between the formation of UCC with the number of cigarettes smoked, duration of smoking, and amount of smoke inhaled for both men and women [16]. In a large meta-analysis, current and former cigarette smokers had 3.33 (95% confidence interval [CI], 2.63–4.21) and 1.98 (CI, 1.72–2.29) greater odds, respectively, of developing bladder cancer compared with non-smokers [13]. The evidence for tobacco smoking and non-urothelial bladder carcinoma is limited, but available data are consistent with an increased risk even in non-urothelial histologies [17,18].

Following the initiation of smoking, epidemiologic studies suggest that a latency period of several decades ensues prior to the development of bladder cancer. Upon smoking cessation there is a 30% decrease in risk per year for several years, but reaching the age-adjusted baseline of non-smokers may not occur even 20 years after cessation [19,20]. Smokers already diagnosed with bladder cancer also benefit from smoking cessation as multiple studies have shown a reduction in both cancer recurrence and time to progression if smokers with bladder cancer quit using tobacco products [21,22].

Cigar smoking, pipe smoking, and secondhand smoke (SHS) have also been implicated as risk factors for UCC. While tobacco smoke is a carcinogen that causes bladder cancer, the association with these sources has been more difficult to prove compared with cigarette smoking as the inhaled concentrations are lower and therefore impart an inherently lower risk for cancer [23]. Both cigar and pipe smoking have been linked to UCC. The relative risk for development of UCC in individuals who smoked only a pipe or cigars are 1.9 and between 1.8–2.3, respectively, of developing UCC compared with non-smokers [24,25].

A definitive link between SHS and UCC has remained elusive despite significant research on the topic. Some epidemiologic studies have suggested an increased risk for women and children, while others show no connection between SHS and UCC [19,23,26–28]. Investigators have also sought to determine risk associated with SHS by comparing biomarkers, most commonly levels of 4-aminobiphenyl hemoglobin adducts, in exposed and nonexposed individuals. Unfortunately, these studies have yielded mixed results [27,29–31]. Further research is still required to determine if the low concentration of inhaled smoke associated with SHS is enough to put one at risk for future development of UCC.

While some of the mechanisms of carcinogenesis from cigarette smoking have been clearly defined, it remains unclear which carcinogens from tobacco smoke, alone or in combination, are chiefly responsible for bladder cancer. The combustion of tobacco releases at least 69 known carcinogens, including nitrosamines, polycyclic aromatic hydrocarbons, 2-naphthylamine, and other aromatic amines, all of which have been directly implicated as mutagens causing UCC [32]. Interestingly, analyses of concentrations for several of these carcinogens have shown increasing levels within cigarette smoke since the 1970s [33]. This worrisome finding may account for the steady rates of bladder cancer incidence and mortality in the United States over the past 40

