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The Etiology of Bladder Cancer and its Prevention

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Abstract

Urinary bladder cancer (UBC), which rinks ninth in worldwide cancer incidence, is a type of malignant growth of abnormal cells. UBC can be caused by: (A) Inhalation of cigarette smoke, smoke from cooking fume hoods, industrial/environmental carcinogens, volatiles of coal tar, and diesel exhaust. (B) Drugs such as cyclophosphazine, chloronaphazine, phenacetin, nitrosamines, and herbal remedies like aristolochic acids. (C) Contact of chlorinated water or hair dyes. (D) Ingestion of bracken fern (*Pteridium aquilinum*) and/or arsenic. (E) Infections of *Schistosoma haematobium* (schizosomiasis), Enterobacteria (Cystitis) and Papilloma viruses. (F) Endogenous carcinogens such as tryptophan metabolites and other amines. (G) Hereditary factors such as acetylator of the *N*-acetyltransferase, and mutations or malfunction of oncogenes/suppressor genes. Prevention of bladder cancer should include cessation of smoking, minimization of exposure to cooking fumes, and elimination of industrial and environmental carcinogens. Other measures worth considering include: (A) Intake of fruits, vegetables, soy products, vitamins, green tea, and decrease of fat consumption. Ingestion of food that is rich in selenium, garlic, lycopene, linoleic acid, various vitamins, gallic acid, and betulinic acid, etc. (B) Intake of non-nutritional factors including astaxanthin, procatachuic, diosmin, hesperidin, 1,4-phenylene diisothiocyanate, crytoxanthin, indomechacin, and silibinin, etc. (C) Administration of drugs such as difluoromethylornithine (DFMO), no steroid anti-inflammatory drugs (NSAIDs), astorvastatin, oitipraz, and Bacillus Calmette-Guerin (BCG). Retinoic acid in combination with ketoconazole was reported to be helpful to bladder cancer patients. In conclusion, the management of interplay of multiple factors of cause, cure and prevention, is the major concern of UBC.

Keywords: Urinary Bladder Cancer (UBC); Squamous cell; Carcinogens; Arylamines

Introduction

The most common type of bladder cancer occurs in cells lining, inside of the bladder, which is called transitional cell carcinoma (urothelial carcinoma). Another type of UBC is squamous cell carcinomas that originated from the thin, flat cells that result in the inflammation or irritation for many months or years. The third type is adenocarcinoma that forms in glands, specialized structures that produce and release fluids such as mucus.

In the United States, urothelial transitional cell carcinomas account for more than 90 percent of all bladder cancers. The remaining 10% are squamous cell carcinomas (3% to 8%) and adenocarcinomas (1%). Other sarcoma, small cell carcinoma, and other cancers can also occur in the bladder. Recurrence of cancer can happen in the urinary bladder or another nearby organ after having been treated [1].

Bladder cancers are classified (staged or graded) by how deeply the bladder wall is invaded. Superficial bladder cancer is limited to the innermost lining of the bladder known as the mucosa and lamina propria. Invasive bladder cancer has at least penetrated the muscular layer of the bladder wall. Nearly all wall cell cancers are invasive. Most urothelial cell carcinomas are not invasive.

More than 90% of case of UBC occur in people older than 55, and 50% of cases occur in people older than 73. Ploeg et al. [2] reported in 2009 that more than 2.7 million people have a history of UBC, and more than 12 million new cases occurred worldwide in 2003 [1]. Of those, 5.4 million occurred in developed countries and 6.7 million in developing countries [2,3]. UBC ranks ninth in worldwide cancer incidence. It is the seventh most common malignancy in men and seventeenth in women [2]. An estimated 386,300 new bladder cases and 150,200 deaths from bladder cancer were diagnosed worldwide in 2008 [4]. It is predicted that the burden of UBC will increase in less developed areas of the world because of smoking prevalence that goes along with economic development [2].

In the United States, UBC is the fifth most common type of cancer with an estimated 68,000 newly diagnosed cases and 14,000 deaths in 2008 [5]. There are multiple factors involved with the etiology of UBC. This paper will review the major factors that have been reported to play an important role in the initiation of UBC and also discuss the measures of preventing this disease.

Etiology of Urinary Bladder Cancer

Caused by inhalation

Cigarette smoke: Smoking is the main known contributor to UBC in most populations. Recent studies by Freedman et al. [6] indicated that the population attributable risk (PAR) of bladder cancer for tobacco is 50 percent to 65 percent in men and 20 percent to 30 percent in women. Current cigarette smokers have a triple risk of bladder cancer relative to those who have never smoked. Smoking is responsible for about half of bladder cancer cases [6]. As with many other smoking-related cancers, smoking cessation was associated with reduced bladder cancer risk.

According to the U. S. Department of Health and Human Services [7], cigarette smoke contains a number of

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carcinogens including acetaldehyde, acrylonitrile, *o*-anisidine hydrochloride, *4*-aminobiphenyl, arsenic, benzene, beryllium, *1,3*-butadiene, cadmium, *1,3*-dimethylhydrazine, ethylene oxide, formaldehyde, furan, heterocyclic amines, hydrazine, isoprene, lead, *2*-naphthylamine, nitromethane, *N*-nitoso-*N*-butylamine, *N*-dinitrosodiethanolamine, *N*-nitrosodimthylamine, *N*-nitroso-di-*N*-propylamine, *4*-(*N*-nitrosomethyamino)-*1*-(*3*-pyridyl)-*1*-butanone, *N*-nitrosononicotine, *N*-nitrosopiperidine, *N*-nitrosopyrrolidine, *N*-nitrososarcosine, polonium-210, polyclclic aromatic hydrocarbons, *N*-toluidine, and vinly chloride. Some of these carcinogens were reported to cause bladder cancer [8-10].

Cooking fume hood: Chiang et al. [11] analyzed cooking fume samples in the kitchens of Chinese homes and found that there were mutagenic *2*-naphthylamine (*2*-NA) and *4*-aminobiphenyl (*4*-ABP), which can cause bladder cancer [9,10]. Concentrations of *2*-NA and *4*-ABP were 31.5 and 35.7 μg/m^3 in fumes from sunflower oil, 31.9 and 26.5 μg/m^3 in vegetable oil, and 48.3 and 23.3 μg/m^3 in refined oil.

Other genotoxicpolycyclic compounds such as benzo [a] pyrene (BaP), benzo[a]anthracene (BaA), dibenz(a,h) anthracene [DBahA], benzo(b)fluoranthene (BbFA), and benzo(a)pyrene [B(a)P] were detected and identified in commercial cooking oil (safflower, olive, coconut, mustard, vegetable, and corn) [12,13]. Yang et al. [14] also detected the carcinogen *2*-amino-*3,8*-dimethylimidazo [*4,5*-f] quinoxaline (MeIQx) in cooking aerosol under domestic conditions. Wu et al. [15] reported that *trans-trans-2,4*-decadienal, *trans-trans-2,4*-nonadienal, *trans-2*-decenal and *trans-2*-undecenal were mutagenic in the *Samonella typhimurium* TA98 and TA100 in the Ames Salmonella test and were detected in the fumes of peanut oil. These results show the enal compounds formed as the mutagens in the fume of peanut oil and indicated that inhalation of cooking fumes might cause carcinogenic risk including bladder cancer (Table 1). Other carcinogens such as 1,3-butadiene, benzene, acrolein, formaldehyde, and other related compounds were quantitatively detected, with emissions tending to be higher for unrefined rapeseed oil and lowest for peanut oil fumes [16,17]. Hecht et al. [18] showed that an increased exposure to the volatile toxicants and carcinogens acrolein, crotonaldehyde, and benzene in Chinese women who regularly cooked provided a plausible lead as the cause of lung cancer. Pan et al. [19] investigated the effect of Chinese restaurant workers of exposure to cooking oil fumes and found that the urinary *8*-hydroxypyrene *(1-OHP)* and *8*-hydroxy-2'-deoxyguanosine (*8*-OHdG) in kitchen staffs were significantly higher than those of service staffs. Ko et al. [20] reported that exposure to fumes from cooking oils was an important risk factor for lung cancer in Taiwanese women nonsmokers. Wu et al. [21] investigated the lung cancer among the nonsmoking Taiwanese found that exposure to fumes samples as a risk factor. Fume samples from three different commercial cooking oils (lard, soybean and peanut) were collected for genotoxicity analysis in SOS chromotest test and sister chromatid exchange (SCE) assay. The induction factors of the SOS chromotest in *Escherichia coli*/PQ 37 were dependent on the concentrations of lard and soybean cooking extracts without S9 mix. In addition, CHO-K1 cells were exposed to condensates of cooking oil fumes for 12 hours. SCEs showed a dose-related increase in extracts of lard and soybean oil fumes.

