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Environmental non-occupational risk factors associated with bladder cancer

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Abstract

Context—Bladder carcinoma (BC), due its high morbidity and relapsing course, generates significant economic and health care costs. Accordingly, we reviewed the environmental nonoccupational risk factors (RF), more or less evidence-based, in the etiology and pathogenesis of BC, because the involvement of urologists is essential for prevention.

Acquisition of evidence—Review of the peer-reviewed literature (1987–2012) on nonoccupational environmental RF associated with BC retrieved from Medline, Embase and Science Citation Index. The search profiles have been “Risk factors/Epidemiology/Tobacco-smoking/Diet-nutrition-water-liquids/Radiation/Infectious/Farmacological drugs” and “Bladder cancer”.

Synthesis of evidence—Smoking was associated with 50% of BC in both sexes. Smokers have a 2–5 times higher risk than nonsmokers, directly proportional to the amount and duration of addiction. Drinking water contaminated with arsenic and chromium chlorination byproducts increases the risk of BC. High consumption of red meat and saturated fat may increase the risk, while high intake of fruits and vegetables decreases it. Patients treated with cyclophosphamide, ifosfamide and ionizing radiation have an increased risk of BC. Frequent and prolonged use of hair dyes and *Schistosoma haematobium* infestation increases the risk of BC.

Conclusions—The reduction or the cessation of smoking decrease BC. The contaminant-free water consumption with the increase of vegetal foods favors BC prevention. Cancer survivors

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Conflict of interests

The authors declare that they have no conflict of interest.

treated with cyclophosphamide, ifosfamide and radiation therapy should be monitored for early diagnosis of BC.

Resumen

El carcinoma vesical (CV), por su elevada morbilidad y evolución recidivante, genera importantes costes asistenciales y económicos. Por ello revisaremos los factores de riesgo (FR) ambientales no ocupacionales implicados, con mayor o menor evidencia científica, en la etiopatogenia del CV, pues la implicación de los urológicos es fundamental para suprevención.

Revisión bibliográfica de los últimos 25 años de los mencionados FR asociados al CV, obtenida de MedLine, Science Citation Index y Embase. Los perfiles de búsqueda han sido *Risk Factors/ Epidemiology/Tobacco-smoking/Diet-nutrition-water-liquids/Infectious/Radiation/Farmacological drugs* y *Bladder cancer*.

El tabaquismo se asocia al 50% de los CV en ambos sexos. Los fumadores presentan riesgos 2–5 veces superiores, dependiendo de la intensidad y duración de la adicción. El agua potable contaminada con arsénico, subproductos de cloración y cromo, incrementa el riesgo de CV. Consumos altos de carne roja y grasa saturada posiblemente aumenten el riesgo, mientras la ingesta elevada de frutas y verduras lo disminuye. La administración de ciclofosfamida, ifosfamida y radioterapia incrementa el riesgo de CV. El uso frecuente y prolongado de tintes capilares y la infestación por *Schistosoma haematobium* se asocian a mayores riesgos.

La reducción o eliminación del tabaquismo disminuirá la prevalencia del CV. El consumo de agua sin contaminantes, con el incremento de alimentos vegetales favorece la prevención del CV. Los supervivientes de cánceres tratados con ciclofosfamida, ifosfamida y radioterapia deben ser monitorizados para el diagnóstico precoz del CV.

Keywords

Bladder cancer; Epidemiology; Risk factors; Smoking; Arsenic; Chlorinationby-products; *Schistosoma haematobium*

PALABRAS CLAVE

Cáncer vesical; Epidemiología; Factores de riesgo; Tabaquismo; Arsénico; Subproductos cloración; *Schistosoma haematobium*

Introduction

In Western countries, one in 26 men and one in 87 women will develop a bladder carcinoma (BC) over the course of their lifetime, especially in the last third.¹This significant morbidity, which generates a great emotional, physical and economic, highlights the transcendent personal and professional involvement of urologists to recognize, reduce or eliminate environmental risk factors (RF) associated to its etiopathogenesis with more or less evidence.²

In this paper we review the major non-occupational environmental RF associated with BC (Table 1), completing our previous contribution.³

Smoking

Smoking is the main RF associated with the incidence and biological aggressiveness of BC. This factor has the largest scientific evidence.^{4–14} Until recent times smoking was associated with 50–60% of the BC in men and 20–30% in women. This difference was due in part to the traditional differences of consumption and the long latency periods of bladder carcinogenesis (30 years). Today, the risks are similar in both sexes and it is associated to 50% of BC, as smoking rates between men and women in Western countries are equal.^{6,7}

