Seminars in Surgical Oncology 1997; 13:291–298

Epidemiology and Etiology of Bladder Cancer

SONNY L. JOHANSSON, MD, PhD* AND SAMUEL M. COHEN, MD, PhD
Department of Pathology and Microbiology, University of Nebraska Medical Center, and the Eppley institute for Research on Cancer and Allied Diseases, Omaha, Nebraska

The incidence of bladder cancer continues to increase, with an estimated 53,000 new cases diagnosed in the United States in 1996—90% of which are transitional cell carcinomas. The male-to-female ratio is 3:1. A number of etiological factors are associated with the development of bladder cancer, but in industrialized countries, cigarette smoking is the most important. Specific chemicals have also been identified as causing bladder cancer, as have a number of occupational exposures to less well-defined specific agents. Treatment with cytostatic drugs, especially cyclophosphamide, is associated with increased risk of bladder cancer, as is treatment with radiotherapy for uterine cancer. In developing countries, especially in the Middle East and parts of Africa, infections with members of the genus ***Schistosoma*** are responsible for a high incidence of bladder cancer—75% of which are squamous cell carcinomas. Arsenic has been indicated as a bladder carcinogen in Argentina, Chile, and Taiwan. The reason for the high incidence of urinary tract cancer in individuals suffering from Balkan nephropathy has yet to be determined. A careful history of patients with bladder cancer is an important and useful process in helping to identify causal factor and, in more than one-half the cases, a known relationship is found. Bladder cancer is a potentially preventable disease, with a significant morbidity and mortality in many parts of the world. ***Semin. Surg. Oncol. 13:291–298, 1997.*** © 1997 Wiley-Liss, Inc.

KEY WORDS: bladder neoplasms; transitional cell carcinoma; squamous cell carcinoma; adenocarcinoma; etiology; epidemiology; mortality; schistosomiasis; smoking; occupational diseases; acetylation; acetyltransferases; nitrates; nitrites; nitroso compounds; carcinogens; radiotherapy/adverse effects; cyclophosphamide/adverse effects; urinary tract infections; risk factors

INTRODUCTION

Bladder cancer is a heterogeneous disease, and its clinical causes are somewhat unpredictable. It was the first cancer identified as being associated with industrialization. In 1895, Dr. Ludwig Rehn reported on bladder cancer in German dye workers who manufactured aniline dyes. Later, this was shown to be related to the presence of 2-naphthylamine in the dyes. Since then, many additional specific chemical mixtures, along with environmental agents and exposures, have been identified as causes of bladder cancer [1–31.

Bladder cancer is most common in western Europe and the United States, while Japan has a lower incidence. For reasons that are unknown, African Americans have a lower frequency of bladder cancer than Caucasian Americans. (There continues to be difficulty in defining Caucasian versus non-Caucasian populations.) There is a marked male predominance in transitional cell carcinoma: the male-to-female sex ratio is at least 3 : 1. Earlier epidemiologic studies focused predominantly on a comparison of the incidences in men. An estimated 53,000 new cases of bladder cancer will be diagnosed in the United States in 1996, at least 90% of which will be transitional cell carcinomas. Adenocarcinoma, which constitutes about 1% of bladder cancer, also shows a male predominance. Thus, in a total of 11 series comprising 247 patients, the sex ratio was 2.7 : 1 [4]. By contrast, the sex ratio in patients with squamous cell carcinoma is significantly lower; in 10 series of squamous cell carcinoma comprising 915 patients, the sex ratio was 1.4 : 1 [4]. It is unclear why squamous cell carcinoma is almost as common in females as in males, but it may be related to its association with inflammatory processes.

Kaye and Lange [5] were the first to point out that bladder cancer appears to be two diseases. Most cases are pap-

*Correspondence to: Sonny L. Johansson, MD, University of Nebraska Medical Center, 600 South 42nd Street, Box 983135, Omaha, NE 68198-3135.

illary tumors, usually of low grade and stage. The tumors are often multiple with a tendency to recurrence. About 15% progress in grade and/or stage over a 10-year period. These papillary type of tumors comprise approximately 75–80% of bladder cancers, although in a recent study from Holland, only 64.5% were found to be papillary [6]. The nonpapillary (solid) type of bladder cancer is generally associated with detrusor muscle or deeper invasion. These tumors are high grade, often associated with carcinoma in situ, and are principally responsible for mortality in patients with bladder cancer.

Chromosomal and genetic differences seem to exist between papillary and nonpapillary carcinoma, including carcinoma in-situ (CIS), high-grade, nonpapillary transitional cell carcinoma usually contains a defect in chromosome 17, which represents an abnormality in the p53 gene. By contrast, changes in chromosome 9 are associated with superficial papillary tumors [7].