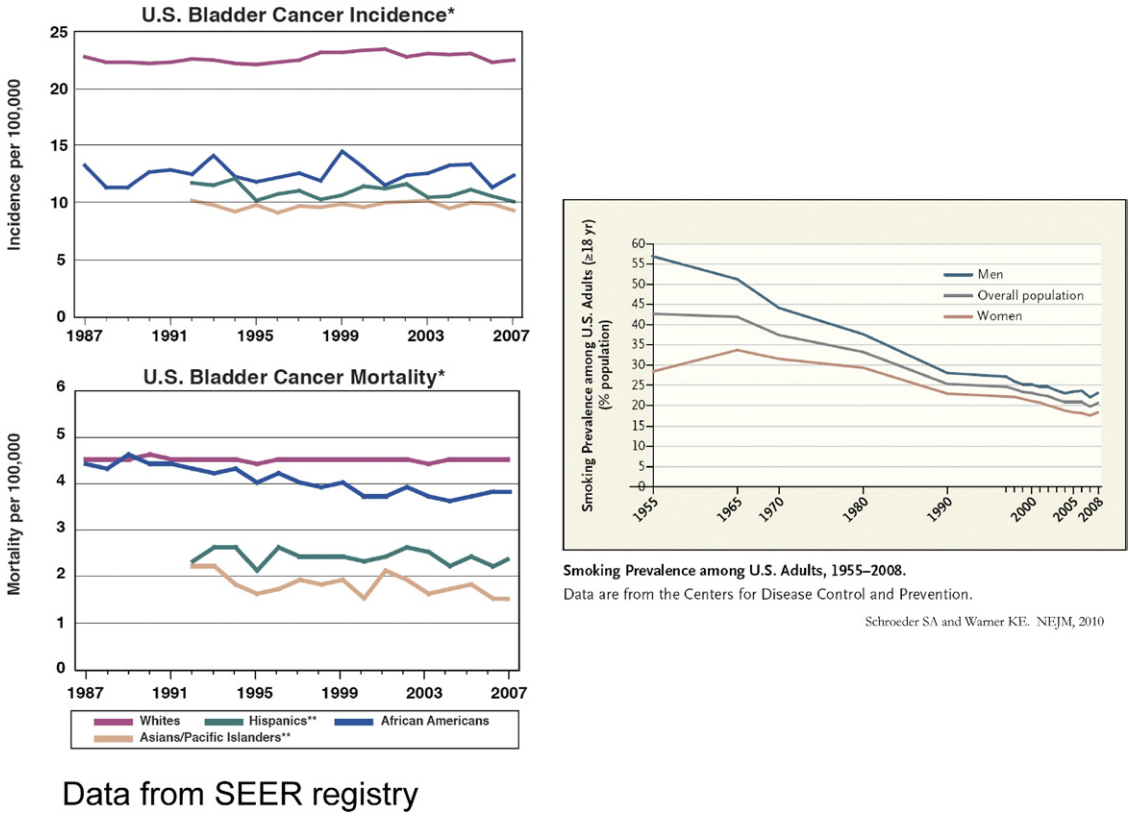

Fig. 1. Trends in bladder cancer incidence, mortality and smoking rates in the United States. Reprinted with permission from Schroeder SA, Warner KE. Don't forget tobacco. NEJM 2010;363:201-4. (Color version of figure is available online.)

years despite declining rates of smoking over the past half century (Fig. 1).

The major pathway of cancer induction in smokers is via DNA adduct formation and genetic damage that alters critical cellular pathways fostering uncontrolled cell growth, eluding intrinsic mechanisms to restrain tumor growth, and spread [32]. While exposure to cigarette smoke increases the risk of UCC, cancer only develops in a select few that seem to have genetic susceptibilities. These susceptibilities are thought to be secondary to polymorphisms within genes responsible for DNA repair or detoxification. Numerous studies have attempted to determine a correlation between UCC, smoking, and polymorphisms within several families of genes, including those found within glutathione S-transferase (GST), cytochrome p450, sulfotransferase, and *N*-acetyltransferase (NAT).

The study of these polymorphisms has failed to demonstrate a definitive correlation with UCC, although the NAT2 genotype has the strongest association with development of bladder cancer within the NAT family [34–36]. NAT2 is an enzyme responsible for detoxification via acetylation, which is particularly important for the clearance of aromatic amines [37]. The NAT2 genotype has a polymorphism associated with a slower rate of acetylation, leading to build-up of aromatic amines. Former and current heavy smokers who have the "slow" NAT2 phenotype have been found to have an increased relative risk of UCC (1.82 and 3.16, respectively) compared with smokers with the wild-type; this risk is present only in those individuals with higher smoking intensity [36].

Multiple studies have also looked at polymorphisms within the GST family. These genes encode for cytosolic enzymes also important for detoxification. Within the GST family, the null variant of GST M1 has been postulated to convey an increased risk for the development of UCC [33]. In 1 study, a 1.8-fold greater risk of developing UCC was found in smokers homozygous for the null gene compared with smokers who had at least 1 wild-type allele [38]. The results of other studies have not been as conclusive and the association between bladder cancer risk and the GST M1 null genotype remains controversial [34,36,39].

A steady accumulation of evidence over the past 50 years has definitively proven that tobacco smoke causes bladder cancer. Currently, researchers are attempting to discover the exact mechanisms by which smoking causes cancer and also determine the association between genetics, smoking, and cancer development. While most individuals will remember that smoking is the greatest risk factor for development of bladder cancer, the importance of smoking cessation on the natural history of the disease should also be discussed. Practitioners should educate patients that the benefits of cessation include both the prevention of bladder cancer as

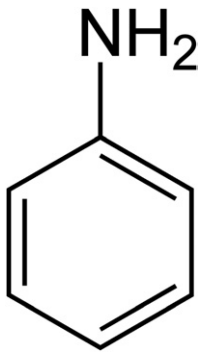

Fig. 2. Chemical structure of aniline, a precursor to many industrial chemicals.

well as decreasing recurrence and progression in individuals already diagnosed with the disease.

Aromatic amines

An aromatic amine is a chemical with some form of nitrogen group attached to an aromatic hydrocarbon. The structure usually contains 1 or more benzene rings; aniline is the simplest of the aromatic amines and often is the parent compound for other molecules in this category (Fig. 2). The use of aromatic amines, or aryl amines, is widespread in industry and agriculture. Furthermore, substances such as azo dyes (which yield bright reds, oranges, and yellows) may be reduced to aromatic amines by enzymatic reactions within human cells, and polycyclic aromatic hydrocarbons may be turned into aromatic amines upon combustion in industrial settings [40]. Aromatic amines are also contained within cigarette smoke and their levels in the urine are significantly elevated in smokers compared with non-smokers [41,42].

