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The Potential Role of Chemoprevention in the Management of Non-Muscle Invasive Bladder Urothelial Carcinoma

Unyime O. Nseyo[1], Katherine A. Corbyons[2] and Hari Siva Gurunadha Rao Tunuguntla[3]
[1]*North Florida-South Georgia Veterans Health System, Gainesville, Florida,*
[2]*University of Florida, Gainesville, Florida,*
[3]*Robert Wood Johnson Medical School, New Brunswick, New Jersey, USA*

1. Introduction

1.1 Epidemiology and bladder carcinogenesis

Cancer represents phenotypic manifestations of abnormal gene expression. Genetic mutations, dysregulation, and gene losses can influence cell proliferation and differentiation, and eventually lead to formation of cancer. Risk factors and etiologic agents involved in the genetic abnormalities influence the distribution of cancer worldwide. This chapter aims at highlighting the epidemiologic significance of urothelial bladder cancer; reviewing its natural history, the roles of industrial and environmental carcinogens and life style factors in urothelial carcinogenesis; and framing possible strategies for chemoprevention in the management of human urothelial cancer of the urinary bladder.

Bladder cancer remains a serious public health problem worldwide, and accounts for 5-10% of all malignancies annually in western countries (*Cancer Treatment of America*). Though the age-adjusted incidence varies in the different parts of the world, the highest rates are found in men from North America (23.3/100,000), North Africa (23.3/100,000) and Southern Europe (22.0/100,000), while the corresponding rates are 5.4, 4.8, and 3.2 per 100000 for women (*Cancer Treatment of America*). These high rates may be influenced by increased industrialization, cigarette smoking, and infection of schistosomiasis (primarily of concern in North Africa). The lowest rates for both sexes have been reported for the Melanesia region of South Pacific and Middle Africa (*Cancer Treatment of America*; Prout, Barton et al. 1992; Grasso 2008; *American Cancer Society* 2010).

Bladder cancer, which is immensely impacted by environmental carcinogens and tobacco smokes, remains a common disease in the United States, and it is estimated that 70, 530 persons (52,760 men and 17,770 women) were diagnosed with cancer of the urinary bladder in 2010, (*Cancer Treatment of America*; *American Cancer Society* 2010) and an estimated 14, 680 died of the disease accounting for 3% and 2% of all cancer deaths in men and women, respectively (*Cancer Treatment of America*; *American Cancer Society* 2010). Estimates of new cancer cases classify *urothelial bladder cancer* (UBC) as the fourth most common in men and the eighth most common in women. The prevalence of UBC in the US is estimated at about

one million cases annually, and worldwide, UBC ranks as the ninth most frequent cancer (*Cancer Treatment of America*; Prout, Barton et al. 1992; Grasso 2008; American Cancer Society 2010).

Bladder cancer is a disease of aging; the incidence of UBC rises with age with an average of onset at 69 for men and 67 for women (*Cancer Treatment of America*; Prout, Barton et al. 1992; Dalbagni and Herr 2000; Grasso 2008; *American Cancer Society* 2010). Bladder cancer that occurs at ages 40 or younger tends to be low grade Ta cancer with almost negligible recurrence potential. Given sufficient time, however 50-70% of UBC patients will develop recurrent disease. Recurrences tend to be characterized by multiplicity in time and space, primarily if the initial tumors occurred early in life and were large or multiple in numbers. A majority, 70-75%, of UBC are superficial, that is, non-muscle invasive, and non-lethal, but they are characterized by frequent recurrences. However, the remaining 25-30% of the annual cases of UBC invades into the muscular propria, making them life threatening, because approximately 50% harbor micro-metastases that often manifest within three years out from diagnosis (Droller 2006).

The non-muscle invasive UBC (NMIUBC) that are confined to the mucosa/urothelium Ta, remain non-lethal with a progression rate of less than 5%, and occur often as large or multiple tumors. Ten to twenty percent of the superficially-invasive UBC that is confined to the lamina propria, T1, converts to muscle invasive disease on repeat resection (Dalbagni and Herr 2000).

Variable morphology, natural history, and prognosis demonstrate that transitional cell carcinoma (TCC) or urothelial carcinoma (UC) of the bladder is not a single disease, but occurs in three distinct forms, each possessing characteristic features that include low grade papillary, noninvasive; carcinoma in situ (CIS); and high grade, invasive (Grasso 2008). Seventy to eighty-five percent of new bladder cancer cases, are superficial or *non-muscle invasive* UBC, which include disease confined to the mucosa in CIS: CIS (10%), and Ta (70%), or lamina propria in T1 (20%) (Prout, Barton et al. 1992; Dalbagni and Herr 2000; Droller 2006; Grasso 2008). These types of tumors are considered to have variable invasive potential with a progression rate to invasive cancer of 15% to 50% (Prout, Barton et al. 1992; Dalbagni and Herr 2000; Grasso 2008). However, more than 70% of patients with NMIUBC have one or more recurrences within 5 years of initial diagnosis (Prout, Barton et al. 1992; Dalbagni and Herr 2000; Droller 2006; Grasso 2008). Further analysis shows that approximately 50% of patients diagnosed with solitary bladder cancer will experience recurrences within 4 years, while 70% of multiple bladder tumors reoccur within one year (Prout, Barton et al. 1992; Dalbagni and Herr 2000; Droller 2006; Grasso 2008).