According to the findings of epidemiologic studies, women exposed to emitted fumes of cooking oils are at an increased high risk of contracting lung cancer [21]. Although most of above mentioned studies pointed out that the lung cancer was specially detected, but oil cooking fumes might likely be an important risk factor for bladder carcinogenesis as postulated by Chiang et al. [11] because the bladder carcinogens such as *2*-NA and *4*-ABP were also detected.

Industrial carcinogens: The involvement of aromatic amines in bladder cancer began with the surgeon Ludwig Rehn who first described three cases of occupational bladder tumors in approximately 45 fuchsine workers in Frankfurt, Germany [22,23], and Wilhelm C Hueper who was the first to apply *2*-NA to induce bladder cancer in dogs [24]. Based on these pioneer studies, there were many aromatic amines identified that caused UBC. Aromatic amines are generally produced for dye industries. Chung et al. [25-27], reported that intestinal microbiota, as Wang et al. [28,29] also reported that many skin and environmental microorganisms could produce aromatic amines by cleavage azodyes ingested from food or contaminated water. The typical examples of aromatic amine produced by azo dyes are listed in Table 2. The specific case of aromatic amines arising from the reduction of the azo bond of azo colorants, their vulnerability to azo bond reduction through different mechanisms, and the lack of data on the biodegradability of the resulting amines were reviewed by Pinheiro et al. [30]. Arylamines can be produced by reduction of nitrated polycyclic aromatichydrocarbons (nitro-PAHs) by anaerobic bacteria of human intestine [31-33]. Nitro-PAHs have also been detected in carbontoners, urban air particulates, diesel fuel emissions, used motor oils, barbecued food, and tealeaves [34-37]. Nitro-PAHs are ubiquitous environmental contaminants that are formed from various combustion sources [35]. Another source of arylamines is from munitions such as dinitrotoluene (DNT). DNT can be reduced by environmental microorganisms to aromatic amines, which contaminate the groundwater [38]. Stayner et al. reported that there was excess hepatobiliary cancer mortality among munition workers exposed to DNT [38]. When these aromatic amines are absorbed through circulation, as reachthe liver, aromatic amines are oxidized to their *N*-hydroxy derivatives in the liver by the cytochrome P-450 IAI isozyme [9]. The *N*-hydroxyl derivatives are esterifies by acetyltransferase to the *N*-acetoxy derivatives or glucuronidated by *UDP*-glucuronidase to form *N*-glucuronidates, both of which are transported by the blood and the urine [39]. The *N*-acetoxy derivatives and *N*-glucuronidates are converted to arylnitrenium ions

Chemicals	References
Acrolein, crotonaldehyde, and benzene	[17]
2-Amino-*3,8*-dimethylimidazo[*4,5*-f]quinoxaline (MeIQx)	[13]
4-Aminobiphenyl (*4*-ABP)Benzo[a]pyrene (BaP),	[11,12]
Benzo[a]anthracene (BaA),	[11,12]
Benzo[b]fluoranthene (BbFA),	[11,12]
1,3-Butadiene, benzene, acrolein, formaldehyde	[15]
Dibenz[a,h]anthracene [DBahA],	[11,12]
2-Naphthylamine (2-NA)	[8,9]

Table 1: Examples of carcinogens detected in cooking hood fumes.

Aromatic amines	Azo dyes
o-Tolidine	Trypan blue
2,6-Dimethylaniline	Ponceau 2R
2,4,5-Trimethylaniline	Ponceau 3R
N,N-Dimethyl-*p*-phylenediamine	Methyl Red, Methyl Yellow, Methyl Orange
1-Amino-2-Naphthol	Red, Orange I, Orange II, Sudan 1, Sudan IV
1,4-Naphthyldiamine	Phenylazo-1-naphthylamine
Sodium Naphthionate	Amaranth (Red# 2)
Benzidine	Direct Black 38
o-Toluidine	Direct Blue 14

Table 2: Examples of potential carcinogenic aromatic amines metabolically produced from azo dyes.

in the bladder, which can interact with DNA to form DNA adducts in the bladder [40,41]. Therefore, these aromatic amines are especially active carcinogens for inducing cancer in the bladder. The NADPH-cytochrome P-450, various forms of P-450, and peroxidase such as bladder prostaglandin H synthase (PHS) can also activate aromatic amines to reactive free radical intermediates or produce reactive oxygen species (ROS). Review of mechanisms of carcinogenic processes of these aromatic amines is available elsewhere and will not be repeated here [42-45]. The International Agency for Research on Cancer (IARC) evaluated some aromatic amines, organic dyes, and related exposure in Leon, France, in 2008 and concluded that benzidine (Bz), dyes metabolized to Bz, auramine production, magenta production,

4,4'-methylenebis(*2*-choroaniline) (MOCA), *4-ABP, NA*, and *o*-toluidine as group 1 carcinogens (the agent is carcinogenic to humans), *4*-chloro-*o*-toluidine, and occupational exposure to hair dyesasa hairdresser as group 2Acarcinogens (the agent is probably carcinogenic to humans), and *4*-chloro-*ortho*-toluidine and auramine as group 2B carcinogens(the agent is possibly carcinogenic to humans) [10]. Likewise, environmental or occupational exposures to those carcinogens in the workplace were responsible for a high incidence of UBC. People who regularly work with certain chemicals or in certain industries have a greater risk of UBC than the general population.

These chemicals are used in dye industries. Other industries linked to bladder cancer include rubber and leather (including shoe) processing, textiles, hair dressing, painting, and printing. Occupations that are at high risk are bus drivers, rubber workers, motor mechanics, blacksmiths, machine setters, and mechanics.

Examples of commonly occurring industrial use or environmentally exposed aromatic amines are *4*-aminoazobenzene, *o*-aminoazotoluene, *4*-amino-*2',3*-dimethylazobenzene, *2*-aminofluorene, 4-aminoazobenzene, *o*-aminoazotoluene, *4*-amino-*2',3*-dimethylazobenzene, *2*-aminofluorene, 4-aminoazobenzene, *o*-aminoazotoluene, *4*-amino-*2',3*-dimethylazobenzene, *2*-aminofluorene, *4*-amino-*2*-nitrophenol, *o*-anisidine, benzidine, *4*-chloroaniline, *4*-chloro-*o*-toluidine, citrus red No 2, *p*-cresidine, *d*-diactylaminoazotoluene, *3,3'*-dichlorobenzidine, *3,3'*-dimethoxybenzidine, *p*-dimethylamino-azobenzene,*3,3'*-dimethylbenzidine, *N-2*-fluorenyl-acetamide, *3,2'*-dimethyl-4-aminodiphenyl, *4,4'*-methylene-bis-(*2*-chloroaniline), *4,4'*-methylenedi-o-toluidine, *4,4'*-methylenedianiline, *4*-methoxy-m-phenylenediamine, *2*-methoxy-*3*-aminodibenzofurane, *2*-naphthylamine, 5-nitro-o-toluidine, oil orange SS, *4,4'*-oxydianiline, *N*-phenyl-*2*-naphthylamine, ponceau 3R, sudan I, sudan II, *4,4'*-thiodianiline, *o*-tolidine, *o*-toluidine. And the commonly used nitorosoamines are *N*-methyl-*N'*-nitrosourea, *N,N'*-dibutylnitrosamine, *β*-butyl-*N*-hydroxybutylnitrosamine, *N*-butyl-*N*-(*3*-carboxypropyl)-nitrosamine, *N*-methyl-*N*-dodecylnitrosamine, *N*-ethyl-*N*-(*4*-hydroxybutyl) nitrosamine, etc.