The original link between UCC and aromatic amines in the 1890s by Rehn was based on the observation of a disproportionately high rate of bladder cancer associated with workers in the dye industry. Other aromatic amines were not implicated as causative agents until 1954 when Case et al. reported bladder cancer mortality rates in exposed dye workers to be greater than 30 times that of the general population [43]. Occupational exposure to aromatic amines is thought to occur primarily via dermal contact. As previously discussed, amount and duration of exposure to environmental carcinogens greatly affects risk of developing bladder cancer. A review of occupational cohort studies demonstrates an increased risk of bladder cancer—independent of smoking—for individuals exposed to aromatic amines working in various industries including farming, chemical plants, rubber industry, and textiles [44–48].

Bladder cancer secondary to environmental exposure to aromatic amines has been difficult to determine. An ecologic evaluation of the population living near the Drake Superfund site (an area contaminated with 2-naphthylamine, benzidene, and benzene) found a doubling of the rate of bladder cancer for the population living in the area from 1950 to 1979, while bladder cancer incidence decreased in the rest of the state during this same time period [49]. Further investigation found no evidence of morbidity related to exposure amongst the community at large; however, higher prevalence rates of bladder cancer do exist for former employees who had significant exposure to aromatic amines [50].

It is important to note that only certain aromatic amines have been demonstrated to cause bladder cancer in laboratory models. Determination of specific aromatic amines that cause UCC is difficult as population exposure to a single aromatic amine is rare [51]. While Rehn proposed aniline to be a causative agent, evidence supporting this has since been refuted [40,43,46,52]. The risk of developing bladder cancer following long term exposure to 1-naphthylamine, 2-naphthylamine, benzidine, and 4-aminobiphenyl has been demonstrated in case-control studies for over 60 years [43,53]. More recently, the International Agency for Research on Cancer has also classified *ortho*-toluidine and chloroaniline (MOCA) as carcinogenic [54]. MOCA and *ortho*-toluidine act as mutagens causing bladder cancer in a similar fashion to 4-aminobiphenyl by creating metabolites, which form adducts with DNA [45,55].

An association between aromatic amines within hair dyes and bladder cancer has been found in multiple epidemiologic studies [56,57]. Similar to tobacco smoking, the risk for developing cancer may be dependent on gene–environment interactions. An increased risk (OR 7.3, 95% CI 1.6–32.6) of developing bladder cancer was found in women with the slow acetylation phenotype of NAT2 and hair dye exposures [58]. The International Agency for Research on Cancer (IARC) has classified the occupational exposure to hair dyes for barbers/hairdressers as probably carcinogenic (IARC Group 2A); however, there is no clear evidence to support an association between UCC and the personal use of hair dye and therefore the risk remains unclassifiable (IARC Group 3) [54]. Nevertheless, the production and use of 4-aminobiphenyl and 2-naphthylamine in all industries, including hair dyes, has been phased out to limit occupational exposures [59].

Arsenic

In the 1960s, consumption of high levels of arsenic from artesian drinking wells was found to be the cause of lackfoot disease, a syndrome endemic to South Taiwan, classified by progressive arterial occlusion resulting in gangrenous limbs [60]. Twenty years later, epidemiologic studies of individuals who were exposed to these high levels of arsenic revealed that this population experienced an increased incidence in multiple malignancies, including bladder cancer [61,62]. The incidence of UCC was 23.53/100,000 from 1981 to 1985 for the exposed population vs. 2.29/100,000

for the rest of Taiwan during the same period [56]. Analysis of arsenic related UCC from the blackfoot endemic area has found that cancer was often limited to the upper tract [63]. The same investigation also found that women were at particular risk for development of UCC as opposed to the male dominated prevalence that is typically seen. This gender-specific finding may be related to the fact that cooking in the endemic area is often performed using steam heating over boiling water. Inhalational arsenic exposure among women who do most of the cooking may be an explanation for these observations.