The fact that the bladder serves as a reservoir for urine and its waste product contents predisposes it to the constant cumulative exposure to carcinogens which include industrial toxins and cigarette smoke chemicals. The multiple-step process of carcinogenesis includes induction/activation, promotion and progression, which exists as a continuum in the bladder environment. Consequently, preventive intervention can be difficult to implement under these conditions of cumulative exposures, and the definitive strategy will be to minimize constant cumulative exposure of carcinogenic agents from smoking and industrial sources. Increased carcinogenic exposure by itself cannot explain the 40% increase in bladder cancer incidence in the last 15 years in the US. The explanation certainly includes increased smoking that has added a large population of women, cumulative industrial exposure, and host factors. These host characteristics are likely to influence racial differences

in the incidence of bladder cancer. Caucasians have overall bladder cancer risk of 3.9% versus 0.8% overall chance in African Americans: 2.8% in men and 1.5% in women (Droller 2006).

Earliest reported association of industrial carcinogenic exposure and development of bladder cancer was by Rehn (Dietrich and Dietrich 2001). Observations have also documented associations between carcinogen ingestion in animals and development of bladder cancer (Okey, Harper et al. 1998; Sporn and Lippman 2003). Several legislative measures have been implemented in an attempt to decrease the intensity and cumulative nature of the carcinogen exposure. However, cigarette smoking trumps all considerations of environmental and industrial exposure and is the major factor underlying the spread and occurrence of bladder cancer around the globe.

It is estimated that 30% of bladder cancer mortality is attributable to a history of tobacco abuse/dependence (*American Cancer Society*), and studies have tried to characterize the different carcinogenic agents in cigarette smoke that define the causal relationship between smoking and development of urothelial cancer (*American Cancer Society*; Droller 2006). Investigators have tried to correlate bladder cancer risk with the manufacturing processes such as the type of filter used, type of tobacco used, and the curing technique: black versus blonde (Droller 2006). The curing technique determines the concentration of the carcinogens in the cigarette. The smoke of black (air-cured) versus blonde (flue-cured) has been analyzed to show higher concentration of carcinogens in black tobacco. How these commercial practices influence urothelial carcinogenesis remains to be elucidated.

Several specific carcinogens in cigarette smoke have been implicated in the development of urothelial cancer, including polycyclic aromatic hydrocarbons, aromatic and aryl amines (including 4-amino biphenyl), unsaturated aldehydes (e.g. acrolein) and oxygen-free radicals (*American Cancer Society*; Sabichi and Lippman; Droller 2006). Aromatic amines were the first carbon compounds of industrial by-products that were suspected in work- related urothelial cancer, found primarily in those workers who were exposed to the dye, rubber, and plastic manufacturing. These epidemiological data suggest up to 100-fold increased risk that is mediated by cumulative intensity and duration of exposure. Regulatory and legislative efforts to retard the work place risk contributed to the birth of occupational safety and health administration in the industrialized countries around the world.

In spite of extensive efforts since then to curb workplace exposure to industrial carcinogens, textile, dry cleaning, hair dressing, and coal gasification continue to generate the carcinogens in the manufacturing process. The culprit agents are per-chloroethylene (an organic solvent used in dry cleaning), chemical dyes, aromatic amines (used in textile industry), and hair dyes that contain chemical carcinogens. These agents have been associated with bladder cancer development. Other carcinogens, outside of the workplace, that have been associated with the development of urothelial cancer include arsenic in ground water in southeastern Michigan in the US and southwestern Taiwan (Haack, Treccani et al. 2000; Kim, Nriagu et al. 2000; Welch, Westjohn et al. 2000; Droller 2006); ingestion of fang chi (Chinese herb used in weight control); ingestion of ochratoxin A in the Balkan countries resulting indirectly from animals that consumed blackened fern (Droller 2006). Several medications and medical therapies have also been associated with urothelial cancer development including phenacetin used to treat headaches, cyclophosphamide (cytoxan) used to treat pediatric and adult hematologic malignancies (lymphoma and leukemia), and pelvic radiation for cervical and prostate cancer.

In parts of the world with endemicity, there are reports of association between *Schistosoma haematobium* infection and the development of urothelial cancer, primarily squamous cell carcinoma, and some cases of transitional cell cancer (Sabichi and Lippman; Okey, Harper et al. 1998; Sporn and Lippman 2003; Droller 2006). The inciting factors include an inflammatory response to the deposited parasitic ova of *Schistosoma haematobium* in the periurethral areas of the bladder ,as well as conversion of nitrates to nitrites with the nitrosamines mediating the development of urothelial cancer. Other carcinogenic exposures such as fertilizers and cigarette smoke may also play putative roles in the urothelial carcinogenesis in these patients.

In urothelial carcinogenesis, several host factors have been recognized as playing either permissive or protective roles. Acetylation of aromatic amines remains an important mechanism of carcinogenic inactivation in urothelial carcinogenesis. The detoxification of carcinogens is mediated by genes namely NAT1 and NAT2 which are responsible for generating the detoxifying enzymes N-acetyl transferase, and NAT2 remains the predominant gene involved. Individuals who are homozygous for NAT2 are classified as slow acylators and they detoxify carcinogens quite slowly allowing prolonged contact with DNA to induce mutations and carcinogenesis (Sabichi and Lippman; Weber 1987; Droller 2006). These individuals have a two- to four-fold increased risk for the development of urothelial cancer. On the other hand, the heterozygous fast acylators are able to rapidly detoxify these aromatic amines that lower their risk of developing urothelial cancer. Researchers have suggested that the potential differences in racial and ethnic risk of urothelial cancer development are attributable to the difference in the expression of these two genes (Sabichi and Lippman; Weber 1987; Droller 2006; Lattouf 2009).The P450 cytochrome oxidase system is also important in metabolism and detoxification of urothelial carcinogens. The CYP1A2 might be particularly important in metabolizing aromatic amines (Sabichi and Lippman; Okey, Harper et al. 1998; Sporn and Lippman 2003; Droller 2006). Also, individuals deficient in the enzyme glutathione transferase may be at risk for deficient metabolism of polycyclic aromatic amines, which could put them at a 30-50% risk of developing bladder cancer (Okey, Harper et al. 1998; Sporn and Lippman 2003; Droller 2006).