Volatiles of coal tar: Coal tar pitch volatiles (CTPVs) are composed of various chemical vapors that become airborne during the heating of coal tar pitch. A black or dark-brown amorphous residue is produced by the distillation or heat treatment of coal tar. CTPVs solid at room temperature and exhibit a broad softening range instead of a defined melting temperature. Synonyms for CTPVs vary depending upon a specific compound (e.g., pyrene, phenanthrene, acridine, chrysene, anthracene and benzo[*a*]pyrene). The National Institute for Occupational Safety and Health (NIOSH) considers coal tars, coal tar pitches, and creosotes to be coal tar products. The following polycyclic aromatichydrocarbons (PAHs) are generally included in the coal tar volatiles:acenaphthene, anthracene, benz(*a*)anthracene, benzo(*b*) fluoranthene, fluorene, and na]hthaene. Coal tars and coal-tar pitches are known to be human carcinogensbased on sufficient evidence from studies in humans [46]. The risk of bladder cancer was increased in tar distillers and patent-fuel workers exposed to coal tars and coal-tar pitches and also in aluminum production workers exposed to coal-tar pitches [47]. Coal tar, pitch creosote, coke oven emissions, and asphalt exposure can also result in the formation of skin tumors and/or lung tumors in animals. Stern et al. [48] also reported that roofers were found to have a significant increased mortality for lung and bladder cancers. Although the major risk of CTPVs is the lung cancer, CTPVs may cause bladder cancer as well.

Diesel and gasoline exhausts: Silverman et al. [49] demonstrated that males employed as truck drivers or deliverymen have a statistically significant (50%) increase in risk of bladder cancer. This finding is based on the National Bladder Cancer Study, a population-based, case-control study conducted in ten areas of the United States in 1986. Elevations in risk were also suggested for taxicab and bus drivers. Colt et al. [50] also reported that male tractor-trailer truck drivers had an elevated risk for bladder cancer (OR=2.4, CI=1.4-4.1), with a significant positive trend in risk with increasing duration of employment (P_{trend}=0.0003). However, Iyer et al. [51] reported that a total of 136 cases of men with urinary bladder cancer and 272 matched hospital controls were examined for potential exposure to diesel exhausts; there was no evidence of elevated risk in occupations with possible or probable exposure. Truck drivers alone were not associated with elevated risk. Guo et al. [52] assayed the risk of esophageal, ovarian, testicular, kidney, and bladder cancers and leukemia among Finnish workers exposed to diesel or gasoline engine exhaust and discovered that a slight elevation of relative risk for bladder and kidney cancers were found even at the lowest exposure level of engine exhausts, largely attributable to drivers. No effect of the exposure was observed for other cancers except the ovarian cancer. Boffetta and Silverman [53] analyzed the relationship between bladder cancer and diesel exhaust and suggested that exposure to the diesel exhaust might increase the occurrence of bladder cancer.

Diesel and gasoline exhausts are certainly cancer causing. However, the geographical parameters such as temperature, humidity, and latitude pressure may have effects in enhancement of risk factor in engine exhaust, cooking fume hood, etc. Different temperature and latitude pressure may significantly affect the expansion of fumes. Experiments conducted in the hot areas of the world might generate data that showed a more close relationship between increased cancer and exposure to diesel exhaust. A controlled experiment is needed to illustrate this viewpoint.

Methenamine vapor: Methenamine with trade names of Cystex or Hiprex, is readily available over the counter for treatment of urinary tract infections (UTI). Methenamine is converted to formaldehyde in an acid urinary environment, which consequently kills bacteria. Formaldehyde is a well-known human carcinogen [54]. Out of various organs in the urinary tract, the bladder will suffer the most exposure due to the storage of urine. Wang et al. [55] showed that as exposure caused DNA damage in the urinary bladder transitional epithelium of rats. Repair of the induced DNA damage occurred within four hours. Unfortunately, in the case of long term use of methenamine, the continuous exposure to formaldehyde more likely creates over whelming repair mechanism [55]. Based on the foregoing, there is good reason to be concerned that formaldehyde in the bladder, as a result of methenamine use, could cause cancer.

Caused by drugs

Cyclophosphamide: Cyclophosphamide was reported to induce cystitis and bladder cancer (transitional-cell carcinoma of the urinary

bladder) in patients with Wegener's granulomatosis [56,57]. However, Hellmich et al. (2009) argued that development of urinary tumors is not necessarily caused by cyclophosphamide alone; rather, bladder cancer appears to be related to the autoimmune disease itself [58].

Chloronaphazine: Chlornaphazine is a derivative of *2*-naphthylamine, a nitrogen mustard that was developed in the 1950s for the treatment of polycythemia and Hodgkin's disease [59]. Thiede and Christensen [60] reported that bladder tumor was induced by chloronaphazine. Laursen [61] reported that patients treated with chloronaphazine developed bladder cancer. Chloronaphazine was discussed and classified by the International Association Research on Cancer (IARC) in 2010 and 2012 as carcinogenic to humen (Group 1) [62,63].

Phenacetin: Angervall et al. in 1969 [64] reported that Phenacetin induced bladder cancer. Castelao et al. [65] further confirmed that phenacetin, but not its metabolite acetaminophen, was related to bladder cancer. Piper et al. [66] also reported an association between the heavy phenacetin, but not metabolite acetaminophen use, and bladder cancer in women aged 20 to 49 years. McCredie et al. [67] also found that phenacetin containing analgesics caused cancer of the bladder or renal pelvis in women. Nagata and Masuda [68] reported that a case of bladder tumor incidence in a 85-year old man who had been heavily engaged in the use of phenacetin since he was 45 years of age.

Nitrosamines: Nitrosamines are generally regarded as cancer causing agents [69]. Many nitrosamines are produced when the food preservative nitrite combines with amino acid in the stomach. Nitrate is mainly used in inorganic fertilizers as a food preservative, especially in cured meats. The compounds are also found in cheese products, beer, and water. Exposure can occur through manufacturing and processing of rubber and latex products as well as fertilizers, pesticides, and cosmetics. Hicks et al. [70] reported that cancer would develop in primates infected with *Schistosoma haematobium* and concurrently exposed to low initiating doses of bladder carcinogen *β*-butyl-*N*-*N*-(*4*-hydroxybutyl)-nitrosamine) (BBN).

4-Hydroxybutyl(butyl)-nitrosamine-induced urinary bladder in mice was demonstrated by Lubet et al. [71]. Some processed meat products like baconcontain nitrosamines. Heavy consumption of bacon has been reported to result a high risk of bladder cancer. Martelli and Brambilla [72] discovered that 105 out of 109 arylamine drugs could be nitrosated with nitric acid to form *N*-nitroso compounds (NOC). Many of these nitro so compounds were positive in short term or long term genotoxic tests. Therefore, nitrosamines would likely be a risk factor for bladder carcinogenesis.

Herbal remedies: Chinese herbs that contain aristolochic acid (AA) called Mu Tong have been reported to increase the risk of urinary tract cancer [73]. Aristolochic acid was first reported to cause aristolochic acid nephropathy--a progressive as a form of renal interstitial fibrosis in a group of young Belgian patients with end-stage renal disease in 1993 [74-76]. Recently, chronically Aristolochia poisoning responsible as etiology of Balkan epidemic nephropathy (BEN), which affects residents in certain rural area in Romania, Croatia, Serbia, Biosnia and Bulgaria. Diet could be the cause of aristiolochic acid (AA) [77,78]. Using evidence from aristolochic (AA)-specific DNA adducts and TP53 mutation spectra in BEN-associated urothelial tumors, the causative role of AA was unambiguously demonstrated [69-82]. Evidence indicated that AA is the common etiological agent for BEN. AA is the plant extracts derived from Aristolochia spp. (*Aristolochia clematitiss*, *Aristolochia fangchi* and *Aristolochia manshuriensis).* AA is a mixture of structurally related nitrophenanthrene carboxylic acid, namely aristolochic acid I(AAI) and aristolochic acid II(AAII) [73]. AA is the botanical Asian remedy for aiding weight loss, easing joint pain, and improving stomach ailments, arthritis, gout, rheumatism, and festering wounds [83-86]. Other Chinese herbal products that contain a substantial amount of aristolochic acid include Guan Mu Tong and Guang Fanchi [87]. Recently, FDA has published a list of botanical products that have been shown to contain AA [88]. Lai et al. [87] conducted a population based case-control study of Chinese herbal products containing aristolochic acid and urinary tract cancer risk and concluded that the consumption of aristolochic acid-containing Chinese herbal products is associated with an increased cancer of the urinary tract in a dose-dependent manner that is independent of arsenic exposure.

Caused by contact

Chlorinated water: Villanueva et al. [89] pointed out that bladder cancer has been associated with exposure to chlorination by-products in drinking water, and experimental evidence suggested that exposure also occurred through inhalation and dermal absorption. Inhalation and dermal absorption of chlorine occurs during showering, bathing, and swimming in pools. Chlorination byproducts were found in drinking water disinfected with chlorine [90,91]. Many chlorinated compounds were identified as carcinogenic [92-94]. Chlorinated water is likely to be a risk factor of bladder cancer.