The connection between high levels of arsenic consumption and the development of bladder cancer has been confirmed [64,65]. Traditionally, studies have focused on intake of arsenic via contaminated water sources. In areas endemic with blackfoot disease, the arsenic concentration in drinking water ranged from 0.7 to 0.93 mg/L [66]. In contrast, the standard for arsenic in drinking water in the United States, as set forth by the Environmental Protection Agency, is currently 0.01 mg/l [67]. Studies demonstrate that chronic consumption of water with high arsenic levels (greater than 0.2 mg/l) is associated with bladder cancer; however the dose–response relationship for arsenic exposures below 0.1 mg/L remains equivocal [68–71]. It is unlikely that such low levels of arsenic are causative of bladder cancer, but further investigation is still required before these levels can be definitively classified as non-carcinogenic.

The mechanism by which arsenic causes bladder cancer remains unclear, but potential sources of arsenic include water, cigarette smoke, air pollution, and multiple occupations including non-ferrous metal smelting, pesticide manufacturing and application, wood preservation, semiconductor manufacturing, and glass production [72]. Arsenic impairs cellular respiration via inhibition of mitochondrial enzymes and the result is a buildup of reactive oxygen species and release of free radicals that may ultimately damage DNA [73]. Little is known in regards to bladder cancer risk from dermal uptake or inhalation of arsenic. When arsenic exposure is oral, a portion of the ingested arsenic is metabolized into an inert form by the liver [73]. Inhaled or contact exposure results in arsenic that bypasses the liver and may therefore potentially confer greater risk.

Polycyclic aromatic hydrocarbons

Polycyclic aromatic hydrocarbons (PAH) represent a group of chemicals that contain 2 or more benzene rings, typically formed following the incomplete combustion of organic material. Exposure to PAH is difficult to avoid given ubiquitous presence in fossil fuels, plastic and rubber containers, and cooked meats. In 1989, the IARC listed occupational exposure to diesel and gasoline engine exhausts as carcinogenic due largely to the presence of PAH [74]. PAH exposure exacts its greatest carcinogenic effects via direct exposure and strong evidence has linked it to development of both lung and skin cancers.

Studies of PAH exposure and bladder cancer risk are less consistent, though workers in industries with high PAH exposure (such as truck driving) have relative risks of 1.2 to 2.3 times greater compared with the general population [75–77]. Despite having increased risk, screening individuals with occupational exposure to PAH or other known carcinogens such as aromatic amines has failed to demonstrate any benefit [78]. At risk individuals for PAH may be found in industries with workplace exposures to coal gasification, diesel engine exhaust, iron and steel foundries, coke, coal tar, carbon black, shale oil extraction, wood impregnation, roofing, road paving, chimney sweeping, aluminum, and carbon electrodes production [79].

PAH exposure via air pollution has also been proposed as a potential causative agent for bladder cancer. Areas with high population density have been shown to confer a greater risk in the development of bladder cancer [80], but whether this increased risk is secondary to air pollution (and more specifically PAHs) has yet to be determined.

Halogenated hydrocarbons

A halogenated hydrocarbon (HH) consists of 1 benzene ring with at least 1 associated halogen group, most often chlorine or fluorine. Perchloroethylene (PER), also known as tetrachloroethylene or tetrachloroethene, is 1 of the more commonly used HHs and is found in dry cleaning and metal degreasing solvents [81].

The evidence linking HH exposure—in particular PER—and cancer has strengthened over the past 20 years. In 1995, the IARC identified dry-cleaning of textiles as possibly carcinogenic (Group 2B) to humans based on HH exposure [82]. Following multiple studies that showed PER was associated with the development of cancers including lymphoma, cervical cancer, and esophageal cancer, the IARC upgraded PER from unclassifiable (Group 3) to possibly carcinogenic (Group 2B) [83]. While multiple animal and observational studies have attempted to find a link between HHs with the development of bladder cancer, at this time there is inadequate scientific evidence to link PER or other HHs to bladder cancer [84].

Ionizing radiation

Much of our original knowledge regarding radiation-related malignancies of the bladder comes from studies on the survivors of the atomic bombs on Nagasaki and Hiroshima at the end of World War II. A dose–response relationship between radiation exposure and bladder cancer has been clearly demonstrated from this cohort with an excess relative risk of 1.02 for each sievert of exposure in atomic bomb survivors [85]. The mutagenic effects of ionizing

radiation are hypothesized to be due to DNA damage either directly from radiation-induced double-stranded breaks or indirectly through the production of free radicals, which then damage DNA.

Today, radiation therapy-related malignancies are typically seen as secondary cancers that can occur decades after treatment of the primary tumor. The use of radiotherapy for the treatment of pelvic malignancies, including cervical, endometrial, and prostate cancer, has been shown to convey an increased risk for the development of subsequent bladder cancer [86–88]. The risk of a secondary bladder cancer may decrease as technologic advances in the delivery of radiation therapy limit dose to non-target organs.