2. Molecular biology of carcinogenesis and chemoprevention

The classic multistep process of carcinogenesis which has been widely accepted includes initiation, promotion, and progression. A clear-cut sequential compartmentalization probably does not always occur, but the multistep structure could be exploited strategically for chemopreventative measures. The first step, initiation, depends upon three cellular functions, namely carcinogen metabolism, DNA repair, and cell proliferation. Cell damage can occur by activation/deactivation mediated by the carcinogen; this cell can cycle through DNA repair or exists as an altered gene (no tumor development) and can be propagated as such, or go through cell proliferation. In the promotion phase, the altered cell continues to undergo repeated bombardment by the promoter agent (initiator or not) leading to additional genomic damage and subsequent clonal expansion into a tumor. In the progression phase, the tumor acquires multicellular defective mutations enhanced by acquired or inherited mutations in the control genes such as p53, Rb, or DNA mismatch repairs (Okey, Harper et al. 1998; Sporn and Lippman 2003; Droller 2006). Consequently a tumor is born that lacks cellular growth controls, and has proliferative autonomy. The

challenge in designing a preventive strategy is selecting whether to target genomic or cellular events as well as determining the order of subsequent sequential targeting.

Genotoxic carcinogens can be enzymatically bioactivated and converted into water soluble metabolites to be excreted in urine or bile. These carcinogens can also be inadvertently transformed into electrophiles which react with DNA. Metabolism of carcinogens or broadly biotransformation may depend upon genetic and environmental factors in an individual who is exposed to the carcinogens. The drug metabolizing enzymes are classified into Phase I and Phase II enzymes, with Phase I enzyme being primarily typified by cytochrome P450 mono-oxygenase (CYP) super family. These enzymes function by unmasking the parent substrates (Okey, Harper et al. 1998; Sporn and Lippman 2003; Droller 2006). The Phase II enzymes including sulfotransferase, glutathione transferase (GST), and acetyltransferase primarily detoxify reactive metabolites. They catalyze the conjugation of bulky water insoluble components into hydroxyl groups which can easily be excreted.

As discussed above, carcinogenesis is a multistep process; therefore chemopreventive agents could affect different mechanisms. In practice chemoprevention would require continuous administration of a non-toxic compound over a long period or lifetime of the at-risk individual. However, the chemoprevention strategy would begin with the population approach that advocates a dietary program of increased consumption of fruits and vegetables which have been reported to reduce general cancer risk (Sabichi and Lippman; Sporn and Lippman 2003; Lattouf 2009). At the individual level, the approach would be to reduce the intensity of cumulative exposure through programs that include reduction/elimination of exposure to the carcinogens, dilution and elimination of bladder content by drinking plenty of water and urinating frequently, followed by introduction of the at-risk individual to the chemopreventive agent(s). The potential chemoprevention agents can be broadly classified into two categories: (a) agents that decrease bioactivation or increase detoxification of carcinogens, and (b) agents that alter promotion and progression (Okey, Harper et al. 1998; Sporn and Lippman 2003).

2.1 Agents that decrease bioactivation or increase detoxification of carcinogens

The cytochrome P450 enzyme family, which typifies the Phase I enzymes, acts bidirectionally by bioactivating procarcinogens into reactive metabolites that bind to DNA, but also enhances overall clearance of both the procarcinogens and carcinogens from the body. The first pass clearance of the carcinogen by the high activity of P450 enzymes in the human liver exposes the susceptible peripheral organ/ tissue to reduced concentrations of the carcinogens (Okey, Harper et al. 1998; Sporn and Lippman 2003)..

In bladder cancer, the Phase II enzymes include the detoxifier glutathione transferases which conjugate reactive metabolites with glutathione. These Phase II enzymes can be induced by plant products such as sulforaphane from broccoli. This induction can be highly protective in animals against major carcinogens. However, they can also act bidirectionally to favor Phase I class of enzymes (Okey, Harper et al. 1998; Sporn and Lippman 2003).

Interestingly, oltipraz, an anti-schistosomiasis drug, functions bidirectionally to inhibit the predominant activating enzyme CYPIA2, and also induces a glutathione S-transferase Phase II enzyme that detoxifies carcinogens by conjugation. Another cytochrome P450 modulator is indole-3-carbinole (I3C) which is abundant in broccoli, brussels sprouts, and cruciferous vegetables (Okey, Harper et al. 1998; Sporn and Lippman 2003).

The phytochemicals that reduce adduct formation include vitamin E (α-tocopherol) and vitamin C (ascorbic acid). These act as scavengers of the reactive metabolites, or act as antioxidants (Okey, Harper et al. 1998; Sporn and Lippman 2003). However, they have not been found to decrease the risk of cancer in high-risk populations.

2.2 Agents that alter promotion and progression

Inflammation, increased cell proliferation/decreased differentiation, deficiency of apoptosis, and cumulative genetic instability constitute putative molecular and cellular events that induce promotion and progression during carcinogenesis (Okey, Harper et al. 1998; Sporn and Lippman 2003; Droller 2006). These cellular events are attractive potential targets for chemopreventative intervention.