Hair dyes: Conflicting results were obtained from research on personal hair dye use and the risk of bladder cancer. There was no evidence of an increased risk of bladder cancer based on analyses of data pulled from 12 studies of personal hair dye use [95]. However, some recent studies have suggested an increased risk of bladder cancer associated with the use of permanent hair dyes [96-98], whereas other studies have not [99-101]. A review by Zhang et al. [102] suggested that the current evidence on the association between personal hair dye use and human cancer risk was limited, except for the possibility of hematopoietic cancer such as non-Hodgkin' lymphoma and to a lesser extent, bladder cancer. Turesky et al. [103] reported that *4*-aminobiphenyl (*4*-ABP), a known bladder carcinogen, was detected in eight of the 11 different oxidative and direct hair dyes within the level of *4*-ABP ranging from non-detectable (<0.29 ppb) to 12.8 ppb. It was found in black, red, and blonde hair dyes but not in brown hair dyes in the U.S. market. The same study reported that research grade 1,4-phenylenediamine (PPD), a key constituent for color development in many permanent hair dyes, could be contaminated with *4*-ABP in concentrations up to 500 ppb. Akyuz and Ata [104] also found that in Turkey *4*-ABP was present in concentrations up to 8.12 μg/g in 28 of the 54 hair dye samples, up to 2.23 μg/g in 11 out of 25 henna samples and upto 2.87 μg/g in four out of 10 commercial natural henna samples tested. So the risk of hair dye use to bladder cancer might be due the contaminants, not due to hair dye components. However, hair dyes use has always been suspected to increase the risk of bladder cancer. Hair dyes research will still attract attention [105].

Caused by dietary factors

Many dietary factors have been reported to be involved in causing UBC.

Chemical contaminants: Polycyclic aromatic hydrocarbons (PAHs) including benz[*a*]anthracene, banzo[*b*]fluoranthene, benzo[*k*] fluoranthene, benzo[*g, h, i*]perlene, benzo[*α*]pyrene, benzo[*e*]pyrene, dibenz[*a,h*]anthracene and indenol[*1,2,3-c,d*]pyrene were detected in

food samples in the city of Barcelonia, Catalonia, Spain, from 2003 to 2004 [106]. Food samples including meat products (fresh and smoked), seafood (cephalopods, crustaceans, and bivalves), vegetable oil, and tea also contained PAHs. The PAHs have been detected in most tea samples, bivalves, and meat products. The PAHs detected most frequently were benzo[*e*]pyrene and benz[*b*]fluoranthene [106]. Alomirah et al. [107] also reported that PAHs including carcinogenic banzo[*a*]pyrene(BaP), benz[*a*]anthracene, chyrysene, benzo[*b*]fluoranthene, benzo[*k*] fluoranthene, indenol[*1,2,3-c,d*]pyrene, dibenz[*a,h*]anthracene, and banzo[*g,h,i*] perlene, samples (extra virgin olive oil, virgin olive oil, olive oil, pomace olive oil, and blended olive oil) as well as cooking oil (corn oil, sunflower oil, sesame oil, palm olein oil, soya oil, canola oil, mustard oil, peanut oil, and mixed vegetable oil), and fats (butter and table margarine), collected from retail stores in Kuwait [107]. There are many ways that these industrial products can get into dietary sources. It is not surprising that contamination of carcinogens of food products is a common phenomenon. Some of these chemical contaminants might cause bladder cancer.

Bracken fern (*Pteridium aquilinum*): Bracken fern, *Pteridium aquilinum*, is considered one of the most abundant plant species, has been used as human food and animal feed in many parts of the world [108]. Two parts areconsumed by humans and animals: fiddleheads that are fern fronds (crosiders) that rise from plants each year in the spring, and the other part is rhizomes. Native American groups (including Chehalis, Cowlitz, Green River, Klallam, Lummi, Makah, Quileute, Quinault, Skagit, Skokomish, Snohomish, Squaxin, Swwinomish, and Lower Chinook) collected the fibrous rhizomes and ate them after roasting and cooking (Leidl and Sheck, North Dakota, no date, no source.). (http://thennatureniche.com/2012/08/bracken-fern). In East Asia, *Pteridium aquilinum* is eaten as a vegetable, called *warabi* in Japan, *gosari* in Korea, and juécéi in China and Taiwan. Bracken fern grows in meadows, roadsides, clearings, sterile sandy soils, burns, avalanche tracks, dry to wet forests and acid sites such as lake-shores and bogs [109].

Bracken fern has been implicated to cause esophageal cancer in humans, bladder cancer in cows, vesicle carcinoma and ilealadenoma, adenocarcinoma, and sarcoma in rats, urinary bladder and intestinal carcinoma, pulmonary adenoma and adenocarcinoma, leukemia in mice, bladder and intestinal tumors in guinea pigs, and adenocarcinoma in Japanese quail [110]. Quercetin, kaempferol and ptaquiloside were present in the fern which were reported to be carcinogenic [111,112]. Pamukcu et al. [113] demonstrated that albino noninbred weaning male and female rats fed a basic grain diet supplemented with bracken fern or quercetin induced bladder and intestinal cancers. Jarrett also reported that bracken fern contains large amounts of quercetin, and quercetin has been shown to be mitogen and carcinogenic in rats [114]. However, Ito argued that there was no evidence of carcinogenic activity of quercetin in lower dose groups of male or female F344 rats fed diets containing 1,000, 10,000 or 40,000 ppm of quercetin. The risk of quercet in for humans is negligible [115]. Another compound identified as shikimic acid is produced by bracken fern. Shikimic acid was reported to be active in the BHK 21 cell transformation assay; shikimic acid might act as a carcinogen-promoting agent [116].

Potter and Baird [117] reported that consumption of the bracken fern was shown to induce bladder and intestinal carcinoma in cattle and to cause a number of diseases in other farm animals. Nineteen of 31 ferns tested by chemotaxonomic methods in Japan have been found to contain potential carcinogenic ptaquiloside as have *Cheilanthes sieberi* and *Pteridium esculentum*. Ptaquiloside was proven to be carcinogenic in 1984 by Hirono et al. [118,119], and to be primarily responsible for the other toxic effects such as clastogenicity, genotoxicity, and bright blindness in sheep [120].

It was reported that ptaquiloside might be the cause of gastric and esophageal cancers in humans in bracken-rich areas [121]. Livestock can consume ptaguiloside. Ptaquiloside has been identified in the milk of cows and groundwater. Humans can be exposed by direct consumption of the plant, contaminated water or milk and spore inhalation [122]. It has been suggested that selenium supplementation can prevent as well as reverse the immunotoxic effects induced by ptaquiloside [123]. Hydrolysis of ptaquiloside leads to pterosins; which is believed to be the primary carcinogenic component.

Other ferns such as Mulag fern, or rock fern (*Cheilanthes sieberi*), were reported to be a major cause of bladder neoplasm in cows in Queensland, Australia [124]. The development of hepatic and vesicle tumors in rats fed Russian comfrey, *Symphytum officino* L, which is used by humans as a green vegetable or tonic, was also demonstrated to be carcinogenic by Hirono and his associates [125].

In cattle, bracken fern toxicity is characterized by the presence of hematuria and tumors of the urinary bladder of both epithelial and mesenchymal origin. The syndrome is known as chronic enzootic hematuria (CEH). A strong relationship between bovine papilloma virus type-2 (BPV-2) and bracken fern in both experimental and naturally occurring bovine bladder cancer was demonstrated by Campo and coworkers in 1992 [126]. It is likely that BPV-2 infects the bladder mucosa producing an abortive latent infection, as no structural proteins or virions were found in the urinary mucosa [127,128]. Chemical carcinogens from bracken fern may cooperate with BPV-2 inducing neoplastic disease. It has been suggested that latent BPV-2 is activated by bracken fern induced immune suppression, thus initiating progress to malignancy [129]. Balcos et al. [130] also discovered that bovine PBV-2 was associated with bladder tumors. BPV-2 DNA was detected by the polymerase chain reaction (PCR) analysis in 68% of the analyzed tumor samples. BPV-2 positive urinary bladders were also immunechemically analyzed for the expression of the major viral on coprotein E5. E5 expression was not observed in normal mucosa. It was suggested that the expression of E5 oncoprotein played a causal role in the carcinogenetic process. Thus, bracken ferm consumption should be seriously considered to be cancer causing.

