Non-occupational risk factors for bladder cancer
Fatores de risco não-ocupacionais para câncer de bexiga

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ABSTRACT
More than 60 thousand new cases of bladder cancer are diagnosed each year in the United States, accounting for approximately 13 thousand deaths annually. In recent decades, the overall incidence of bladder cancer seems to be rising and this may be due to the latent effects of tobacco abuse, other non-occupational risk factors, industrial carcinogens, as well as the overall aging of our population. Cultural and socioeconomic factors also contribute substantially to the etiology of bladder cancer and may play an even more important role than the occupational environment. In this paper, it is reviewed the main established or proposed non-occupational factors associated with bladder cancer development.

Keywords: Urinary bladder neoplasms; Risk factors; Epidemiology

INTRODUCTION
More than 60 thousand new cases of bladder cancer are diagnosed each year in the United States, accounting for approximately 13 thousand deaths annually. It is the fourth most common cancer (and second most common urologic cancer) found in men in this country. In recent decades, the overall incidence of bladder cancer seems to be rising and this may be due to the latent effects of tobacco abuse, other non-occupational risk factors, and industrial carcinogens, as well as the overall aging of the population. An increased risk of bladder cancer was detected in a number of occupational exposures that will not be approached in this paper. Culture-mediated (habits) and socioeconomic factors also contribute substantially to the etiology of bladder cancer and may play an even more important role than the occupational environment.

The most important known risk factor for bladder cancer is cigarette smoking. Also, urine plays a major role in bladder carcinogenesis, acting as a transport mechanism for carcinogens, containing factors that stimulate cell proliferation, and indirectly affecting chemicals by altering the concentrations of normal urinary components, such as electrolytes, water and proteins. These latter effects are greatly modified by diet composition and consumption. There is, nowadays, a broader view that bladder cancer may be related to diet.

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In this paper it is presented the main established or proposed non-occupational factors associated with bladder cancer development. This new cancer prevention paradigm demands that we limit exposure to avoidable environmental and occupational carcinogens, in combination with additional important risk factors, such as diet and lifestyle.

**RISK FACTORS**

**Tobacco**

Cigarette smoking is the most important risk factor for bladder cancer, accounting for 50% of cases in men and 35% in women. A meta-analysis reported that current cigarette smokers have a risk of 2.57 (95% CI = 2.20-3.00) compared with non-smokers(3). A positive dose-response relationship was found with both number of cigarettes smoked daily and number of years of smoking. The risk for non-transitional cell carcinoma is also increased in smokers. Upon cessation of cigarette smoking, the excess risk for bladder cancer falls over 30% after one to four years and over 60% after 25 years of cessation(3,4). People who exclusively smoke unaltered cigarettes have a 30-70% higher risk than those who smoke only hand-rolled cigarettes. Inhalation of tobacco smoke moderately increases the risk compared with no inhalation. Black tobacco consumption is associated with an increased risk compared with blond tobacco. Some studies have reported an increased risk of bladder cancer among pipe smokers(6).

**Soy food**

A population-based cohort study indicated that high intake of soy food is significantly associated with an elevated risk of bladder cancer(5).

**Coffee and tea**

Over the past four decades, several risk factors for bladder cancer have been investigated. Recently, an updated meta-analysis on coffee and tea consumption showed a small elevated risk of bladder cancer for current coffee drinkers and did not identify an association for tea drinkers compared with non-drinkers(6). The current results suggest a possible positive association between coffee consumption and bladder cancer risk for the male population. Consuming seven cups per day was found to have the highest risk of bladder cancer. In women, a probable inverse association was found. Tea was inversely associated with bladder cancer in both men and women(7).

**Meat**

N-Nitrosamines are known bladder carcinogens in animal models. They are present in cigarette smoke, and are found in the urine of patients who are at high risk of bladder cancer, namely patients with indwelling catheters or schistosomiasis infections. Bacon is the major food source of preformed nitrosamines. Frequent consumption of bacon was associated with an elevated risk of bladder cancer(8).

**Analgesic abuse**

Consumption of large quantities (5 to 15 kg over a period of ten years) of analgesic combinations containing phenacetin is associated with an increased risk of bladder cancer(9).