Synthetic retinoids have been shown to alter gene expression and stimulate apoptosis. However, these have failed as primary chemopreventive agents, but have been shown to delay the appearance of secondary primary cancers of head and neck (Sabichi and Lippman; Okey, Harper et al. 1998; Sporn and Lippman 2003). However, natural retinoids such as β-carotene have shown a paradoxical increase in lung cancer in smokers and asbestos-exposed workers.

Targeting inflammation has become an attractive approach in chemoprevention as scientists gain better understanding of the association between inflammation and increased cancer risk, particularly colon cancer. Both the older-generation non-specific inhibitors of cyclooxygenase including: aspirin and non-steroidal anti-inflammatory agents (NSAIDS) and the newer synthetic selective COX-2 inhibitors such as Celecoxib have shown promising results in preventing colon cancer in rodent models and in humans(Sporn and Lippman 2003).

3. Conventional strategies in preventing recurrence/occurrence and progression

Approaches to bladder cancer prevention include primary prevention which aims at avoiding cancer development in healthy populations, secondary prevention, which aims at preventing premalignant lesions from undergoing promotion and progression into cancer under conducive conditions during carcinogenesis; and tertiary prevention, which aims at aborting cancer progression in patients who have been treated for the cancer. In bladder cancer, primary prevention is widely regarded as impractical. Even if good chemopreventive agents were available the risk-benefit ratio would have to be low in such a large at risk population. The other challenges to primary intervention strategy are discussed in the sections above about the uncertainty of appropriate molecular/cellular targets to prevent tumor initiation. In practice techniques of secondary and tertiary prevention are indistinguishable.

Following the initial diagnosis with transurethral resection of bladder tumor (TURBT), there are several interventions that may be undertaken to retard cancer recurrence and progression: selected patients may undergo repeat TURBT to better delineate the nature of their disease (Prout, Barton et al. 1992; Oosterlinck, Kurth et al. 1993; Lamm, Blumenstein et al. 1995; Dalbagni and Herr 2000), approximately 20% will receive intravesical chemotherapy to potentially eradicate residual disease (Prout, Barton et al. 1992;

Oosterlinck, Kurth et al. 1993; Lamm, Blumenstein et al. 1995; Dalbagni and Herr 2000) and the majority will be placed on some type of endoscopic surveillance schedule. The necessity for early adjuvant treatment, mainly intravesical instillation of immunotherapeutic or chemotherapeutic agents in the management of high-risk CIS, Ta/high grade and T1/any grade is recognized globally (Prout, Barton et al. 1992; Oosterlinck, Kurth et al. 1993; Lamm, Blumenstein et al. 1995; Dalbagni and Herr 2000). The hope is that this treatment, by altering the neoplastic potential of the urothelium, will reduce the risk for recurrence and progression. The subsets of the patients with NMIUBC who fail the conventional intravesical therapies will ultimately be subjected to radical cystectomy with resultant loss of bladder function, body image and sexual function (Prout, Barton et al. 1992; Oosterlinck, Kurth et al. 1993; Lamm, Blumenstein et al. 1995; Dalbagni and Herr 2000). The newest strategy in the management of NMIUBC is Photodynamic Diagnosis (PDD) with Hexvix® (*PhotoCure ASA, Oslo, Norway*) to minimize recurrences/occurrences and progression. PPD uses Hexvix which is an ester derivative of 5-Aminolevulinic Acid (ALA) (Jichlinski, Guillou et al. 2003; Fradet, Grossman et al. 2007) was recently approved by the US Food and Drug Administration (FDA) for management of NMIUBC primarily to improve the diagnostic and staging accuracy of cystoscopy leading to improvement in survival. Photodynamic diagnosis occurs when a photosensitizing agent is first concentrated in malignant or abnormal tissue, and then activated by light (Henderson 1992). The activated photosensitizer either returns to ground state, and releases energy as fluorescence, which can be used in detection (PDD), or the photosensitizer enters into its triplet state, and causes physico-chemical reactions to generate reactive oxygen species (ROS), for therapy as in Photodynamic therapy (PDT). Hexvix-PDD has been reported to improve the diagnostic rate of Ta and T1 papillary bladder cancers by 16.4% and the detection of CIS by 31% (as compared to white light cystoscopy) (Jichlinski, Guillou et al. 2003). Recently, Karl et al., reported that PDD during initial TURBT for T1G3 NMBIC exhibited a significant reduction in recurrence rate; led to detection of additional 35.4% CIS versus 21.8% in the control group (standard white light TURBT).The authors concluded that the initial use of PDD-directed TURBT could provide a superior cancer control and effective treatment of patients with T1G3 NMIBC (Karl 2010).

Bacillus Calmette-Guerin (BCG), an immunotherapy, remains the most effective and widely used intravesical agent to prevent recurrence and progression (Oosterlinck, Kurth et al. 1993; Lamm, Blumenstein et al. 1995; Dalbagni and Herr 2000). Mitomycin, thiotepa and epirubicin are the commonly used intravesical chemotherapeutic agents. while intravesical Valrubicin is FDA-approved as an alternative intravesical therapy to radical cystectomy for BCG refractory CIS patients (Dalbagni and Herr 2000). Administering Mitomycin or epirubicin immediately following TURBT has been reported as effective in preventing tumor implant; however, this approach has failed to ultimately prevent disease progression or mortality (Oosterlinck, Kurth et al. 1993). Of course, each intravesical agent is associated with both local and systemic side effects. Despite current treatment strategies, 30-80% of these patients develop recurrences within 5 years, and this high rate of recurrence of NMIBC invariably leads to a high economic impact (Hedelin, Holmang et al. 2002; Botteman, Pashos et al. 2003; Uchida, Yonou et al. 2007; Hong and Loughlin 2008; Sievert, Amend et al. 2009). The disease progression rate to muscle invasiveness is 42-83% in BCG-treated patients who have concomitant CIS and papillary NMIUBC, and 30-50% in those BCG-treated patients