Inflammation, infection, and the immune system

There is substantial evidence demonstrating inflammation is a critical component of tumor development [89]. Studies linking chronic inflammation with squamous cell carcinoma (SCC) of the bladder are strong and widely accepted. The role of chronic inflammation and the development of other non-SCC bladder cancers such as UCC is less clear. Multiple retrospective analyses have linked history of urinary tract infection with future development of UCC [90]. However, these studies may be limited by bias and, to date, no prospective studies have been performed. In this section, we will briefly discuss the association of bladder cancer development to infection, inflammation, and the immune system.

Schistosoma haematobium

The most widely known infectious agent to cause bladder cancer is the parasitic flatworm *Schistosoma haematobium*. The disease is mainly limited to Africa and the Middle East where over 100 million individuals are estimated to be acutely or chronically infected [91]. Spread of the disease is typically from drinking water contaminated with sporocytes released from a snail host (Fig. 3). Adults of this species migrate into the veins surrounding the bladder to lay eggs. These eggs traverse the bladder wall resulting in hematuria, fibrosis, and in some cases, SCC of the bladder. Despite the presence of this disease since prehistoric times, it was not until 1911 when schistosomiasis was first associated with bladder cancer [92].

The rate of cancer secondary to schistosomiasis is likely high, but difficult to determine as individuals infected with the disease typically have high rates of exposure to other bladder carcinogens such as tobacco smoke [93]. In Egypt, a country with high rates of schistosomiasis infection, bladder cancer accounts for 16.2% of all cancers in men vs. only 7% of male cancers in the United States [94]. Furthermore, in 1 study, the percentage of patients in Egypt with bladder cancer who had schistosomal ova on pathologic evaluation was 55% [95].

The exact reason for mutagenicity within urothelial cells following *S. haematobium* infection remains unclear, although multiple factors are believed to contribute to the oncologic potential of schistosomal infection. The schistosoma ova as well as chronic bacterial infections that accom-

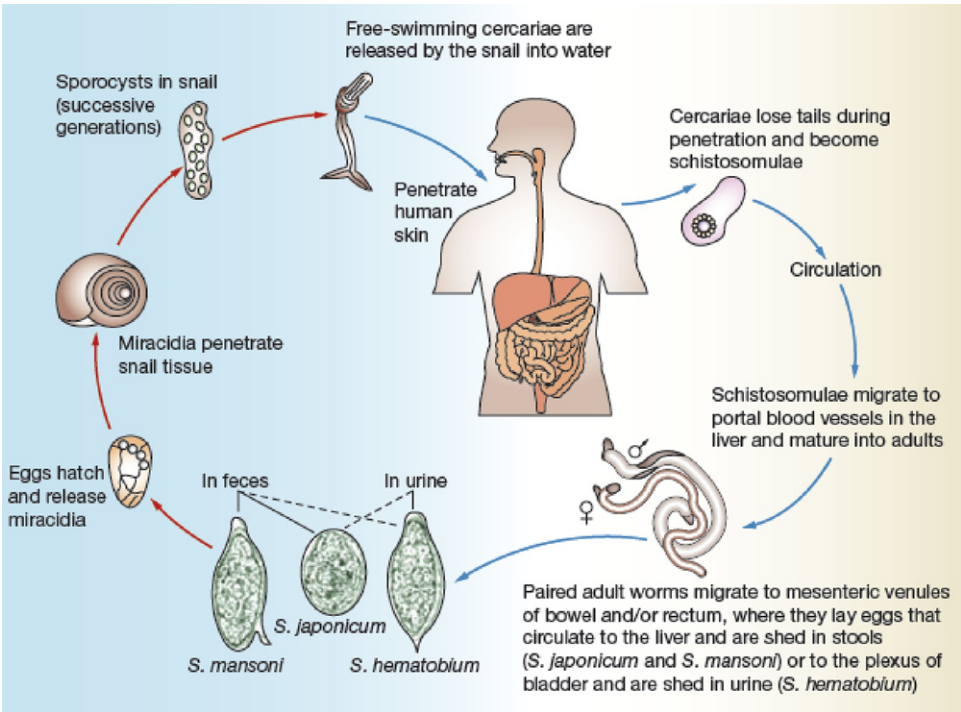

Fig. 3. Life cycle of Schistosoma parasite. (Color version of figure is available online.)

pany schistosomiasis may cause an inflammatory response releasing reactive oxygen species (ROS) and reactive nitrogen species (RNS) that cause genetic damage and disrupt cell signaling and homeostatic mechanisms [93]. In vitro studies have demonstrated *S. haematobium* total antigen levels can initiate an inflammatory response that leads to the development of urothelial cell dysplasia [96].