In addition to the general distribution of bladder cancers throughout the world, specific areas exist that have consistently elevated incidence of cancer of the lower urinary tract, often associated with other disease processes. Individuals in countries where endemic schistosomiasis exists have a very high incidence of bladder cancer [8].

Furthermore, certain areas of the Balkan countries, including the former Yugoslavia and Bulgaria, have increased death rates due to nephropathy. The patients also have a high prevalence of urothelial tumors involving both the upper and lower urinary tracts. So far, extensive research has failed to reveal specific etiologic factors responsible for the carcinogenicity in these patients. A mycotoxin, ochratoxin, induces nephropathy in pigs similar to the Balkan type in humans, but it is unclear whether this compound is involved in the human disease or is related to their urothelial malignancies [3].

Certain regions of the island of Taiwan have an increased incidence in peripheral vascular disease commonly referred to as "blackfoot disease," and individuals suffering from this condition have an increased incidence of urinary tract carcinoma [3]. Arsenic has been suggested to be the culprit responsible for the vascular disease process and may also be involved in the development of urothelial cancer. A similar relationship between high levels of arsenic exposure and bladder cancer have recently been reported from Chile and Argentina [9].

CHEMICAL AND OCCUPATIONAL CARCINOGENESIS

The 1895 and 1896 papers by Rehn suggested a relationship between exposure to specific chemicals used in the dye industry and bladder cancer [1,2]. However, the carcinogenic compound was not aniline, as Rehn suspected, but 2-naphthylamine, as demonstrated by Hueper and Wolfe in a dog model 47 years later [1,2]. 2-Naphthylamine was commonly used in Germany and elsewhere in the manufacture of various dyes. World War II halted the investigations into the carcinogenic agent. In 1954, Case et al. [10] published a classic study of the relationship between exposure to aromatic amines and bladder cancer in a large number of British industrial workers, not only in the dye industry but also in the rubber, textile, and chemical industries. These investigators studied the exposure to such co'mpounds during 1915–1950 and confirmed the carcinogenicity of 2-naphthylamine. They also found that exposure to other aromatic amines, such as 4-aminobiphenyl and benzidine, was associated with increased risk for bladder cancer. The mean induction time was 22 years (range 15–40 years). Although 1-naphthylamine has occasionally been suggested to be associated with bladder cancer, subsequent investigations have produced considerable evidence that this chemical is not carcinogenic; instead, exposure to 1-naphthylamine is related to bladder cancer development because it is often contaminated with 2-naphthylamine. Besides 2-naphthylamine, several other aromatic amines have been found to be associated with bladder cancer development (Table I). Exposure to these chemicals occurs in specific industries; 4-aminobiphenyl, along with other aromatic amines, is present in cigarette smoke [1–3].

The results obtained by Case et al. [10] concerning 4-aminobiphenyl were confirmed by Koss [11], who also found that the risk of developing bladder cancer after exposure to this compound is not fully dose related. Some workers suffering from low-level exposure developed bladder cancer, while in most workers, bladder cancer did not occur despite massive exposure [11]. These results supported the existence of powerful detoxification mechanisms.

Some carcinogenic compounds are derivatives of other aromatic amines and amides, including many azodyes derived from the aromatic amine, benzidine. Exposure to many of these chemicals has been associated with the development of bladder cancer in both humans and animal models—for example, in a group of kimono painters in

TABLE I. Etiologic Factors for Bladder Cancer

Occupational	Nonoccupational
2-Naphthylamine	Cigarette smoking
4-Aminobiphenyl	Chlornaphazine
Benzidine	Phenacetin-containing analgesics
4,4′ Methylenebis(2-chloroaniline)	Cyclophosphamide
4-Chloro-o-toluidine	Thiotepa[a]
o-toluidine	Melphalan[a]
Methylene dianiline	Radiotherapy
Benzidine-derived azodyes	Balkan nephropathy
	Arsenic
	Calculi

[a]In association with radiotherapy.

Japan who licked their paint brushes to obtain the fine points needed for the delicate paintings on the fabrics, the dyes were metabolized rapidly by cleavage of the diazo bond, resulting in free benzidine [3].

During the 1990s, additional aromatic amines and chemically related compounds have been identified that appear to be associated with the development of bladder cancer in humans, including 4,4-methylene bis(2-chloroaniline) (MBOCA) and o-toluidine [3]. MBOCA is a compound related to benzidine, found to produce low-grade papillary tumors in exposed workers [11]. The carcinogenicity of these compounds is no surprise, as the metabolism is similar to that of established carcinogenic aromatic amines. However, it is often difficult to pinpoint a specific etiologic agent because workers are often exposed to multiple chemicals, many of which are chemically related.