Coffee and alcohol: An association between coffee drinking and urinary cancer was suggested more than 30 yearsago [131]. Relationships between consumption of coffee and occurrence of cancer as well as mortality were explored in a Norwegian study of 13,664 men and 2,891 women, who reported their coffee consumption from 1967 to 1969. However, no statistically significant positive associations were found between coffee consumption and the disease [132]. For cancer of the pancreas and bladder, no increase in incidence was found among those who are high coffee drinkers [133]. In subjects less than 65 years of age at the start of follow-up, coffee drinking showed a significant inverse association with colon cancer [132]. Tavani and La Vecchia [133] reviewed the 1990-1999 epidemiological studies between coffee consumption and cancer and concluded that a strong association between coffee drinking as bladder cancer could be excluded, although it was still unclear whether the weak association was causal or nonspecific due to some bias or confounding factors. Sala et al. [134] also reported that nonsmokers who were heavy coffee drinkers might have a small risk of bladder cancer. Although these results could not be attributed to confounding by smoking, the possibility of bias in control selection cannot be discounted. Pelucchi et al. [135] concluded

that coffee drinkers have a moderately higher relative risk of bladder cancer compared to nondrinkers. The association may partly be due to residual confounding by smoking or dietary factors. Again in 2009, Pelucchi et al. [135,136] concluded that results from epidemiological studies allowed excluding a strong association between coffee drinking and bladder cancer.

Alcohol drinking was considered to have a correlation with bladder cancer [137,138]; however, Jiang et al. [139] investigated the alcohol consumption and risk of bladder cancer in Los Angeles County and discovered that alcohol consumption was strongly associated with the reduced risk of bladder cancer. Recent analyses on epidemiological data on alcohol drinking and bladder cancer were suggestive of no association, although findings were not always consistent [137,138]. For both alcohol and coffee drinkers, an explanation of the moderate increase in risk in some investigations might be attributed to residual confounding by smoking, or to an association between alcohol, coffee, and yet another unidentified risk factor for bladder cancer.

Saccharin and bladder cancer: Hicks et al. [140] reported that a combination of dietary saccharin with a single dose of methynitrosourea (NMU) produced bladder tumors in female Wistar rats. As a consequence, all food containing saccharin was labeled with a warning. However, it was later found that an impurity in saccharin, particularly *o*-toluene suphonamide, could be responsible for the case of bladder cancer observed in saccharin consumers [141]. Because the bladder tumors seen in rats are due to a mechanism not relevant to humans and because there is no clear evidence that saccharin causes cancer in humans, saccharin was delisted as a carcinogen in 2000 in the U.S. National Toxicology Program's Report on Carcinogens, where it had been listed since 1981 as a substance reasonably anticipated to be a human carcinogen. The EPA has officially removed saccharin and its salts from their list of hazardous constituents and commercial chemical products. In a December 14, 2010, EPA stated that saccharin is no longer considered a potential hazard to human health [142].

Arsenic: Ingestion of arsenic in drinking water has been reported to cause bladder, liver, or lung cancers [143-146]. However, Bates et al. [147] in a case-control study of bladder cancer and arsenic in drinking water, found that there was overall no association of bladder cancer with total cumulative exposure or intake concentration. But among smokers, the positive trends risk for arsenic exposure was found. The exposure estimated for decade-long time periods, especially in the 30-39 year prior to diagnosis. Steinmaus et al. [148] also found no increased risks of bladder cancer in exposure greater than 80 µg per day and that overall no clear association was identified between bladder cancer risk and exposure in the western United States. Likewise, Lamm et al. [149] reported that no arsenic-related increase in bladder cancer mortality over the exposure range of 3 to 60 µg/L using stratified analysis and regression analyses both unweighted and weighted by 133 U. S. counties population and 30 years of observation as mean and median concentrations. It seems that the association of arsenic by drinking water and bladder cancer is still a controversial issue.

Caused by endogenous carcinogens

Tryptophan is an essential aromatic amino acid with indole as a functional group and is a constituent of all structural proteins and enzymes. Tryptophan is present in all kinds of food especially in milk, cheese, yogurt, eggs, spirulina, chicken, turkey, pork, salmon, potatoes, and bananas (USDA, National Nutritional Database). But tryptophan is the least abundant amino acid in most proteins. It accounts on the average for 1% of the total amino acid in a typical plant and 1.5% of animal protein [150]. In the presence of carbonyl compounds and/or at a high temperature such as above 200°C in grilling meat or fish, pyrolyzation can occur to produce highly mutagenic compounds such as Try-P1 [3-amino-1,4-dimethyl-5*H*-pyrido-(4,3-*b*)indole] and Try-P-2 [3-amino-1-methyl-*5H*-pyrido-(4,3b)indole] [151]. Tryptophan may also interact with nitrite to form nitroso compounds, which are potential carcinogens [152,153]. Information relating to the carcinogenicity of these compounds is available elsewhere, and most of these heterocyclic aromatic compounds are concerns for colon cancer [154]. However, the excess amount of tryptophan in the diet or stimulation of tryptophan metabolizing enzymes would lead to overproduction and/or accumulation of some tryptophan metabolites, particularly from the kynurenine (nicotinamide) pathway. This is particularly so in the administration of oestrogens [155] and/or vitamin B_6 deficiency [156-158]. Bryan [159] reported that rats implanted with tryptophan metabolites in wax pellets produced a high incidence of bladder tumors. The study of implantation of the tryptophan metabolites with cholesterol as a vehicle revealed that *3*-kynurenine, acetyl-kynurenine, *3*-hydroxykynurenine, anthranilic acid, *3*-hydroxyanthranilic acid, xanthurenic acid, *8*-methyl ether of xanthurenic acid, quinaldic acid, and 8-hydroxyquinaldic acid are potential carcinogens [160,161]. Chung and Gadupudi [162] reviewed the possible roles of excess tryptophan metabolites in carcinogenesis, particularly in bladder cancer. These metabolites could interact with nitrite to become mutagenic nitrosamines. They act as promoter in the promoter-inhibitor model of carcinogenesis. They can produce bladder cancer when implanted in the bladder. They also interact with transition metals such as copper or iron to form reactive radical and/or reactive oxygen species (O_2^-, OH^-, H_2O_2). A metabolite such as *3*-hydroxyanthranilic acid was auto oxidized to mutagenic cinnabarinic acid and anthranilyl radical intermediates. These radical intermediates could also be ligands that interact with aryl hydrocarbon receptor (AhR) and induce xenobiotic metabolizing enzymes (XMEs) to metabolize contaminated carcinogens. When tryptophan is exposed to either visible or UV light, a photoproduct of *6*-formylindolo [*3,2b*]-carbazole is formed, which has a very high affinity for AhR that plays a role in carcinogenesis. It could be concluded that tryptophan metabolites play a complementary role in promoting carcinogenesis along with carcinogens like aflatoxin, CCL_4, *2*-acetylaminofluorene, *4*-aminobiphenyl, *2*-naphthylamine or *N*-{[*4*(*5*-nitro-*2*-furyl]-*2*-thiazolyl}formamide. The underlying mechanisms could be their autooxidation, exposure to either visible or UV light, interaction with nitrite or transition metals to form reactive intermediates, serving as ligand to interact with an AhR that is known to play a role in carcinogenesis through the induction of XMEs [163]. Recently, Opitz et al. [163] revealed that tryptophan catabolite kyrurenine as an endogenous ligand to human AhR that is constitutively generated by human tumor cell via tryptophan-*2,3*-dioxygenase (TDO). TDO-generated kynurenine suppresses antitumor-cell survival and motility through the AhR in an autocrine/paracrine fashion. The TDO-AhR is active in human brain tumors and is associated with malignant progression and poor survival. Previously, Heath-Pagliuso et al. [164] also demonstrated the endogenous metabolite tryptamine and indole acetic acid (IAA) as AhR agonist, inducing AhR dependent transformation and gene expression of cytochrome P-450 1A1 that will activate the promutagens/procarcinogens to proximate or ultimate mutagens/carcinogens.