Chronic cystitis

The development of bladder cancer, in particular SCC, has been found to be increased in individuals with chronic cystitis secondary to chronic indwelling catheters or calculi [97]. Historically, up to 10% of paraplegics with chronic indwelling catheters were found to develop bladder cancer; however, incidence is declining toward the general population as other methods of bladder emptying have replaced the use of an indwelling catheter [98]. Similar to high-risk individuals with occupational exposures, screening of asymptomatic individuals with long-term indwelling catheters has not been shown to improve outcomes [99]. Nevertheless, practitioners should remain vigilant as over half of these individuals who develop bladder cancer present with muscle-invasive disease [98]. Similar to schistosomiasis, years of chronic bladder inflammation and higher rates of cystitis and urinary tract infection likely serve as the etiology for development of these cancers.

Human papilloma virus

Viral infections, in particular the high-risk serotypes of human papillomavirus (HR-HPV), have been found to be a causative factor in multiple malignancies. Unlike other infectious or inflammatory conditions, malignant transformation from HR-HPV is not due to the formation of ROS or RNS. Initially, the human papilloma virus (HPV), a small double stranded DNA virus, transfects a target cell and integrates into its genome. Two HR-HPV genes, E6 and E7, transcribe for oncoproteins, which alter regulators of cell cycle progression, telomere maintenance, and apoptosis [100]. The precise mechanism of carcinogenesis from infection by the high-risk serotypes of HPV, especially HPV16, is not completely understood.

Some of the most convincing data showing an association between bladder cancer and HPV come from studies of immunosuppressed patients [101,102]. Individual retrospective epidemiologic studies on the association between HPV infection in the general population and subsequent cancer formation yield mixed results; however several meta-analyses have found a 2.3 to 2.8 increase in the odds of bladder cancer in HPV-positive individuals [103,104].

Immunosuppression

A 3.3-fold increased risk for development of urothelial cancer in kidney transplant recipients was noted in a retrospective analysis of over 3,000 consecutive renal transplant patients [105]. This risk stems from immunosuppression, rather than renal failure, as analysis of patients with end stage renal disease compared with those with renal transplant found the transplant group to have a greater incidence of multiple malignancies (and worse outcomes) including bladder cancer [106,107]. This may relate to medical immunosuppressive therapy as individuals on prolonged oral glucocorticoid therapy have been found to have an increased likelihood of developing UCC (OR 1.85) and, importantly, invasive UCC (OR 2.12) [108]. As further investigations into the mechanisms of immune modulation and cancer remain ongoing, transplant recipients and those on chronic immunosuppression should be considered at higher risk for the development of UCC and other malignancies.

Oxazaphosphorines

Alkylating agents encompass a wide variety of medications used as chemotherapeutics to treat malignancies or rheumatologic diseases. While many alkylating agents have been found to cause secondary malignancies, only oxazaphosphorines are associated with hemorrhagic cystitis and development of bladder cancer [109–111]. The 2 most commonly known oxazaphosphorines are cyclophosphamide and ifosfamide. Without the use of urothelial protective agents, a direct correlation between cumulative dose and the risk of developing UCC has been seen with a 6-fold and 14.5-fold risk of UCC from cumulative doses of 20–49 g and 50 g or more, respectively [112].

Both cyclophosphamide and ifosfamide are prodrugs, and their metabolites exert the neoplastic and carcinogenic effects. Of the subsequent metabolites, acrolein is often quoted as being the offending agent that causes hemorrhagic cystitis, and ultimately, bladder cancer [113]. However, no definitive studies have shown whether this is truly the case, and it is unclear if it is acrolein, another metabolite, or a combination of metabolites that leads to development of bladder cancer [114].

2-Mercaptoethanesulfonate (MESNA) has long been known to exert protective effects when given in combination with oxazaphosphorines [115]. MESNA is quickly metabolized and excreted in the urine where its metabolites (free thiol groups) bind to acrolein and other urotoxic oxazaphosphorine metabolites to form stable nontoxic compounds. The use of MESNA prior to administration of oxazaphosphorines is recommended in all patients receiving cyclophosphamide or ifosfamide to prevent urothelial damage that may lead to hemorrhagic cystitis and bladder cancer [116]. While MESNA is considered protective, physicians

should still have a very low threshold to perform bladder cancer screening in symptomatic patients with prior exposures to oxazaphosphorines.