A large number of occupations are associated with an increased risk of bladder cancer development, without any identifiable specific chemicals responsible. The risk is especially increased for workers in the chemical, dye, rubber, and textile industries. An estimated 20–25% of the male population in the United States develop bladder cancer as a result of occupational exposure [3].

Researchers in the field of chemical carcinogenesis believe that elucidation of the metabolic processes that lead from the activation of chemicals on to DNA adduct formation, and ultimately on to cancer can provide a better understanding of the carcinogenesis [7]. This, in turn, could permit identification of high-risk individuals and allow the development of methods to prevent cancer. There are two main routes of metabolism of aromatic amines: (1) N-acetylation, and (2) N-hydroxylation (the routes are not mutually exclusive). In general, it is considered that the N-acetylated arylamide is not carcinogenic to the urothelium, while the N-hydroxylated metabolites formed in the liver are further metabolized by N-glucuronidation and excreted in the urine. The acid environment leads to the formation of the highly reactive and mutagenic arylnitrenium ion. Alternatively, N-hydroxylation or other metabolic steps may occur directly within the bladder epithelium [7].

A result of this hypothesis is that N-hydroxylated derivatives should be more carcinogenic to the bladder urothelium than their parent amines. This has been demonstrated for the human carcinogen 4-aminobiphenyl.

Humans express different metabolic phenotypes for xenobiotics, including aromatic amines, which could be associated with different susceptibilities for the development of bladder cancer. For example, since aromatic amines can be inactivated by acetylation, individuals who are slow acetylators would be expected **to** be more susceptible to bladder cancer development than rapid acetylators—and this has been found to be the case. Two N-acetyltransferase genes (NAT1 and NAT2) have been cloned, and the basis for the slow acetylator phenotype is the homozygous expression of the slow acetylator allele of the NAT2 gene. Patients who are heterozygous or homozygous for the fast acetylator allele express fast acetylator phenotype. Cartwright et al. [12] demonstrated the risk of bladder cancer to be 17 times higher in slow acetylators. Furthermore, 96% of the patients with occupationally related aromatic amine-induced bladder cancer were found to be slow acetylators. Several studies have confirmed the excess percentage of slow acetylators in bladder cancer patients, especially in patients with documented exposure to aromatic amines [7]. In addition, a review of a number of case-controlled studies suggests that slow acetylators are also associated with more invasive disease. The relationship between acetylator phenotype, smoking, and bladder cancer is less clear, and some studies have failed to demonstrate any correlation. It is interesting, however, that studies have shown that smokers of black tobacco have a higher risk of bladder cancer than smokers of blonde tobacco (the type most commonly used in the United States). Bartsch et al. [13] demonstrated that the level of 4-aminobiphenyl adducts was highest in smokers of black tobacco who were also slow acetylators.

Investigations on aromatic amines have focused particularly on chemicals related to occupational and cigarette smoke exposure, but during the past 25 years evidence has mounted to suggest that aromatic amines may be of more general relevance than previously realized. During the processing of foods at high temperatures, for example, carcinogenic heterocyclic aromatic amines are formed, especially during grilling or barbecuing of meat [3].

Other environmental pollutants have been identified in diesel exhaust. These chemicals include aromatic nitro compounds, which have been shown to be mutagenic and carcinogenic in several experimental models, producing tumors of several different organs, including the urinary bladder. These compounds are metabolically activated to reactive intermediates identical to analogous aromatic amines.

Animal testing, especially in rodents, has shown that other compounds produce bladder tumors, but it remains unclear whether these compounds contribute to the development of human bladder cancer. Included in this controversy are nitrosamines, which are ubiquitous in the environment and can also be formed endogenously under acidic conditions, such as in the stomach or urine, by nitration of secondary amines. Several nitrosamines have been shown to produce bladder cancer in animal models [14]. Different nitrosamines have also been identified in the urine, especially in association with lower urinary tract infections.

Epidemiologic studies have demonstrated increased risk of bladder cancer in individuals with chronic urinary tract infection, and urinary tract infection enhances experimen-

tal bladder cancer carcinogenesis. The mechanisms implicated are formation of nitrosamines or other carcinogenic compounds in the urine or increased cell proliferation, or both. It is interesting to note that certain nitrosamines, upon direct instillation into the bladder, do not cause bladder cancer, and exposure to other nitrosamines in the urine can result in systemic distribution of the nitroso compounds with induction of tumors in other organs [14]. This is likely to be related to absorption of nitrosamines from the urine as a result of increased permeability or damage to the urothelium, which may occur in humans with urinary tract infection. The role of nitrosamines in human bladder cancer, however, remains to be defined [3].

CIGARETTE SMOKING

Several epidemiological studies have shown a strong association between cigarette smoking and the development of bladder cancer. The relative risk is increased, is dependent on the number of pack-years smoked, and varies between 2–10 in different studies [1–3]. The risk is increased not only in patients with transitional cell carcinoma, but also in individuals with squamous cell carcinoma and adenocarcinoma [3]. It is estimated that cigarette smoking accounts for 25–60% of all cases of bladder cancer cases in industrialized developed countries, making it the single most important cause of bladder cancer.