with primary CIS (Oosterlinck, Kurth et al. 1993; Lamm, Blumenstein et al. 1995; Dalbagni and Herr 2000). Frequent follow ups and re-treatment of patients due to the recurrences exert heavy untold burden on the affected patients; eventually leading to morbidity as well as increased expenditure because of continuous treatment (Hedelin, Holmang et al. 2002; Botteman, Pashos et al. 2003; Uchida, Yonou et al. 2007; Hong and Loughlin 2008; Sievert, Amend et al. 2009).

3.1 Chemoprevention in the armamentarium of management of NMIUBC

Early detection and advances in treatments over the last two decades have resulted in an overall reduction in bladder cancer mortality (Cancer Treatment of America; American Cancer Society 2010). The public health and socioeconomic burden of bladder cancer could be reduced through practice of systematic prevention measures including elimination/minimization of exposure to carcinogens, hydration for dilution and frequent urination to expulse potential carcinogens; and practice of active dietary and/or pharmacologic preventative interventions. Unfortunately, in bladder cancer there are still no definite interventions that have been shown to be effective, and research in this area has yielded no evidence-based data to inform on strategies for systematic practice of bladder cancer prevention. Bladder urothelial cancer has biologic and clinical characteristics that favor it as an ideal cancer for chemoprevention. These special features include its susceptibility; carcinogenesis; frequent recurrences, and clinical presentation.

3.2 Cessation of smoking

The most cost-effective measure in bladder cancer prevention strategy would certainly be smoking cessation. This, of course, would be very difficult because of the addictive nature of the current cadre of manufactured cigarettes. In the meantime therapeutic intervention is needed to complement and perhaps even supplant the current socio-cultural as well as the legislative strategies to reduce the economic burden, suffering and death from bladder cancer through tobacco control. In the following section we will review the available evidence for the various chemotherapeutic agents.

4. Bladder cancer chemoprevention strategies: Non-pharmacologic and dietary approach (see also Table 1)

4.1 Fluid intake

The Health Professional Follow Up Study validated the concept that increased fluid intake could substantially lower the risk of UBC due to lowered intensity and cumulative exposure of carcinogens (Michaud, Spiegelman et al. 1999). The study involved mailing questionnaires to 47,903 men; and analysis of their responses regarding daily fluid intake. The data showed inverse association between total daily fluid intake and risk of urothelial cancer (UC) with a relative risk of 0.51 (0.32-0.81, 95% confidence interval: CI) in those who consumed the largest amount of fluid. Daily water consumption offered the best protection when compared with other fluids. However, Geoffrey-Perez and colleagues countered by reporting that there was an absence of association between bladder cancer risk and fluid consumption (Geoffroy-Perez and Cordier 2001). Intuitively it remains logical that dilution of bladder carcinogenic contents with frequent urination would be beneficial and less expensive practice.

4.2 Fat and caloric intake

In the Spanish study, Riboli and associates reported an association between fat consumption and urothelial cancer that showed a 2-fold increase in cancer incidence (Riboli, Gonzalez et al. 1991). Surveillance Epidemiology and End Results (SEER) population-based study data provided further evidence that fat rich diets are associated with an increase in incidence of UC (OR 2.24 for the highest quartile, 95% CI, 1.25-4.03, P=0.006) (Bruemmer, White et al. 1996). A Swedish study suggests a dose dependent effect of fat diet on the incidence of UC (Steineck, Hagman et al. 1990). In a meta-analysis of 36 studies evaluating 6 dietary variables in relation to UC, Steinmaus and group reported a positive association between intake of fat and UC (Relative ratio, RR 1.37, 95% CI, 1.16-1.62), but not with meat consumption (RR 1.08, 95% CI, 0.82-1.42) (Steinmaus, Nunez et al. 2000). However, there was no positive association between total caloric intake and UC over 12 years in the Health Professional Follow-Up Study (Michaud, Spiegelman et al. 2000). The traditional flaws of epidemiologic studies certainly affect the results of these studies including recall bias and lack of prospective randomized data. Other confounding factors include concomitant increased in caloric intake with increased fat intake. Despite these drawbacks of the reports, decreased fat intake should be a recommendation for prevention strategy of UC.

4.3 Green tea

Drinking tea has been reported to confer protective health benefits which include prevention of human cancers including prostate and bladder cancers (Trevisanato and Kim 2000).

The polyphenols found in green tea are potent antioxidants; they also inhibit ornithine decarboxylase which is an enzyme that promotes tumor proliferation via nucleic acid regulation (Steele, Kelloff et al. 2000). The incidence of UC in Asian populations with increased tea consumption is lower than in North America; a weak inverse relationship between tea intake and UC has been reported in one epidemiological study (Kemberling, Hampton et al. 2003). In order to settle the ongoing controversy, NCI-sponsored phase 2 and 3 clinical trials are in progress (National Cancer Institute).

4.4 Soy

Soy products have potential apoptotic and anti-angiogenic actions attributable to their high isoflavone content (Su, Yeh et al. 2000).Their role in UC chemoprevention, unlike in prostate cancer, has yet to be elucidated. Contrary Su and group reported in a Singapore-based population study an increased UC incidence associated with high consumption of soy food (95% CI, 1.1-5.1) (Su, Yeh et al. 2000).This risk was independent of smoking. There is no data yet favoring recommendation of soy for chemoprevention in UC.