Numerous epidemiological case–control and cohort studies convincingly demonstrate the direct relationship between active smoking and BC.^{4,12} Except for neoplasms of the respiratory tract and oral cavity, the BC is the best smoking-related neoplasia documented.^{8,9} Overall, smokers have 2–3 times greater risk than non-smokers, being even up to 5 times for those consuming 1 pack daily.^{4,8} Similarly, patients who smoke have more infiltrating varieties and increased BC mortality compared to non-smokers.^{5,9,10,14}

The risk increases with the intensity of smoking (number of cigarettes per day), with RR (relative risk) of 2.0–5.0 among moderate to heavy smokers compared to nonsmokers.^{4,6,9} The studies demonstrate a very convincing dose–response curve, although some researches show stabilization from moderate to severe consumptions, but they are attributed to confounding factors (recall bias, lower relative inhalation among large consumers, genetic polymorphisms, etc.).

Another variable involved in the risk is the relationship with the years of exposure.^{4,6,8} The same applies to the depth of inhalation, which increases the risk 30–40% when compared to those who inhale very little or nothing.^{5,9} Studies conducted to compare gender differences in the risk of BC in smokers do not find differences between men and women when analyzing equivalent doses of intensity, duration, depth of inhalation and variety of tobacco consumed.

The different varieties of cigarettes (filters, black, blond) have been also studied as well as the consumption without cigarettes (pipes, cigars and smokeless tobacco).^{4,9} The results on the effects of cigarette filters have been inconsistent. The black tobacco smokers have risks of 1.5–3 times higher than those who smoke blond tobacco. Pipe smokers have a RR of 1.3–3.9 with respect to non-smokers and cigar smokers have a RR of 1.3–1.6. The sniffers and tobacco chewers have been poorly evaluated to obtain valid results.

In a hospital-based study conducted in Spain¹² 1219 BC patients and 1271 controls were analyzed in relation to the consumption of tobacco. Current smokers (men OR = 7.4 [CI 95%: 5.3–10.4]/women OR = 5.1 [CI 95%: 1.6–16.4]) and former smokers (men RR = 3.8 [IC 95%: 2.8–5.3]/women RR = 1.8 [95% CI: 0.5–7.2]) had higher risks, statistically significant, than never-smokers. Direct relationship between risk and the longer duration and intensity of consumption was observed. After adjusting the duration and amount, the risk was 40% higher in smokers of black tobacco compared to smokers of blond tobacco (OR = 1.4 [95% CI: 0.98–2.0]). This difference may be due to higher concentrations of N-nitrosamines and 2-naphthylamines in black tobacco.^{4,8} The study also documented that deep inspiration increases the risk between 50 and 70% compared to those who hold the

smoke in their mouth. The researchers found that snuff is responsible for 42% of BC in men and 13% in women. Finally, if the effect of tobacco was eliminated, the man/woman relation in the BC incidence decreased from 8.2 to 1.7, suggesting that the great gender difference in our country was due to the consumption of tobacco and its black variety.

Smoking cessation is associated with a 30–60% reduction in BC risk in most studies; however, the pattern of change of risk in relation to the cessation period is not sufficiently established.^{9–11} However, the rapid decline of risk in the early years of the cessation suggests that tobacco smoke carcinogens play a role in the later stages of bladder carcinogenesis.

Exposure to environmental tobacco smoke has also been associated with increased risk of BC, but the results are not unanimous. A large study documents increased risk in women exposed to tobacco during childhood and adulthood with OR = 3.08 (IC 95%: 1.16–8.22)⁹ (95% CI: 1.16–8.22).⁹ The effect was greater especially in women who had never been smokers. The mechanisms underlying these gender differences are unknown

The mechanisms of action of the 62 carcinogens contained in snuff smoke are well established, but it is not clear how many of them, individually or in combination, are primarily responsible for the development of BC.^{8,9} As it can be seen in Table 2, various aromatic amines such as 2-naphthylamine, 2-toluidine and 4-aminobiphenyl, numerous n-nitrosamines, polycyclic aromatic hydrocarbons such as benzo(a)pyrene and dibenzo(a,h)anthracene, aromatics hydrocarbons such as benzene and 1,3-butadiene, have proved decisive involvement bladder carcinogenesis. Curiously, from the seventh decade of the last century, the analyses of concentrations of these carcinogens in tobacco smoke are increasing and this partly explains the maintained persistence of cancers associated to them, such as BC, despite the decrease in the consumption of tobacco in Western countries.⁸

Dietary factors (Table 3)

Water pollutants

Arsenic—Water intake with high concentrations (>0.2 mg/l) of inorganic arsenic is well a documented cause of BC. Likewise, populations exposed to such use show an increase of mortality attributed to BC in cohort studies.⁵ Carcinogenesis activity of arsenic on bladder mucosa is biologically demonstrated by the increase of chromosomal aberrations in exfoliated bladder cells of healthy people exposed, and by higher percentages of chromosomal deletions in bladder tumors associated with high levels of exposure.¹⁵ Also a linear relationship between the concentrations of arsenic in water and increased risk of BC has been demonstrated. RRs were 1.9, 8.2 and 15.3 for concentrations of 10.1–50.0, 50.1–150.0 and >100 mg/l.⁴ Also, in populations exposed to high concentrations in the public water supply, the replacement for bottled water without arsenic has decreased the incidence of BC¹⁵ (Table 3).