The risks seem to vary, depending on which type of tobacco is smoked. Thus, smokers of black tobacco have a higher risk of bladder cancer than do smokers of blonde tobacco (the type most commonly used in the United States [13]). The risk **of** bladder cancer appears to be small in pipe and cigar smokers.

The precise mechanism by which smoking causes bladder cancer has yet to be determined, although it seems most likely that it is related to some of the large number of chemicals present in smoke. Smoke contains, among other chemicals, polycyclic aromatic hydrocarbons, aromatic amines, and unsaturated aldehydes. All these major classes of chemicals have been investigated with respect to bladder cancer [1–3]. Although polycyclic aromatic hydrocarbons have been associated with tumor development in various organs, there is little evidence to support their involvement in the etiology of human bladder cancer. They are metabolized at the site of exposure and excreted in the urine in metabolically inactive forms. By contrast, aromatic amines, especially 4-aminobiphenyl, are associated with the development of bladder cancer [3]. Other aromatic amines, including pyrolysis products, are possible contributors. Nicotine and its metabolites and tobacco-specific nitrosamines are implicated in lung and oral cancer but do not seem to play a role in experimental or human bladder cancer. Acrolein is the simplest of the α,β-unsaturated aldehydes-compounds that are ubiquitous in the environment. A cigarette contains approximately 100 μg of acrolein, the simplest of these aldehydes. These aldehydes are toxic, mutagenic, and possibly carcinogenic. Systematic administration of acrolein to rats results in diffuse urothelial hyperplasia of the bladder, and acrolein has been shown to be an initiator in bladder carcinogenesis in rats [15].

Besides the fact that many compounds in cigarettes can cause genotoxic events in the urothelium, cigarette smokers have been found to have an increased proliferative response, as evidenced by hyperplasia of the bladder epithelium. This appears to be dose-related and may have **a** synergistic effect, along with the genotoxic effects, on the bladder carcinogenicity of cigarette smoking [14].

CAFFEINE

Considerable controversy exists as to whether coffee and other caffeine-containing beverages are involved in urinary tract carcinogenesis [3]. The results of epidemiological studies show marked variation, with studies indicating either no **risk** or a slight increase in relative risk. Interpretation of the studies is often difficult because of the presence of confounding factors, especially cigarette smoking, but also occupational exposure and diet, which can be controlled only to a variable extent in the different studies. Experimental studies have failed to demonstrate that caffeine is carcinogenic to the **urinary** bladder. Thus, both long-term carcinogenicity studies and multistage studies have been negative for caffeine. The genotoxicity of caffeine also remains problematic and is largely dependent on the type of assay being used and the caffeine concentrations attained in the assay system. The evidence strongly favors the conclusion that caffeine is not mutagenic in humans.

TREATMENT-RELATED CARCINOGENESIS

Chlomaphazine is an alkylating agent that was originally used in the treatment of hematologic malignancies. It was quickly discontinued when a large percentage of patients treated with the compound developed bladder cancer after only a few years. The explanation was simple: chlornaphazine is an alkylating agent that is metabolically converted in the body to 2-naphthylamine, a known human bladder carcinogenic aromatic amine [3].

The intake of phenacetin-containing analgesics was initially associated with the development of renal papillary necrosis and chronic interstitial nephritis. Later studies demonstrated that such patients also had an increased risk of developing urinary tract tumors, particularly in the renal pelvis but also in the ureter and bladder. The relative risk (RR) varied from 2.3 to 12.2 in different series [3,16]. The patients had consumed several kilograms of analgesics, and the induction time was similar to that of occupational bladder cancer caused by other aromatic amines and amides. Phenacetin is an aromatic amide that can be metabolized to N-hydroxyphenacetin, which is carcinogenic

in animal models. In addition to phenacetin, the drugs used also contained caffeine, antipyrine, or acetylsalicylic acid. Experimentation has provided evidence supporting the association of phenacetin with urothelial cancer, but it is not completely conclusive. The data suggest that the process and interactions are complex and may not be the result of a single agent. Exposure of rats to phenacetin results in significant hyperplasia of renal pelvic and renal papillary epithelium, as well as increased cell proliferation of the renal pelvis and bladder urothelium. Occasional renal pelvic tumors are produced [3].