5. Bladder cancer chemoprevention strategies: Pharmacologic agents

5.1 Vitamins and supplements

Researchers have long regarded vitamins and the so-called micronutrients as ideal agents for primary chemoprevention for human cancer. For the reasons discussed earlier primary chemoprevention in human bladder cancer lacks an effective agent as well as evidence-based data to encourage wide clinical practice.

5.1.1 Vitamin A and analogues

Epidemiologic data in humans regarding the efficacy of Vitamin A are inconsistent. Many reports have suggested a therapeutic benefit from retinoid supplements. Data includes the SEER database controlled study, which compared 1592 UC participants to a matched neighborhood controls (Castelao, Yuan et al. 2004). Carotenoids were found to be beneficial in previous or current smokers. Authors using fenretinide in a randomized study failed to demonstrate the difference in tumor detection by flow cytometry between treatment and placebo arms in a sample of 99 participants (Decensi, Torrisi et al. 2000). Fenretinide is a synthetic derivative of Vitamin A which is FDA approved for the treatment of macular degeneration, and cystic fibrosis; and it has been investigated for use in cancer chemoprevention. Studer and group treated 90 Ta and T1 patients after transurethral resection with etretinate (Studer, Jenzer et al. 1995). They observed that time to first tumor occurrence was the same in both treatment and placebo groups, however, time to second tumor occurrence was lower for treatment group versus placebo (20.3 v 12.7 months, P>0.006). The data suggests that the agent acts not on established bladder cancer, but acts to prevent new cancer. Vitamin A overdose is known to cause low blood pressure, fever, and pulmonary insufficiency. Synthetic formulations of vitamin A are reported to show less significant adverse events (Sporn and Lippman 2003).

Sabichi and colleagues reported on a negative Phase III chemoprevention trial that showed that Fenretinide was well tolerated but failed to show a significant reduction in high incidence of recurrent non-muscle invasive urothelial bladder cancer (Sabichi, Lerner et al. 2008). The authors speculated that variable of dosing and scheduling could have affected the clinical results. However, data from other randomized clinical studies in contralateral breast cancer, ovarian cancer and oral premalignancy suggested preventative benefit of fenretinide in these malignancies (Sporn and Lippman 2003). In another clinical prevention trial in bladder cancer, this agent was reported as being less toxic and more efficacious than the retinoid etretinate (Sabichi, Lerner et al. 2008).

5.1.2 Vitamin B6 (Pyridoxine)

Vitamin B6 has been evaluated in patients with history of recurrent UC. The Veterans Administration Study by Byar and group showed that Pyridoxine provided the best benefit (P=0.03) in a 3-ARM trial of intravesical thiotepa, Pyridoxine and placebo in 121 patients with history of recurrent NMIUBC (Byar and Blackard 1977). The authors also showed that the efficacy of Pyridoxine was equivalent to that of thiotepa. The theory was that Pyridoxine would correct the abnormalities of Tryptophan metabolism often found in patients with bladder cancer. This data was not supported in a large study of 291 patients in the EORTC trial of Pyridoxine versus placebo with neither treatment showing any benefit in preventing occurrence or recurrence of UC (Newling, Robinson et al. 1995).

5.1.3 Vitamin C

Ascorbic acid (Vitamin C) is a potent antioxidant reported in human epidemiological studies to prevent UC (Shibata, Paganini-Hill et al. 1992; Michaud, Spiegelman et al. 2000). The effect is also thought to be dose dependent, with improved benefit associated with higher consumption (Shibata, Paganini-Hill et al. 1992; Michaud, Spiegelman et al. 2000). Favorable reports are inconsistent in large cohorts.

5.1.4 Vitamin E

Vitamin E is another antioxidant and is capable of reducing the carcinogenic N-nitroso compounds. Vitamin E has been reported in multiple studies to show benefit in reducing incidence of UC (Bruemmer, White et al. 1996; Michaud, Spiegelman et al. 2000). However, a meta-analysis by Miller and associates showed a potential increased in all-cause mortality associated with Vitamin E consumption (Miller, Pastor-Barriuso et al. 2005). This finding has dampened enthusiasm in the use of Vitamin E in chemoprevention for UC.

5.1.5 Selenium

There is no data yet suggesting a chemopreventive role for this oligoelement in UC.

5.1.6 Mega dose vitamins

Vitamins and dietary supplements/modifications have received slightly skewed publicity as alternative protective strategies against bladder cancer (Kamat and Lamm 2002). Individual vitamins including Vitamin A, and its analogues, Vitamin B6 (pyridoxine), Vitamin C, Vitamin E have been studied individually, reported and proposed as dietary supplements to prevent bladder cancer.as discussed above (Byar and Blackard 1977; Shibata, Paganini-Hill et al. 1992; Newling, Robinson et al. 1995; Studer, Jenzer et al. 1995; Decensi, Torrisi et al. 2000; Kamat and Lamm 2002; Castelao, Yuan et al. 2004; Miller, Pastor-Barriuso et al. 2005; Sabichi, Lerner et al. 2008). However, Lamm et al. combined mega doses of Vitamins A(40,000U), B6(100mg), C(2000 mg), E(400U) and Zinc (90mg) in a randomized 2x2 factorial design study in which 65 patients were randomized to receive intraderrmal BCG (Lamm, Riggs et al. 1994). Participants who demonstrated a response to induction intravesical BCG, were randomized to receive either Megadose vitamins or recommended daily allowance (RDA).The use of intradermal BCG did not appear to affect the clinical outcome. The Mega-dose vitamins treatment group showed a 50% reduction in overall NMIUBC recurrence at 4 years, The fact that there was no reduction in tumor recurrence rate in the Megadose vitamins group in the first 10 months, would suggest that these supplements/agents do not affect existing tumors but hinder the formation of new tumors.