By-products of water chlorination

The chlorine, added to disinfect drinking water, reacts with organic matter generating the so-called chlorination byproducts (SPC). The most studied are trihalomethanes, iodomethanes,

halonitromethanes and hidroxy-furanes. Numerous studies of control–cases with water intake with high concentrations of BPCs (~50 µg/l, levels observed in many western countries and regions), identified a 50% increased risk of BC with regarding consumption of dechlorinated water.⁴ The risk is lower in populations where disinfection is done by ozone.⁵ The exposure to BPCs through inhalation and transdermal absorption along with the intake are the routes that contribute to the total exposure to trihalomethanes, and it has been evaluated in an epidemiological study documenting an increased risk in showers, baths and swimming pools.¹⁵

Hexavalent chromium

It has also been suggested that the contamination of drinking water with hexavalent chromium derived from industrial activity and listed as a human carcinogen, is associated with an increased incidence, recurrence and mortality of BC.¹⁶

Fluid intake

Studies comparing total fluid intake with the risk of BC have given mixed results.⁴ High consumptions of liquids have been associated with lower risk, higher risk and null effects. The disparity of results is subject to methodological flaws and logistical difficulties of these studies. We will highlight one of the best studies on a cohort of health professionals,¹⁷ which shows a protective effect of high intake, with a risk reduction of 7% for each 240 cc of total liquid increase. This study also documents that the use of e 2.531 cc/day reduces the risk between 24–40% compared to those that ingest 1.290 cc/day. The assumptions underlying these results are that high intake dilutes urinary carcinogens and increased urinary frequency decreases contact time with the bladder mucosa.

Intake of coffee, alcohol, tea and mate

A direct association between coffee intake and increased risk of BC was published in 1971, with RR of 1.3 for men and 2.5 for women.⁵ Numerous subsequent studies differ in results with respect to gender, but document RR ~2.0. Listed by IARC in 1991 as 2 B (possibly carcinogenic to the bladder). A meta-analysis published in 2001 documents OR = 1.26 (95% CI:1.09–1.46) for men and OR = 1.08 (95% CI:0.79–1.46) for women, and OR = 1.18 (IC 95%: 1.01–1.38) 1.18 (95% CI: 1.01–1.38) for the 2 genres combined.¹⁸

Regarding alcohol intake results are still mixed. A recent meta-analysis documents an increased risk but without statistical significance.¹⁹ The possible association with specific alcoholic beverages has been also studied, but the data are inconsistent.

Regarding tea consumption, epidemiological studies control–cases, cohort and meta-analysis found no protective effects of tea polyphenols on bladder carcinogenesis. A recent meta-analysis²⁰ found that only the variety of green tea is associated with statistically significant lower risk with OR = 0.814 (95% CI: 0.678–0.976).

High and maintained intake of mate, infusion of the herb *Ilex paraguariensis*, popular in South American countries, increases the risk of BC.²¹

Artificial sweeteners

Saccharin was suggested as RF by the results obtained in intrauterine exposure to high doses in rats, but not postnatally.⁴ Numerous investigations performed on humans have ruled out the association.²²

Fruits and vegetables

Among the dietary RF that have been evaluated with respect to the risk of BC, a wide scientific evidence shows that high consumption of fruits and vegetables has protective effects.²² Numerous epidemiological studies show that consumption of natural fruits, juices and vegetables (carrots, cruciferous and dark-green leafy) decreases the risk of BC.²³ A meta-analysis found that diets low in fruits increase the RR 1.4 (95% CI:1.1–1.8) and in vegetables RR 1.2 (95% CI:1.0–1.3).⁵ The role of specific micronutrients is less clear. In animal dietary supplements of natural or synthetic retinoids inhibit bladder carcinogenesis. In humans, some studies suggest that supplements of vitamin A, vitamin C, folate and carotenoids as well as vitamin E and selenium are protective, but most results are inconsistent.^{22,23}

Other dietary factors

Risk increases have been associated with high intakes of meat, especially red meat, animal fats and cholesterol, fish, animal foods cooked at high temperatures, smoked and salted. Temperatures > 200° generate the formation of heterocyclic amines, classified as probable human carcinogens.^{4,5,22}

Biological plausibility of dietary RF (Table 3) in the bladder carcinogenesis is based on: (a) the protective effect of fruits and vegetables is consistent and similar to that observed in other neoplasias; (b) the high consumption of red meat cooked at high temperatures is also associated with increased risks in other cancers, and elevates the levels of heterocyclic amines in urine; (c) flavonoids provided by many fruits and vegetables inhibit the mutagenicity of heterocyclic amines in cell cultures; and (d) experimentally, urinary acidity influences the metabolism of bladder carcinogens, increasing the formation of genetic alterations in bladder mucosa. Foods of animal origin generate acidic urine, while consumption of vegetables generates alkaline urine.