Cyclophosphamide and related chemotherapeutic agents induce bladder cancer in humans and in rodent models [3]. The first human case attributed to cyclophosphamide exposure was reported 25 years ago [17]. Cyclophosphamide is currently used to treat both neoplastic and non-neoplastic diseases in approximately 500,000 patients worldwide annually [18]. In a recent study of 6,171 2-year survivors of patients with non-Hodgkin's lymphoma who were treated with chemotherapy, including cyclophosphamides, 48 patients developed urinary tract cancer. The overall RR for these patients to develop bladder cancer was 4.5. It is important to note that for the first time the authors were able to demonstrate a dose-response relationship [18]. Thus, if the total dose was less than 20 g, the RR was 2.4; if the dose was 20–50 g, the RR was 6.3; and if the dose was over 50 g, the RR was 14.5. In a recent case-controlled study of patients with ovarian cancer treated with cyclophosphamide alone, it was found that these patients had a four-times higher relative risk for bladder cancer [19]. Bladder cancer following cyclophosphamide therapy appears to be unrelated to drug-induced hemorrhagic cystitis, which is a toxic manifestation of acrolein (a major metabolite of cyclophosphamide) [20]. The length of exposure has varied from months to a few years, and tumors develop faster from cyclophosphamide than after exposure to aromatic amines. Thus, in one study, the mean latency time for bladder cancer development after cyclophosphamide treatment was initiated was 8.5 years, with a range of 3–21 years. Similar results were presented by Kaldor et al. [19], who found that after chemotherapy with cyclophosphamide, tumors appeared before 10 years and continued to increase in frequency thereafter. Data from experimental studies on urinary bladder carcinogenesis show that acrolein, a major toxic metabolite of cyclophosphamide, is the likely carcinogenic intermediary [19]. The tumors appearing in patients exposed to cyclophosphamide cover the entire histological spectrum of those appearing normally in the bladder, although most are of high grade and high stage.

Kaldor et al. [19] also showed an association between bladder cancer and administration of the alkylating agents, thiotepa and melphalan. However, the relative risk was much higher in patients also receiving radiotherapy than in patients treated with radiation alone. The apparent interaction between radiotherapy and these two alkylating agents is surprising and could not be explained, either by methodological bias or by biological mechanisms. Additional studies are needed to verify these results. Other drugs used in intravesical treatment of bladder cancer include mitomycin C and Adriamycin. In the preliminary study by Soloway et al., two animals (9%) treated with intravesical mitomycin C developed bladder tumors, and one developed carcinoma in situ (MS Soloway, RB Matheny, WM Murphy, personal communication). Ohtani et al. [21] found that mitomycin C and adriamycin acted as strong promoters in N-butyl-N-(4-hydroxybutyl)nitrosamine (BBN) induced two-stage carcinogenesis in the Fischer rat, but there are no data to support the carcinogenicity of these substances in the human bladder. In a more recent study evaluating the effect of intravesical instillation of thiotepa, mitomycin C, and Adriamycin on normal rat bladder urothelium, 8%, 46%, and 0% of the rats, respectively, treated with these drugs, showed urothelial atypia. No bladder tumors were identified [22].

Radiotherapy to the pelvis for benign disease increases the RR of bladder cancer about 2.5 times, while treatment with higher doses (30–60 Gy) in patients with cervical carcinoma increased the relative risk four times [22]. In the study by Travis et al. [18] of patients with non-Hodgkin's lymphoma, radiotherapy alone was associated with a statistically nonsignificant increased RR of 2.8 [18]. In a study of ovarian carcinoma by Kaldor et al. [19], radiotherapy was found to increase the risk of bladder cancer 1.9 times; however, the figures were not statistically significant. The RR of radiotherapy for cervical cancer, which resulted in a mean bladder dose of about 45 Gy, was 4.0, in contrast to a RR of 1.3 with a mean dose of 35 Gy among women treated for ovarian cancer [19,23]. Apart from chance variation and differing dose distributions, the explanations for the discrepant relative risk may have been a longer follow-up time among the cervical cancer patients than among the women with ovarian cancer, or differences in the reference bladder tumor rates in the two studies related to geographical, temporal, or other factors in the study populations. Another difference may have been in the quality of the radiotherapy.

In the study by Kaldor et al. [19], cyclophosphamide produced a relative increase in bladder tumor risk about twice as high as that due to radiation. There was no evidence of a synergistic effect between radiation to the bladder and cyclophosphamide. The risk of bladder cancer was slightly higher among the women who had received cyclophosphamide alone, as compared to those who had received cyclophosphamide as well as radiotherapy involving exposure to the bladder. Patients receiving cyclophosphamide alone had an increased RR of 4.2–5.2, and the route of cyclophosphamide administration did not seem to matter [18,19]. It is interesting that the combination of cyclo-

phosphamide and radiotherapy did not further increase the risk of developing bladder cancer significantly, compared to either alone. These results did not substantiate a prior report that cyclophosphamide-induced urothelial proliferation contributes to an early expression of radiation injury [24]. Rather, it appears that cyclophosphamide by itself is carcinogenic.