5.2 Difluoromethylornithine

Difluoromethylornithine (DFMO) is a competitive inhibitor of ornithine decarboxylase (ODC) which is an enzyme that induces polyamine production necessary for tumor growth. A negative study was reported by Messing and associates who observed that daily oral supplementation of difluoromethylornithine (DFMO) compared with placebo, did not prevent frequent recurrence and progression of low grade NMIBC in patients who had been completely resected at enrollment (Messing, Kim et al. 2006).

5.3 COX Inhibitors

NSAID inhibit the cyclooxygenase (COX) enzyme, which breaks down arachidonic acid into leukotrienes and prostaglandins. Prostaglandin-2 can enhance cell proliferation, angiogenesis, and inhibit apoptosis (Sabichi and Lippman; Okey, Harper et al. 1998; Sporn and Lippman 2003). In vitro evidence suggests that there is an over expression of COX 2 isoform in UC (Okey, Harper et al. 1998; Sporn and Lippman 2003). Theoretically, COX 2

isoform inhibitors could be used in chemoprevention of UC. Castelao and colleagues reported on a population-based, case-control study, in which they evaluated non-steroidal anti-inflammatory drugs (NSAIDs) in NMIUBC (Castelao, Yuan et al. 2000). This study found a 19% decrease in UC risk in those patients treated with oral agents, except those patients treated with phenacetine and pyrazolone derivatives (Castelao, Yuan et al. 2000). Therefore, COX-2 remains a very viable target for future evaluation in bladder cancer chemoprevention.

Preventive Strategy	**Methodology**	**Mechanism**	**Published studies**	**Significance**	**Current status**
Fluid intake	Mailing Questionnaires	Increased fluid intake results in lowered cumulative exposure of urothelium to carcinogens with *reduced risk*	The Health Professional Follow up Study (n = 47,903)	High	Recommended (Level 4 evidence; Grade C recommendation)
Fat and calorie intake	Population based study (SEER) and meta-analysis of 36 studies evaluating 6 dietary variables in relation to UC	2-fold increase in cancer with increased fat consumption	Riboli et al & SEER studies: positive correlation; Health Professionals follow up study: no correlation	Intermediate	Recommended (Level 2 evidence; Grade B recommendation)
Green Tea	Epidemiological	Polyphenols contents of green tea are potent antioxidants; also inhibit ornithine decarboxylase which is an enzyme that promotes tumor proliferation via nucleic acid regulation; a *weak inverse relationship between tea intake and UC*	NCI-sponsored phase 2 and 3 clinical trials are in progress	Low	Recommended (Level 4 evidence; Grade C recommendation)

Preventive Strategy	Methodology	Mechanism	Published studies	Significance	Current status
Soy	Population based	potential apoptotic and action attributable to the high isoflavone content; *no data yet favoring recommendation*	Singapore-based population study	Very low	Not recommended
Smoking	Population based	Smoking cessation correlates with decreased incidence	Population based	High - most cost-effective measure in bladder cancer prevention strategy	Highly recommended (Level 3 evidence; Grade B recommendation)
Vitamin A	compared 1592 UC participants to a matched neighborhood controls	Agent does act not on established bladder cancer, but *prevents new cancer*	SEER database controlled study	Low - lacks an effective agent as well as evidence-based data to encourage wide clinical practice	Recommended (Level 3 evidence; Grade B recommendation)
Vitamin B6	3-arm trial; placebo controlled trial	Pyridoxine provided the best benefit (P=0.03) in a 3-Arm trial of intravesical thiotepa, placebo, and Pyridoxine; however, this data was not supported in EORCT trial (n=291) of Pyridoxine versus placebo, *both showing no benefit in preventing occurrence or reoccurrence*	The Veterans Administration Study (Byar et al)	Intermediate	Not recommended
Vitamin C	Human epidemiological studies	potent antioxidant; *effect dose dependent, better with higher consumption*	Large cohort studies	Inconsistent	Not recommended

Preventive Strategy	Methodology	Mechanism	Published studies	Significance	Current status
Vitamin E	meta-analysis	antioxidant capable of reducing carcinogenic N-nitroso compounds in urothelium	Miller et al.	Potential increase in all-cause mortality with Vitamin E consumption	Not recommended
Selenium	No data	no data yet suggesting a chemopreventive role for this oligoelement in UC	No data	N/A	Not recommended
Megadose vitamins	randomized 2x2 design study in which 65 patients were randomized to received intraderrmal BCG or not, and also randomized after response to induction intravesical BCG to receive Megadose vitamins versus daily recommended daily allowance	Possible anti-oxidant role	Small trial from a single institution	Mega-dose vitamins-treated group showed a 50% reduction in overall NMIBC recurrence at 4 years	Not recommended
Difluoromethylornithine (DFMO)	Messing et al	DFMO is a competitive inhibitor of *ornithine decarboxylase* that induces polyamine production necessary for tumor growth	Negative study	daily oral supplementation vs. placebo, did not prevent recurrence and progression of low grade NMIBC following prior TUR-BT	Not recommended