Gadupudi and Chung [165] recently also demonstrated that *3*-hydroxyanthranilinc acid in the presence of a metal cofactor Cu(II) caused DNA breaks *in vitro*. Furthermore, *3*-hydroxyanthranilinic

acid in the presence of low concentration of Cu(II) caused a significant increase in the number of revertants of reactive oxygen sensitive tester strain TA102 of *Salmonella typhimurium*. Evidence suggested that the role of tryptophan metabolites in bladder carcinogenesis cannot be ignored. There are other arylamines such as serotonin, spermine, spermidine, putresine, tyramine, glutamine, cadaverine, arginine, ornithine, histamine, dopamine, epinephrine, norepinephrine, tyroxine, triiodothyronine, sphingosine (sphingenine), etc. are present endogenously [166]. Whether they can be involved in bladder cancer formation remains to be studied.

Caused by infection

Virus: Fioriti et al. [167] studied a group of 32 patients affected by primary bladder neoplasia along with a control group of 20 autoptic samples of healthy bladders. The DNAs of the following viruses has been searched by polymerase chain reaction (PCR): adenovirus, herpes simplex virus type 1 (HSV-1), herpes simplex virus type-2 (HSV-2), human pappiloma viruses (HPV), polyomaviruses (BKV and JCV). It was found that there was no association between bladder carcinomas and BKV and JCV. Fioriti et al. [167], however, also showed that high significant percentages of human polyomaviruses were present in the samples of the bladder cancer patients. The data indicated that BKV and JCV (polyomavirse) might play a role in the etiology of bladder cancer. In particular, the BKV, which was found in significant percentage both on single infection (p=0.0036) and co-infections with other viral species (0=0.035), may be an important co-factor in the pathogenesis of bladder carcinoma. BK virus is oncogenic in newborn hamsters and can be transfered to mammalian cells *in vitro*. The link of human bladder cancer with polyomavirus remains to be studied.

Only a small number of cases of vesical carcinoma, in the setting of human immunodeficiency virus (HIV), have been reported to date in bladder cancer patients. The rare occurrence of bladder cancer in HIV patients and lack of correlation with the laboratory markers of HIV disease progression may suggest a trivial association between two unrelated disorders [168].

Studies also showed no correlation between herpes simplex virus (HSV) and bladder cancer. But bladder cancer patients become infected with HSV much more easily than non-neoplastic urothelium. Up to the present, no conclusion of having an association between the occurrence of bladder cancer and HSV infections can be drawn [167,168].

Husain et al. [169] reported that human pappilomas virus (HPV) was detected in four of five transitional cell carcinomas arising in renal transplant recipients and suggested that HPV 16 might play an etiological role in the development of bladder cancer. However, Youshya et al. [170] reported that 47 out of 78 samples were positive for HPV antigen but not positive for HPV DNA. HPV DNA was also not detected in the 20 additional paraffin wax embedded transitional cell carcinomas (TCCs) or the 20 paired unfixed samples. They suggested that HPV was unlikely to play an etiological role in the development of bladder TCC. Ben Selma's et al. [171] study of the human pappiloma virus in bladder in a series of Tunisian patients also showed that no evidence of HPV infection was detected by morphological examination and PCR in any case of bladder carcinoma. Yavuzer et al. [172] recently reported that although almost 10% of the worldwide cancer burden was linked to human pappiloma virus infection, their data indicated there was no HPV DNA in the 70 urothelial bladder carcinoma tissues screened by nested with invasive cervical carcinoma and cervical intraepithelial neoplasia II (cin III). In the control group, 15 out of 18 samples (83.3%) were positive for the HPV DNA. The result indicated that there was no association between HPV infection and urothelial carcinomas. The possibility that infection by human pappiloma virus (HPV) is a risk factor contributing to bladder cancer remains open. Whether the HPV infection would enhance the carcinogenesis induced by dietary carcinogens such as bracken fern deserve further studies.

Cystitis: Kantor reported that squamous cell metaplasia often occurred in the transitional epithelium of chronically inflamed bladder mucosa [173]. Cohen [174] demonstrated that preneoplastic lesions of the bladder in humans and rodents include various types of proliferative cystitis, which are caused by infection. Chronic infections in the human urinary bladder, therefore, may be an important risk factor in the pathogenesis of bladder cancer. Adris and Chung [175] also revealed that endogenous bacteria, including cystitis causing bladder bacteria and some intestinal opportunistic *Pseudmonas aeruginas,* would metabolically activate the bladder procarcinogens. The metabolic activation was achieved by the presence of cytochrome P450-107SI of *Pseumonas aeruginosa* [176]. However, Abol-Enein's [168] review of the PUBMED literature database from inception to January 2008, revealed that no prospective study has examined the association between urinary tract infection and bladder cancer risk.

Schistosomiasis: As Schistosomiasis is also called bilharziasis and is caused by the parasite *Schistosoma haematobium*. Mostafa et al. [177] reported that Schistomiasis is closely related to bladder cancer, particularly squamous cells, which are nearly always invasive. *Schistosoma haematobium* is the predominant species in the Middle East, Asia, and Africa and the most implicated in the schistosomal bladder tumors (SBT) in these regions [177,178]. Rosin [179] reported that deposition of Schistomes induced chronic inflammation and irritation in the urinary bladder at the site of inflammation, which was found to be associated with cancer initiation. It had also been noted that inflammatory cells such as macrophages and neutrophiles are an important source of endogenous reactive oxygen species (ROS), which have been implicated in theformation of N-nitrosamine [180]. It has been shown that radical formation occurs during peroxidase metabolism of carcinogens and xenobiotics [181], and mutation caused by phagocytes [182] as Salim et al. [183] demonstrated that there was a positive correlation as between *Schistosoma haematobium* infections and increased oxidative DNA damages (measured of 8-hydroxy-2'-deoxyguanosine as an indicator), accompanied by increased production of reactive ROS (nitrogen monoxide NO) and subsequently higher expression of repair genes. Schistosomiasis is likely a cause of bladder cancer.

Caused by hereditary factors

Aromatic and heterocyclic amines require metabolic activation to electrophilic intermediates that initiate carcinogenesis-actyltransferase (NAT1) and (NAT2) are important enzymes in the biotransformation of these carcinogens. Hein [184] reported that the high frequency of NAT1 and NAT2 acetylation polymorphism in human populations together with ubiquitous exposure to aromatic and heterocyclic amines suggested that NAT1 and NAT2 acetylator genotypes are important modifiers of human cancer susceptibility. For cancers in which N-acetylation is a detoxification step such as aromatic acid-related urinary bladder cancer, NAT2 slow acetylator phenotype is at a higher risk. Multiple studies have shown that the urinary bladder risk is particularly high in the slowest NAT2 acetylator phenotye or genotype (NAT2*5). In contrast, for cancer in which *N*-acetylation is negligible and *o*-acetylator is an activation step such as for heterocyclic amine related colon cancer, NAT2 rapid acetylator is a higher risk although the associations between NAT1 genotype and various cancers were

less consistent and were not well understood [184]. Since cancer risk requires exposure to aromatic and/or heterocyclic amine carcinogens modified by NAT1 and/or NAT2 acetylator genotype the results from human epidemiology studies are dependent upon the quality and accuracy of the exposure assessment and genotype determination. Conclusions require understanding the relationship between genotype and phenotype, as well as the role of genetic variation in carcinogen metabolism, DNA repair, and host susceptibility [184].

Numerous oncogenes were thought to participate in the onset as well as in later stages of tumor development [185]. Kroft and Oyaso [186] indicated that 20% of bladder cancer patients had mutations in the H-ras gene, which were reported to be associated with less-invasive cancer. Kroft and Oyasu [186] also discovered that the oncogenec-erbB-2, a member of the receptor tyrosine kinase family that encodes a protein that is known to be over-expressed in bladder cancer patients correlates with high-grade, high-stage tumors. Badawi [187] also showed that *p53*, another H-*ras* related oncoprotein, was found to occur more frequently in transition cell cancer patients, a staggering 50%. Mutations of the most studied tumor suppressor genes in human cancer p53 are associated with invasive bladder cancer cases more than non-invasive cancer; thus, schistosome-induced bladder cancer would be expected to show a higher *p53* mutations as compared to the non-schistosome induced form [187,188]. Two additional tumor suppressor genes, *cdkn2* and *Rb* have been examined in human bladder carcinogenesis. The cdkn2 tumor suppressor gene encodes the cell-cycle regulatory protein, *p16*, which binds to *cdk4/cyclin-D* and inhibits its catalytic activity [189]. If the *p16* protein is inactivated, it cannot phosphorylate cyclin and will result in the loss of cell cycle control, also known as a cause of cancer formation. It has been established that there is an inverse correlation between increased expression of *cdkn2 (p16)* and inactivation of the Rh TNF-α compared gene. Furthermore, inactivation of *Rb* is considered an indicator of a more invasive (squamous cell cancer) phenotype; thus, one would expect a higher occurrence of *Rb* gene inactivation as compared to non-schistosome bladder cancer patients.