URINARY TRACT INFECTIONS INCLUDING SCHISTOSOMIASIS

Although members of the genus *Schistosoma* may infect some 300 million people worldwide, the resultant pathology depends on the species and the number of parasites. Since most individuals harbor few worms, the actual number suffering from urinary schistosomiasis is much less. Infection with *Schistosoma hematobium*, an organism endemic to the Nile River valley in Egypt and many parts of Africa, has been linked to bladder neoplasia for almost a century [3,8]. The eggs of the parasites are deposited in the bladder wall, and the morbidity and mortality of the disease are associated with intensity and duration of the infection, as well as the activity of the disease. In sites of recent oviposition, granulomatous inflammation results in large polypoid masses protruding from the bladder mucosa into the lumen. This is followed by fibrosis and calcification and is often associated with squamous or glandular metaplasia. The proliferation rate of the epithelium is much higher than that of normal urothelium. The tumors formed are mainly squamous cell carcinomas (75%) and adenocarcinomas (6%); the remaining tumors are transitional cell carcinoma or undifferentiated carcinoma [8]. The squamous cell carcinomas are often of low grade, but due to patient delay, tumors often present at a high stage, with a 5-year survival rate of approximately 30% [8]. The mean age of patients with schistosomiasis-associated squamous cell carcinoma is 46 years — approximately 20 years younger than bladder squamous cell carcinoma patients in the United States and western Europe.

The mechanism by which *Schistosoma* induces bladder cancer is yet to be determined, but two factors appear to be important. First, there is increased cell proliferation of the epithelium as a result of inflammatory and regenerative processes. Chronically increased cell proliferation has been suggested as a mechanism providing an increased risk of spontaneous genetic mistakes, which may result in higher incidences of cancer in the bladder as well as other organs [25,26]. Second, many patients have coexistent urinary tract infections and nitrosamines, including volatile nitrosamines and BBN (a bladder carcinogen for rodents and dogs), have been identified in urine from such patients [27].

Epidemiologic studies support the association between urinary tract infection and bladder cancer, especially in women [3]. A similar effect has been observed in paraplegic patients with indwelling catheters [28]. These patients invariably suffer from chronic urinary tract infection. Analysis of urine from such patients reveals the presence of significant levels of volatile nitrosamines, which have also been found in patients with schistosomiasis [29,30]. The similarities suggest that endogenous nitrosamine formation, which occurs in the urinary tract of paraplegics and individuals with schistosomiasis, plays an etiological role in the carcinogenesis of squamous cell carcinoma of the bladder.

OTHER CHEMICALS

A number of agents and processes have been associated with inhibition or enhancement of the rate of bladder cancer in humans. Based on a number of experimental studies, there has been a suggestion that artificial sweeteners, especially sodium saccharin and cyclamate, are associated with increased risk of the development of bladder cancer [3]. Male rats fed high doses of these compounds, generally 5% of their diet, develop a higher rate of bladder cancer, especially if the sweeteners are administered for two generations or begun at birth and continued for the lifetime of the rat. A large number of epidemiologic studies have been performed to evaluate the relationship between exposure to these sweeteners and the development of bladder cancer in humans but have failed as yet to find such a relationship. There is also one report suggesting that not only is there lack of epidemiologic evidence for tumor formation in individuals who consume saccharin, but there is no increase in urothelial proliferation in individuals exposed to artificial sweeteners [31]. Detailed studies have shown that the mechanism in rodents appears to be related to the urinary formation of silicate-containing calcium phosphate crystals or precipitate, mainly in male rats, which have a high level of α2u-globulin in the urine. These crystals or precipitates appear to be cytotoxic to the urothelium, resulting in a chronic proliferative state, and ultimately, the formation of tumors. Similar factors necessary for the development of silicate-containing crystals and precipitate are not present in human urine; therefore, it seems highly unlikely that sodium saccharin or any other salt form of saccharin is related to the development of human bladder cancer [3].

Some 40 years ago, it was suggested that the amino acid tryptophan–especially its aromatic amine metabolites—is associated with an increased risk of development of bladder cancer in humans [1,2]. Studies indicated that the increased risk might be related to increased cell proliferation in individuals who have a high intake of tryptophan in the diet, but this idea has not been corroborated in subsequent studies [3]. The relationship between tryptophan metabolites and bladder carcinogenesis has not been completely resolved, however, it does not appear to be an important factor in the development of human bladder cancer.