Analgesic use

Phenacetin abuse and subsequent development of bladder cancer was identified in animal models during the 1970s [117,118]. Production of phenacetin was then halted within the United States after several epidemiologic studies confirmed the relationship between heavy phenacetin use and development of UCC (RR 2.6 compared with non-users) [119,120]. The mechanism of action by which phenacetin causes UCC is unknown but thought secondary to 1 of its metabolites following de-ethylation by cytochrome P450 1A2 [121]. As the first step in phenacetin metabolism results in the formation of acetaminophen, other NSAIDs and analgesics were scrutinized but studies have failed to determine any causal relationship between these drugs and bladder cancer. In fact, data suggest use of these medications actually reduces risk of UCC [122–124].

Pioglitazone

There are recent concerns regarding increased risk of bladder cancer in people using pioglitazone, a thiazolidinedione antidiabetic medication used in treatment of type 2 diabetes. In a recent large scale study, use of pioglitazone for more than 2 years was weakly associated with increased risk (RR 1.4; 95% 1.03–2.0) of bladder cancer [125]. After reviewing findings from this study and an epidemiologic analysis from France with similar results, the Food and Drug Administration released a statement recommending against use of pioglitazone in patients with active bladder cancer and cautious use in patients with a history of bladder cancer [126]. France suspended the use of pioglitazone and Germany advised against starting pioglitazone in new patients. Ongoing investigations hope to further elucidate the relationship between pioglitazone and development of bladder cancer and perhaps identify a potential mechanism.

Aristolochia fangchi

The herb *Aristolochia fangchi*, found as a contaminant in Chinese herbal weight loss pills, has been found to result in nephropathy, renal failure, and increased incidence of urothelial cancers (typically occurring in the upper tract) [127]. This association was confirmed by demonstrating high levels of *A. fangchi* DNA adducts in tissue from individuals with UCC, and patients who ingested a cumulative dose of 200 g or greater of *A. fangchi* were found to have occult UCC in 46% of prophylactic nephrectomy specimens [128].

Artificial sweeteners

There is no clear relationship between saccharin and development of bladder cancer in humans. Small animal studies in the 1960s demonstrated an association between high saccharin diets and the development of bladder cancer [129]. However, all subsequent nonhuman primate models failed to corroborate this association [130]. Ultimately, this etiology for bladder cancer was found only in rats as they possess a unique urinary composition, which causes a carcinogenic precipitate to form when given high doses of saccharin [131]. Unfortunately, the misconception that artificial sweeteners cause bladder cancer remains despite multiple studies of other artificial sweeteners that also failed to demonstrate increased risk of UCC [132].

Nitrates and nitrites

Common sources of nitrates include drinking water with fertilizer runoff in agricultural areas and processed meats. Excessive consumption of nitrates has been proposed a potential carcinogen, but studies to link dietary nitrates to development of bladder cancer have conflicting results [133–136]. Other studies suggest nitrosamines, a byproduct of urinary tract infection by nitrite-forming organisms, may be carcinogenic but confirmatory evidence is still lacking [96].

Chlorinated water

Several of the main disinfection byproducts (DBPs) in chlorinated water, trihalomethanes (THM) and haloacetic acids, have been found to be mutagenic in bacterial assays and animal models [137]. However, the IARC and World Health Organization both found insufficient evidence to link chlorinated drinking-water to bladder cancer in humans [137,138]. Determination of carcinogenicity is difficult due to the relatively low toxicity of DBPs and the low concentrations to which the public is typically exposed. Recent multiple large scale analyses and meta-analyses do suggest a link between THM exposure and bladder cancer risk [139,140]. Men exposed to an average residential THM level > 50 μg/l have been found to have an increased risk (OR 1.47; 95% CI 1.05–2.05) of developing bladder cancer compared with men exposed to levels ≤ 5 μg/l [140].

Vitamin D

The vitamin D–cancer hypothesis was first proposed in 1980 to explain significant increased colon cancer mortality in the northeastern United States [141]. An inverse relationship to annual hours of ultraviolet B (UVB) radiation and cancer mortality was identified, and the postulated protective effect of vitamin D on cancer was supported by the finding that dietary vitamin D and calcium were inversely

correlated with colorectal cancer risk [142]. Several large scale studies have demonstrated a link between low vitamin D levels and multiple cancers. In a prospective study of male smokers, low levels of serum vitamin D were associated with an almost 2 times greater risk of developing bladder cancer compared with men with higher levels (25(OH)D $\geq$ 50 nmol/l) [143]. Epidemiologic studies comparing UVB exposure and case control studies comparing dietary intake of vitamin D have yielded similar results [144–146]. In light of this evidence supporting the protective effect of vitamin D on development of bladder cancer, randomized controlled trials seem warranted.