Abdulamir et al. [190] examined the gene expressions to comparatively elucidate the underlining molecular pathways and clinicopathological criteria in schistosomal bladder tumor (SBT) versus non-schistosomal bladder tumor (NSBT). SBT was associated with high grade invasive squamous cell carcinoma (SCC) while NSBT was associated with low grade, less invasive transitional cell carcinoma (TCC). The expression of *p53, bcl-2, c-myc,* and *EGFR* was higher in SBT than in NSBT, while the *Rb* was higher in NSBT than in SBT. *P53* was associated with high grade SCC in both SBT and NSBT. *Bcl-2* was associated with high grade invasive tumors in SBT and in NSBT. *P16* was associated with high grade, invasive late stage, and recurrent NSBT. *Rb* was associated with SCC in SBT, invasive tumors in NSBT, as well as late stage and recurrent presentation in both SBT and NSBT. *C-myc* was associated with high grade, invasive, and late stage SBT and SCC, high grade, invasive, and late stage NSBT. *EGFR* was associated with SCC in SBT and invasive, high grade, and late stage TCC in NSBT. *ki-67* was associated with invasive SBT and high grade late stage. NSBT and NBT showed distinct molecular profile of tumor development and progression [190].

Metwally et al. [191] also conducted a study on tissue samples from 25 patients and serum samples from 30 patients versus 10 healthy individuals to serve as controls. They investigated various parameters in serum samples and found that schistosome induced bladder cancers had higher levels of xanthine oxidase (XO), fructsoamine, lactate dehydrogenase (LDH), aspartate aminotransferase (AST), alanine aminotransferase (ALT), hydroxyproline, immnuoglobin E (IgE), and TNF-α compared to non-schistosome induced bladder cancer and to that of the controls. The two forms of bladder (schistosome vs. non-schistosome) cancer showed distinct biochemical markers, which can be monitored at the time of diagnosis to identifying the source of tumor formation. These genes may be involved in the overall carcinogenetic processes.

Sjödahl et al. [192] reported that a significant association between *FGFR3* and *PIK3CA* mutations in urothelical carcinoma (UC). They also emphasized the importance of the P-13 kinase pathway in UC. The TSC2 and TSC1 mutations underlined the involvement of mTOR signaling in UC. A tale of divergent pathways was reviewed by Wu [193], who reported that low-grade papillary tumors rarely become muscle-invasive, and they frequently harbor gene mutations that constitutively activate the receptor tyrosine kinase-Ras pathway. By contrast, most high-grade invasive tumors progress to life threatening metastases and have defects in the *p53* and the retinoblastoma protein pathway [193]. The mechanism of human bladder cancer carcinogenesis is a complicated process. There are a number of genes in bladder cancer known to harbor frequent mutations, including fibroblast growth factor receptor 3 (FGFR3), CNKN2A, *PIK3CA, Rb1*and *TP53*. Other less common mutations involve the gene *EDFR, K-RAS, N-RAS, B-RAF, RET, PDGFRA* and others [194-196]. Unraveling the signal pathways and genes involved may be an attractive strategy for molecular therapy of bladder cancer.

Recently, Menashe et al. [197] applied a large-scale pathway-based analysis of bladder cancer genome-wide association data from five studies (3,532 cases and 5,120 controls) of European background (n=5 studies). 1399 pathways were drawn from five public available resources (Biocarta, Kegg, NCI-PID, HumanCyc, and Reactome), and 22 additional contrasted 22 candidate pathways previously hypothesized to be related to bladder cancer. In total, 1,421 pathways, 5,647 genes and about 90,000 SNPs were included in their study. Logistic regression model adjusting for age, sex, DNA source, and smoking status was used for analysis of the marginal trend effect of SNPs on bladder cancer risk. Two complementary pathway-based methods Gene-set enrichment analysis (GSEA), and adapted rank-truncated product (ARTP) were used to assess the enrichment association signals within each pathway. Eighteen pathways were detected by either GSEA or ARTP at $P \leq 0.01$. To minimize false positives, they used the I^2 statistic to identify SNPs displaying heterogeneous effects across the five studies. After removing SNPs, they revealed that seven pathways remained. These are "Aromatic amine metabolism," "NAD biosynthesis,""NAD salvage," "Clathrin derived vesicles budding," "Lysosome vesicle biogenesis," "Retrograde neurotrophin signaling," and "Mitotic metaphase/anaphase transition" pathways. These pathways seem to belong to three fundamental cellular processes, i.e. metabolic detoxification, mitosis, and clathrin-mediated vesicles. identification of the aromatic amine metabolism pathway provided support for the ability of this approach to identify pathway with established relevance to bladder carcinogenesis. In summary, metabolic pathway related to different genes in the expression of bladder cancer is complicated and still needs to be further illustrated.

Prevention

Although there is not a guaranteed method to prevent bladder cancer, people can surely reduce the risk of getting it. For example, smokers are much more likely to develop bladder cancer than nonsmokers. Also, those exposed to industrial or environmental

carcinogens such as azo dyes and arylamines are at a higher risk. People working with dyes, rubbers, textiles, paints, pesticides, insecticides, leathers, and chemicals are more vulnerable. Avoiding any potential carcinogens by inhalation, ingestion, or direct contact would certainly reduce risk not only of bladder cancer but also of other cancers.

Nutritional factors

Nutritional factors have been widely investigated in cancer prevention. A few of those factors seem effective.

Ingestion of fruits and vegetables: In 1997, an international review panel considered vegetables as preventive agents for bladder cancer [198]. A high intake of cruciferous vegetables, particularly green and yellow vegetables, has been shown to be linked with a reduced risk of bladder cancer, especially in nonsmokers [199,200].

Fat consumption: A high intake of saturated fat was associated with a greater than two-fold increase in the incidence of bladder cancer [201]. Steinmaus et al. [202] identified an association between a decreased bladder cancer risk and lower dietary intake of fat.

Soy products: The isoflavone gentistein, a natural product, has been reported to have anti-urothelial cancer activity [203,204]. Increased intake of soy products has been linked to reduced risk of breast, colon, and prostate cancer [204,205].

Vitamins: Vitamin A, also known as retinol, can be derived from carotenoids, which are rich in carrots. Sporn et al. reported an inhibition of experimentally-induced transitional and squamous cell bladder with 13-*cis*-retinoic acid [206]. The chemopreventive role of vitamin A may be based on their antioxidative activity via reduction of DNA damage induced by free radicals [207]. Vitamin B6 (pyridoxine) has also been reported to have a potential chemopreventive effect for bladder cancer [208].

Vitamin C (ascorbic acid) has also been reported to reduce bladder cancer risk [209,210], but high concentration should be avoided because high concentration of Vitamin C was reported to have an adverse effect [211].

Vitamin E was also reported to decrease bladder cancer mortality in patients who took vitamin E supplements [209,212], but overdose can be fatal [213].

Green tea: Epidemiological evidence pointed out that there is an inverse relationship between green tea consumption and bladder cancer risk [214]. Makena and Chung [215] demonstrated that epicatechin (EC), epicatechingallate, gallocatechin (GC) were inhibitory on benzidine-induced mutations [215]. Kemberling reported the inhibition of bladder tumor growth by green tea derivative epigallocatechin-3-gallate [216]. Catechins such as epicatechin, epicatechin-*3*-gallate, epigallocatechin and epigallocatechin-*3*-gallate (EGCG) were thought to play a role in the anticarcinogenic effects, but clear mechanism of proven inhibition of carcinogenesis has yet to be established [217].

Specific compounds

Selenium: Helzlsouer et al. [218] analyzed various serum nutrients from 25,802 subjects in Washington County, Maryland, and found the level of selenium was lower in individuals with bladder cancer compared to the matched control. Decreased levels of selenium in the serum were associated with approximately linear increase in the risk of bladder cancer. Recently, Amaral also found that there is a beneficial effect of high selenium in take for bladder cancer patients [219].