Individuals who are immune-suppressed as a result of disease, such as genetic immunodeficiencies or acquired

immunodeficiency syndrome (AIDS), or as a result of treatment, such as transplant patients, have an increased risk of developing malignancies. However, most of these tumors seem to be related to viral etiology. Further, the majority of those tumors that develop in immune-suppressed patients are hematologic malignancies, although there are also a number of epithelial malignancies often associated with viruses, especially human papillomavirus (HPV). There is no evidence that immune suppression increases the risk of bladder cancer development [32]. Patients undergoing treatment with cyclophosphamide become immune-suppressed, but the carcinogenic effect of this drug is more likely to be secondary to metabolic activation, rather than immune suppression, as discussed earlier.

Dietary factors in experimental animals and humans have been observed to influence the development of bladder cancer, although the specific relationships remain poorly defined [3]. There is some support for the observation that individuals with greater vitamin A or carotene ingestion have a lower rate of bladder cancer than is found in individuals who consume lower amounts of these substances. To some extent, experimental studies have supported this contention and have formed the basis for the use of retinoids as potential chemopreventive agents in patients with a previous papillary transitional cell carcinoma. Epidemiologically, there is some evidence that high doses of vitamin C reduce the development of bladder cancer. However, experimental studies have failed to lend support to that observation. Administration of extremely high doses of sodium ascorbate (5% in the diet) results in enhancement of bladder carcinogenicity in the rat [3]. However, the mechanism is likely to be similar to that for sodium saccharin and is unrelated to the antioxidant properties of vitamin C, and thus not relevant to human exposure.

Exposure to drinking water in areas with a high pesticide usage is associated with an increased risk of the development of bladder cancer [3], although the reason for this is unclear. These findings may explain the regional differences in the distribution of bladder cancer in the United States; however, because bladder cancer is more prevalent in parts of the country where there is heavy industrialization, the regional differences more likely would appear to be related to industrial exposure, rather than to the drinking water. From time to time there have been suggestions of an association between development of bladder cancer and different viruses such as retroviruses, papillomavirus, herpes virus, and adenoviruses, but there is little evidence to support such an association.

Urinary tract calculi have also been associated with a relatively slight increased risk of bladder cancer [33]. This is likely due to repeated abrasion of the urothelium with regenerative hyperplasia and is frequently associated with squamous cell carcinoma rather than transitional cell carcinoma. In rats and mice, calculi are much more commonly associated with the development of bladder cancer.

Other circumstances, such as bladder diverticuli, neurogenic bladder, and paraplegia, are associated with urinary stagnation in humans and are related to an increased risk of bladder cancer. These circumstances are usually associated with chronic urinary infections, a known risk factor for human bladder cancer.

Finally, a relationship between bladder extrophy and the development of bladder adenocarcinoma has been shown for some time, although the mechanism by which this occurs remains unknown [4].

CONCLUSIONS

Several causal factors of bladder cancer have been identified, including specific chemicals, occupations, infections, and environmental exposures. A careful history of patients with bladder cancer is an important and useful process in helping identify causal factors, with a known relationship identifiable in more than one-half of cases. Additional inquiry should help us to identify additional factors.

REFERENCES

1. Clayson DB, Cooper EH: Cancer of the urinary tract. [Review] Adv Cancer Res 1970;13:271–381.
2. Price JM: Etiology of bladder cancer. In Maltry E Jr (ed): "Benign and Malignant Tumors of the Urinary Bladder." Flushing, NY: Medical Examination Publishing, 1971:189–251.
3. Cohen SM, Johansson SL: Epidemiology and etiology of bladder cancer. [Review] Urol Clin North Am 1992;19:421–428.
4. Peterson RO: "Urologic Pathology." 2nd Ed. Philadelphia: JB Lippincott, 1992, 328–338.
5. Kaye KW, Lange PH: Mode of presentation of invasive bladder cancer: Reassessment of the problem. J Urol 1982;128:31–33.
6. Kiemeney LA, Witjes JA, Verbeek AL, et al: The clinical epidemiology of superficial bladder cancer. Dutch South-Eastem Cooperative Oncology Group. Br J Cancer 1993;67:806–812.
7. Stadler WM: Molecular events in the initiation and progression of bladder cancer. [Review] Int J Oncol 1993;3:549–557.
8. El-Bolkainy MN: Schistosomiasis and bladder cancer. In Cohen SM, Bryan CT (eds): "The Pathology of Bladder Cancer." Vol. 1. Boca Raton, FL: CRC Press, 1983, 57–89.
9. Hopenhayn-Rich C. Biggs ML, Fuchs A, et al: Bladder cancer mortality associated with arsenic in drinking water in Argentina. [comment in: Epidemiology 1996;7:113–115] Epidemiology 1996; 7:117–124.
10. Case RA, Hosker ME, McDonald DB, Pearson JT: Tumours of the urinary bladder in workmen engaged in the manufacture and use of certain dyestuff intermediates in the British chemical industry. I. The role of aniline, benzidine, alpha-naphthylamine, and beta-nephthylamine. Br J Ind Med 1954;11:75–104.
11. Koss L: "Diagnostic Cytology of the Urinary Tract With Histopathologic and Clinical Correlation." Philadelphia: Lippincott-Raven, 1995, 71–139.
12. Cartwright RA, Glashan RW, Rogers HJ, et al: Role of N-acetyltransferase phenotypes in bladder carcinogenesis: A pharmacogenetic epidemiological approach to bladder cancer. Lancet 1982;2(8303):842–845.
13. Bartsch H, Malaveille C, Friesen M, et al: Black (air-cured) and blond (flue-cured) tobacco cancer risk. IV. Molecular dosimetry studies implicate aromatic amines as bladder carcinogens. [Review] Eur J Cancer 1993;29A:1199–1207.
14. Lijinsky W, Thomas BJ, Kovatch RM: Systemic and local carcinogenesis by directly acting N-nitroso compounds given to rats by intravesicular administration. Carcinogenesis 1992;13:1101–1105.