**Chronic cystitis and other infections**

Chronic cystitis in the presence of indwelling catheters or calculi is associated with an increased risk of squamous cell carcinoma (SCC) of the bladder(10). Similarly, *Schistosoma haematobium* cystitis seems to be causally related to the development of bladder cancer(11).

Griffiths and Mellon concluded that human papillomavirus (HPV), plays a role in cell tumorigenesis in immunocompromised patients(12).

**Pelvic irradiation**

Women treated with radiation for carcinoma of the uterine cervix or ovary have a two-fold to four-fold increased risk of developing bladder cancer subsequently compared with women undergoing only surgery(13).

**Cyclophosphamide**

Patients treated with cyclophosphamide have up to nine-fold increased risk of developing bladder cancer, although the specific relationship has not yet been formally demonstrated in case-control epidemiologic studies(14).

**PROTECTION FACTORS**

**Fluid intake**

The cause of bladder cancer is not well understood, but it may be related in part to direct contact of the bladder urothelium with carcinogens excreted in the urine. High consumption of fluids may reduce this exposure by diluting the urine and reducing contact time through increased frequency of urination. Total daily fluid intake was inversely associated with the risk of bladder cancer.
Michaud et al. showed that the multivariate relative risk was 0.51 for the highest quintile of total daily fluid intake (> 2,531 ml per day) as compared with the lowest quintile (< 1,290 ml per day) in a ten-year follow-up study involving more than 47 thousand participants and analyzing 252 new cases of bladder cancer\(^{(15)}\). Additional studies are needed to evaluate the temporal relation between increased fluid consumption and changes in the risk of bladder cancer.

**Fruits and vegetables**

Bladder cancer is associated with fruit (as a protection factor) but not with vegetables. Prospective studies have provided weaker evidence than case-control studies of the association between fruit and vegetable consumption and reduced cancer risk. The discrepancies may be related to recall and selection biases in case-control studies. In contrast, the association may have been underestimated in prospective studies because of the combined effects of imprecise dietary measurements and limited variability of dietary intakes within each cohort\(^{(16)}\).

**Carotenoids**

Case-control and prospective studies have shown an association between the consumption of foods rich in carotenoids (i.e. fruits) and a relatively low incidence of various cancers, including lung, bladder, stomach, prostate, head and neck, and liver. Schabath et al. demonstrated that a high intake of carotenoids was associated with an overall decrease in bladder cancer risk and also among individuals susceptible to induced DNA damage\(^{(17)}\).

**No Relation With Bladder Cancer**

**Alcohol drinking**

Many studies have evaluated the role of alcoholic beverage consumption on bladder cancer risk and have provided inconsistent results. A recent meta-analysis indicated no evidence for alcohol consumption with Odds Ratio (OR) for alcohol consumption being 1.3 (95% CI= 0.9-2.0) for men and 1.0 (95% CI= 0.6-1.7) for women\(^{(18)}\).

**Toenail selenium**

Geographic variations in bladder cancer risk, observed in the United States and other countries, have been ecologically related to soil selenium levels. Evidence from clinical trials, observational, and animal studies suggests that selenium has anticarcinogenic properties and can affect the risk of cancer development. Common malignancies, such as those of the lung, prostate, and colon, largely account for the reported associations between selenium and total cancer incidence, but with few data, little is known about the link between selenium and other cancers.

Michaud et al., in a randomized, double-blind, placebo controlled prevention trial, observed no association between toenail selenium concentrations and bladder cancer risk among male smokers\(^{(19)}\).

**Fish and marine fatty acids**

Holick et al., in a prospective study, demonstrated that there were no statistically significant association between baseline total fish or marine fatty intake and the risk of bladder cancer among men or women\(^{(20)}\).

**Dietary supplements, macronutrients, micronutrients**

Michaud et al., in a prospective cohort study involving 320 cases of bladder cancer, concluded that there was no association observed for total caloric or macronutrient intake and bladder cancer risk. Similarly, these authors found no association for dietary intake of potassium, sodium, calcium, magnesium, phosphorus, iron, or water-soluble vitamins and bladder cancer risk. Total vitamin E intake and vitamin E supplements were inversely associated with the risk. Finally, a suggested inverse association was seen with the dose of vitamin C supplement used\(^{(21)}\).

**References**