Garlic: Various tumor cells have been reported to be inhibited by ingredients in dietary garlic, such as allylmercaptocysteine [220]. Garlic has also been evaluated in several epidemiological studies for the prevention of prostate [221], breast [222], colorectal [223], lung [224], and stomach cancers [225] with conflicting results. It is possible that garlic can also prevent bladder cancer. Further clinical trials are necessary.

Lycopenes: Lycopenes are unsaturated, non-provitamin A carotenoids found in tomatoes, guava, rose hips, watermelon, and pink grapefruit giving these fruits their red color. Lycopenes are potent antioxidants, and have been suggested to reduce the risk of bladder cancer. Okajima discovered that tomato juice (rich in lycopenes) would inhibit urinary carcinogenesis in rats induced by a bladder carcinogen, *N*-butyl-*N-(4*-hydroxybutyl) nitrosamine(OH-BBN) [226].

Linoleic acid: Linoleic acid is a polyunsaturated fatty acid found in vegetable oils and meats. Both linoleic acid and its stereoisomer, conjugated linoleic acid, which is derived from ruminant animals and their daily products, were reported to suppress proliferation and enhance apoptosis in bladder cancer cell lines [227,228].

Gallic acid: Gallic acid is a naturally occurring phenolic compound obtained by the hydrolysis of tannins, which are abundant in a variety of plants utilized as food. These plants include food grains such as sorghum, millets, barley, dry beans, faba beans, peas, carobs, pigeon-peas, winged beans, and other legumes. Fruits such as apples, bananas, blackberries, cranberries, dates, grapes, plums, peaches, pears, hawthorns, persimmons, raspberries, and strawberries also contain gallic acid. Similarly, gallnuts, sumac, tea leaves, red, and white wines contain gallic acid as well. Forages such as crownvetch, lespedeza, lotus, sainfoin and trefoil are also reported to contain tannins [229-232]. It has been reported that gallic acid possesses cytoxicity against a variety of cancer cells including bladder cells [233-240]. Ou et al. [234] demonstrated that gallic acid induced G2/M phase cell *via* regulation 14-3-3β release from Cdc25C and Chk2 activation in human bladder transitional carcinoma cells. Liu et al. [241] also showed that gallic acid inhibited murine leukemia WEHI-3 cells *in vivo* and promoted macrophage phagocytosis. Recently, Huang also demonstrated that gallic acid at 5 and 10 μg/ml, a major component of *Toona sinens*is extract, caused G(1) arrest through regulation of cell cycle regulatory proteins against HL-60 human premyelocytic leukemia [242]. It is also of interest to note that gallic acid ester derivatives were antimutagic [243-245]. The biochemical mechanisms of how gallic acid work may require further investigation. Gallic acid sure is a potent anticancer agent.

Betulinic acid: Betulinic acid [*(3β)-3*-hydroxy-lup-20(29)-en-*28*-oic acid] is a naturally occurring pentacyclictriterpenoid, which is present in persimmons. Antitumor activity of betulinic acid was first reported in 1995 when Pisha et al. [246] discovered that betulinic acid induced the apoptosis of human melanoma. That was confirmed by the Schmidt et al. [247] who demonstrated that betulinic acid could also cause apoptosis in human neuroblastoma cell lines *in vitro* and *in vivo*. Betulinic acid was also found by Fulda to be effective in inhibiting neuroectodermal tumors including neuroblastoma, medulloblastoma and Ewing's sarcoma [248]. Malignant brain tumors [249,250], ovarian carcinoma [251], human leukemia HL-60 cells [252], and malignant neck squamous cell carcinoma SCC25 and SCC9 cell lines were also reported to be inhibited by betulinic acid [253]. Chadalapaka also reported that betulinic acid inhibited bladder cancer cell growth by down regulated epidermal growth factor receptor in bladder cancer cells [254].

Persimmons were reported to contain another anticancer compound, shibuol, but literature about the anticancer effects of shibuol is not available at present. Nevertheless, persimmons contain several anticancer compounds such as tannin catechin, gallocatechin, *p*-courmaric acid, protocatachic acid, gallic acid, betulinic acid, and shibuol. Besides, persimmons also contain proanthocyanidins and vitamin C, which were reported to reduce cancer risk. The anticancer effects of these compounds are available elsewhere and will not be discussed in detail here. One persimmon per day is possibly the best for cancer prevention.

Non-nutritional agents

Some nonutritional natural compounds were reported to suppress experimental bladder carcinogenesis in animals. These compounds include astaxanthin [255], protocatechuic acid [256], diosmin [257], hesperidin [257], *1,4*-phenylene diisothiocyanate [258], and crytoxanthin [259].

Lubet et al. [71] reported that indomethacin had chemopreventive effects of tobacoo smoke carcinogen *4*-hydroxybutyl(butyl)nitrosamine (OH-BBN)-induced urinary bladder cancer in mice. Chemopreventive effects of silymarin and silibinin (a major flavonolignan component in silymarin), which is a mixture of flavonoids present in milk thistle, had been reported in OH-BBN induced urinary carcinogenesis in male ICR mice [260]. Silibinin has also been reported to have a strong anticancer efficacy against human bladder cancer *in vitro*. Silibinin would inhibit the growth and proliferation of human transitional-cell carcinoma cells by causing cell cycle arrest and induction of apoptosis [261,262].

There may be some other compounds not included in this review. Recently, Tanaka et al. [217] gave a detailed review of the pathobiology of bladder carcinogenesis and discussed the nutritional and non-nutritional factors, which might serve as chemoprevention of bladder cancer.

Drugs

It is known that non-invasive bladder cancers in western countries have a high propensity for recurrence and progression. Recurrence rates of such cancers vary between 30%-70% over a five-year period, depending on the stage and grade [263,264]. Due to these high recurrence rates, prevention is an important clinical priority. The current standard of care involves administration of intravesical bacillus Calmette-Guerin (BCG) of chemotherapy in high risk patients. The result seems to be promising with low risk superficial bladder cancer patients. Only a little information is available on the response of SCCs patients with schistosomiasis-associated inflammation to the above mentioned treatment [265,266]. Hameed et al. [267] found that the combination of retinoic acid and ketoconazole was effective in preventing recurrences in patients with non-invasive bladder cancer. The mechanism of the effects of the retinoic acid/ketoconazole combination is still not clear. Further tests are necessary [268].

The synthetic drug, difluoromethylornithine (DFMO), has been reported to selectively inhibit the development of carcinogen-induced urothelial cancer in rodents and other animals [269,270]. DFMO was a competitive inhibitor of the ornithine decarboxylase (ODC), which was found to be closely associated with tumor promotion and activities of both hormone and growth promoting factors [269].

Nonsteroid anti-imflammatory drugs (NSAIDs) have been reported to be the most potent bladder cancer chemopreventive agents in clinical studies [271]. The NASIDs' agent celecoxib and NS-398 were reported to cause apoptosis in three bladder cancer cell lines [272,273]. Fischer et al. [273] indicated that aspirin seemed to be the most promising NSAIDs for preventing human colorectal, bladder, and skin cancer.

A class of hydroxymethylglutaryl-coenzyme A reductase inhibitors-atorvastatin has been reported to exhibit significant antiproliferative and pro-apoptotic activity in human bladder cancer cells [274]. Oitipraz, an antiparasitc agent (*5*-[*2*-pyrazinyl]-*4*-methyl-*1,2,3*-thione), was also reported to prevent carcinogenesis by bladder cancer agent, BBN, by enhancing detoxification of this carcinogen in the liver and urinary bladder [275].

Discussion and Summary

Multiple factors are involved in the causes of bladder cancer. Most of the causative factors can be prevented such as cessation of smoking, improving the efficacy of home cooking fume hood, and avoiding the exposure of industrial or environmental carcinogens. We can also increase the intakes of beneficial diets and fruits, vegetables, and supplements such as vitamins or specific compounds mentioned in this paper. Many of these measures are readily available or can be disseminated to the public effectively. The interplay of multiple factors including exposure through the direct contact, inhalation, ingestion, drinking of a variety of industrial/environmental carcinogens, drugs, dietary factors, and infections or hereditary factors are the major concern for cause, prevention, and cure of UBC. Clinical challenges related to prevention and treatments of this disease remain to be further researched. Although much progress has been made in drug development and treatment of UBC in the past, prevention is vital. UBC is relatively a preventable disease compared to many other incurable diseases in which the causative agents are not yet known. The appropriate plan for each treatment may vary with the status of different societies such as industrial/economic development, medical facilities, and social welfare systems.

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