15. Cohen SM, Garland EM, St. John M, et al: Acrolein initiater rat urinary bladder carcinogenesis. Cancer Res 1992;52:3577–3581.
16. Bokemeyer C, Thon WF, Brunkhorst T, et al: High frequency of urothelial cancers in patients with kidney transplantations for end-stage analgesic nephropathy. Eur J Cancer 1996; 32A:175–176.
17. Worth PH: Cyclophosphamide and the bladder. BMJ 1971; 3(767):182.
18. Travis LB, Curtis RE, Glimelius B, et al: Bladder and kidney cancer following cyclophosphamide therapy for non-Hodgkin's lymphoma. J Natl Cancer Inst 1995;87:524–530.
19. Kaldor JM, Day NE, Kittelmann B, et al: Bladder tumours following chemotherapy and radiotherapy for ovarian cancer: A case-control study. Int J Cancer 1995;63:1–6.
20. Pedersen-Bjergaard J, Ersboll J, Hansen VL, et al: Carcinoma of the urinary bladder after treatment with cyclophosphamide for non-Hodgkin's lymphoma. N Engl J Med 1988;318: 1028–1032.
21. Ohtani M, Fukushima S, Okamura T, et al: Effects of intravesical instillation of antitumor chemotherapeutic agents on bladder carcinogenesis in rats treated with N-butyl-N-(4-hydroxybutyl)-nitrosamine. Cancer 1984;54:1525–1529.
22. Friedman D, Mooppan UM, Rosen Y, Kim H: The effect of intravesical instillations of thiotepa, mitomycin C, and adriamycin on normal urothelium: An experimental study in rats. J Urol 1991;145:1060–1063.
23. Boice JD Jr, Engholm G, Kleinennan RA, et al: Radiation dose and second cancer risk in patients treated for cancer of the cervix. Radiat Res 1988;116:3–55.
24. Edrees G, Lutz A, Stewart F Bladder damage in mice after combined with cyclophosphamide and x-rays: The influence of fining and sequence. Radiol Oncol 1988;11:349–360.
25. Cohen SM, Ellwein LB: Cell proliferation in carcinogenesis. [Review] [comment in: Science 1991;251 (4990):142–1441 Science 1990;249(4972):1007–1011.
26. Cohen SM, Purtilo DT. Ellwein LB: Pivotal role of cell proliferation in human carcinogenesis. [Review] Mod Pathol 1991; 4:371–382.
27. Hicks RM, Ismail MM, Walters CL, et al: Association of bacteriuria and urinary nitrosamine formation with *Schistosoma haematobium* infection in the Qalyub area of Egypt. Trans R Soc Trop Med Hyg 1982;76:519–524.
28. Dolin PJ, Darby SC, Beral V Paraplegia and squamous cell carcinoma of the bladder in young women: findings from a case-control study. Br J Cancer 1994;70:167–168.
29. Tricker AR, Mostafa MH, Spiegelhalder B, Preussmann R: Urinary excretion of nitrate, nitrite, and N-nitroso compounds in schistosomiasis and bilharzia bladder cancer patients. Carcinogenesis 1989;10:547–552.
30. Tricker AR, Stickler DJ, Chawla JC, Preussmann R: Increased urinary nitrosamine excretion in paraplegic patients. Carcinogenesis 1991;12:943–946.
31. Auerbach O, Garfinkel L: Histologic changes in the urinary bladder in relation to cigarette smoking and use of artificial sweeteners. Cancer 1989;64:983–987.
32. Penn I: Cancers complicating organ transplantation. [editorial][comment in: N Engl J Med 1990 323:1723–1728] N Engl J Med 1990;323:1767–1769.
33. Burin GJ, Gibb HJ, Hill **RN:** Human bladder cancer: evidence for a potential irritation-induced mechanism. [Review] Food Chem Toxicol 1995;33:785–795.