Identifying new environmental risk factors for bladder cancer

Bladder cancer mortality has not changed in the last 30 years in the United States, despite increased awareness and cancer screening guidelines set in place by the American Urological Association and National Comprehensive Cancer Network. The proportion of patients presenting with advanced disease remains static in certain areas [147]. In addition, bladder cancer is rarely diagnosed at autopsy, which is clearly distinct from other genitourinary cancers and likely signifies that bladder cancer incidence, progression, and eventual mortality accurately reflects the true natural history of the disease [148]. Over 90% of bladder cancer patients are age 55 years and older, and it is suspected that occupational and environmental exposures have long latency periods before cancer manifests. Given that bladder cancer is the most expensive cancer to treat on a per patient basis, from diagnosis to death, there is a national effort to improve cancer detection and better characterize racial and gender disparities in disease outcomes [149,150].

While demographic differences such as gender and race have been attributed to bladder cancer mortality, risk of disease has long been known to be influenced by environmental factors and contaminants [151]. The relationship between genetic variability in individuals (e.g., slow *N*-acetylation genotype) may explain how similar environmental exposures lead to different phenotypic expression of bladder cancer in the population [152].

Geographic differences in bladder cancer cases and deaths within the United States have long been noted [153]. Previous epidemiologic studies have mapped out regional variance but not linked regional data to potential causes of bladder cancer in a rigorous fashion on a national level [154]. This may be due to a lack of modeling tools that can layer multiple potential causes of bladder cancer to the regional incidence and mortality. In addition, differences in gender and ethnic bladder cancer incidence and mortality may be studied within common environments (and presumably common exposures).

Geospatial tools are being increasingly utilized to model regional variance of cancer mortality and suspected environmental exposures using geographic information systems (GIS) technology. GIS methodology allows for multiple environmental exposures (i.e., toxins in water supply, industrial toxins, levels of air pollution, etc.) to be collected and integrated at different city, county, regional, and state levels over multiple time points. GIS tools can integrate heterogeneous data and perform geographically weighted regression analyses to assess the association between exposures and outcomes. Asset mapping instruments may also be utilized with these models to visualize the spatial distribution of resources which may impact health disparities and equitable access to care. This science is distinctly underrepresented in the urologic literature and is only beginning to appear in the general oncology literature [155].

As noted earlier in this review, ample evidence exists for the significance of modifiable environmental risk factors in bladder carcinogenesis. Although studies hypothesize the link between urban industrialization and bladder cancer, national efforts have not attempted to link or test these hypotheses. This may be due to study logistics limiting the processing of large amounts of data and integrating it within established data sets. In addition, the data is limited to 1 point in time. These limitations have made broad understanding of the natural history and epidemiology of bladder cancer at the population level elusive. GIS allows for controlling of spatial confounders and can potentially demonstrate geographically-linked epidemiologic factors associated with bladder cancer incidence and death. Latency effects can also be addressed using bilinear and exponential decay latency models as done in other epidemiologic studies examining occupational exposures [156]. GIS technology provides powerful epidemiologic research tools to study the complex interactions between bladder cancer outcomes and a diverse range of data to better elucidate the relationships between disease and a multitude of environmental exposures.

Conclusion

The past several decades offered significant progress in the diagnosis and treatment of bladder cancer in the United States. Development of medical treatments for both superficial and muscle-invasive bladder cancer has decreased disease recurrence and progression, while improvements in surgical technique allowed for a greater population to receive appropriate and timely care. Our understanding of the genetic factors that influence the development and aggressiveness of bladder cancer is exponentially increasing. Smoking rates have fallen almost 50% over the same period with improved public awareness regarding the harm of tobacco products. Despite this progress, however, the rate of new bladder cancer diagnoses and mortality has not decreased over the past 3 decades.

Epidemiologic case-control studies have linked bladder cancer to environmental and occupational exposures for over 200 years. In addition, significant differences in blad-

der cancer mortality by both race and gender cannot be completely explained by our current understanding of genetics. We hypothesize that there are environmental and/or occupational causes that lead to changes in gene expression that modulate tumor initiation, recurrence, and progression. The geographic identification of areas of increased bladder cancer diagnoses and deaths ("hot spots") allow for regional and individual level assessment of human exposures to better identify and potentially eliminate the inciting causes of bladder cancer. As only a small fraction of cancer risk can be explained by genetic factors alone, identification of external factors that interact with genetic and acquired susceptibility is critical in cancer prevention. Given the complexity of environment–susceptibility interactions, further research is required to understand the inter-individual variation in genetic and epigenetic responses to environmental risk factors. Further research and public health strategies are not only needed to identify susceptible genetic variants but also modulate risk to genetically susceptible subgroups and the population at-large.

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