Preventive Strategy	Methodology	Mechanism	Published studies	Significance	Current status
COX inhibitors	Castelao et al.	Prostaglandin-2 can enhance cell proliferation, angiogenesis, and inhibit apoptosis. In vitro evidence suggests over expression of COX 2 isoform in UC	a population-based, case-control study - NSAIDs in NMIUBC showed a19% decrease in UC risk in those treated with oral NSAIDs (except phenacetine and pyrazolone derivatives)	COX-2 remains a very viable target in bladder cancer chemopreventi on	Recommended (non-evidence based)

Table 1. Summary of Reports (discussed above) of various Chemopreventative Strategies (refs:28-51)

6. Future research and experimental cancer chemoprevention

Research continues intensely in the evaluation of pharmaceutical agents for chemoprevention in bladder cancer. However, dietary supplement, multivitamins and phytochemicals/botanical agents are being evaluated in the prevention of many human cancers (Byar and Blackard 1977; Shibata, Paganini-Hill et al. 1992; Lamm, Riggs et al. 1994; Newling, Robinson et al. 1995; Studer, Jenzer et al. 1995; Castelao, Yuan et al. 2000; Decensi, Torrisi et al. 2000; Michaud, Spiegelman et al. 2000; Kamat and Lamm 2002; Castelao, Yuan et al. 2004; Miller, Pastor-Barriuso et al. 2005; Messing, Kim et al. 2006; Sabichi, Lerner et al. 2008). Investigators have reported on results of screening strategies for synthetic pharmaceuticals in an experimental bladder cancer prevention model using the chemically-induced rat bladder tumor model (Sindhwani, Hampton et al. 2001; Lubet, You et al. 2006; Park, Kim et al. 2006; Tian, Wang et al. 2008; Parada, Reis et al. 2011). They reported that low dose aspirin and resveratrol were least effective in preventing large tumor formation, while naproxen and Iressa were most effective (Lubet, You et al. 2006).

In recent years there has been a substantial interest in the application of botanically derived phytochemicals to reduce the incidence of variety of human tumors. Intense research is ongoing to provide evidence-based recommendations to incorporate plant foods or botanical products or dietary modifications into the practice of clinical cancer chemoprevention. There is the salient speculation that Curcumin, a very popular Indian food spice, derived from the rhizome plant called curcuma longa Linn (Zingiberaceae), has been responsible for lower incidence of urothelial malignancies (Sindhwani, Hampton

et al. 2001; Tian, Wang et al. 2008)and lower rate of colorectal cancer (Tian, Wang et al. 2008) in the populations that consume Curcumin as a staple part of their diet (Sindhwani, Hampton et al. 2001; Tian, Wang et al. 2008). Investigators have reported on Curcumin induced apoptosis in MBT-2 cells[56] G2/M cell cycle arrest in T-24 cells (Sindhwani, Hampton et al. 2001; Tian, Wang et al. 2008). Curcumin inhibition of intravesical tumor implant in mouse model (Sindhwani, Hampton et al. 2001) and prevention of OH-BBN induced bladder carcinogenesis in rodent, as well as inhibition of tumor development and growth in an intravesical murine bladder model (Sindhwani, Hampton et al. 2001; Tian, Wang et al. 2008).

Seventy-five percent of all pharmaceuticals were discovered by studying the use of plants in traditional medicine. Of the 92 antitumor drugs approved by the FDA between 1983 and 1994, 62 (67%) were either of natural origin or based on a natural compound (Chung, Anscher et al. 2001).

7. Conclusions and clinical practice suggestions

Bladder cancer is a common, but serious health problem globally. It is immensely impacted by environmental carcinogens, tobacco smokes, and infectious etiologies in endemic areas. The bladder urothelial cancer special features which include its susceptibility; carcinogenesis; frequent recurrences, and clinical presentation favor it as an ideal cancer for chemoprevention. Unfortunately, in bladder cancer there are still no definite interventions that have been shown to be effective, and research in this area has yielded no evidence-based data to inform on strategies for systematic practice of bladder cancer prevention. The positive data from the clinical trials with vitamins individually or in combinations suggest that these agents might act not on established bladder cancer, but act to prevent occurring of new cancers, probably by hindering promotion of altered cells to overt cancer. Cessation of smoking will always remain the lofty but impractical goal of prevention strategies in urothelial bladder cancer; however, a plausible paradigm would suggest a chemoprevention strategy that should begin with the population approach that advocates a dietary program of increased consumption of fruits and vegetables which have been reported to reduce general cancer risk. The at–risk individual would embark on additional programs to reduce/eliminate the intensity of cumulative exposure to the carcinogens, dilution and elimination of bladder content by drinking plenty of water and urinating frequently, followed by introduction of the specific chemopreventive agent(s), probably in combination with the vitamins.

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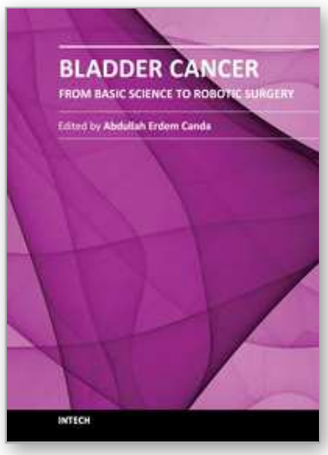

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This book is an invaluable source of knowledge on bladder cancer biology, epidemiology, biomarkers, prognostic factors, and clinical presentation and diagnosis. It is also rich with plenty of up-to-date information, in a well-organized and easy to use format, focusing on the treatment of bladder cancer including surgery, chemotherapy, radiation therapy, immunotherapy, and vaccine therapy. These chapters, written by the experts in their fields, include many interesting, demonstrative and colorful pictures, figures, illustrations and tables. Due to its practicality, this book is recommended reading to anyone interested in bladder cancer.

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