Medicines/drugs

Analgesics

High consumption of phenacetin increased between 2–6 times the risk of BC.^{4,5} This drug was banned for developing chronic interstitial nephropathy and it was replaced by acetaminophen paracetamol, aromatic amino metabolite of phenacetin, with no effects on the risk of BC in the short and medium term.

NSAIDs, including acetylsalicylic acid, are associated with a lower risk of BC. The biological plausibility is supported by experimental evidence that NSAIDs are potent inhibitors of BC developed by chemical carcinogens.²⁴

Phenobarbital

Its long-term use as anticonvulsant drug decreases up to 40% risk of BC.^{5,25} Apparently, both phenobarbital and phenytoin induce deactivation of bladder carcinogens, especially those contained in tobacco smoke.

Antineoplastic

Alkylating agents—Alkylating agents are a family of drugs used in the therapy of neoplastic and rheumatic diseases. Its side effects include second neoplasms, and therefore they are classified as human carcinogens. Only 2 of them, cyclophosphamide (CFM) and ifosfamide (IFM), are associated with the development of hemorrhagic cystitis and BC.^{4,5,25} CFM and MFIs need to be metabolized in order to develop antineoplastic and carcinogenic actions. The major metabolite involved in bladder toxicity is acrolein. If uroprotector Mesna (2-mercaptoethane sulfonate) is not used concomitantly, the direct association between cumulative doses and risk of BC shows RR of 2.4, 6.0 and 14.5 in survivors with total doses of 20 g, 20–49 g and 50 g, respectively.⁴ However, it is not entirely clear what role corresponds to acrolein and other metabolites in bladder carcinogenesis. Although concomitant use of Mesna is universal, all treated with CFM and IFM survivor should be monitored for BC.

Chlornaphazine

This former antineoplastic drug was associated with increased risk of BC, but its therapeutic use was very limited.^{24,25}

Other drugs

Pioglitazone, drug used in the treatment of diabetes mellitus type 2, increases the risk of BC.²⁷

Isoniazid and some laxatives have been associated with an increased risk of BC, but with inconsistent results.^{4,27}

Ionizing radiation

Consistent evidence of an association between ionizing radiation (IR) and the BC exists. Numerous epidemiological studies have documented that people exposed to RI for medical reasons or because of nuclear accidents, nuclear plant workers and survivors of atomic explosions are associated with increased risk of BC with respect to that expected in the normal population.²⁸

It has been demonstrated an excess RR of 1.02 per Sievert of exposure in the population cohorts exposed to atomic blasts of Hiroshima and Nagasaki.²⁹ The underlying biological mechanisms are of two types: (a) the direct action on the DNA double helix and (b) indirect actions generated by oxygen free radicals.

Hair dyes

Certain hair dyes contain 4-aminobiphenyl, substance that is considered as occupational carcinogen of BC.³ People who use hair dyes usually excrete larger amounts of urine. Epidemiological studies at the end of the last century did not document any association. In 2001, a case-control study found that women population with regular use of hair dyes had a 70% higher risk of BC with respect to non-users.³⁰ The risk was directly related to the time of use and the frequency of application. However, this association has not been subsequently replicated by other researchers.³¹

Urologic diseases

Urinary tract infections

Positive associations between bladder infections and increased risk of BC have been described in most case-control studies.^{4,25} A research carried out in U.S.A. has documented the direct relationship between cystitis and BC in both sexes, and that patients with 3 infectious episodes present a 2-fold increased risk of BC with respect to unaffected individuals.^{5,25} Furthermore, the squamous cell histological subtype is predominant among the BCs of people with a history of chronic cystitis (paraplegics, SCI patients carrying catheters). The mechanisms underlying the association cystitis-BC are: (a) chronic inflammatory phenomena (oxygen free radicals), (b) alteration of the mucosal barrier to urinary carcinogens and (c) the formation of N-nitroso compounds by bacterial growth.

Infestation by the parasite *Schistosoma haematobium* is typically associated with the squamous cell variety. In countries where the parasite is endemic such as Egypt, more than 70% of BCs are squamous cell carcinoma, while in Western countries this type of cancer accounts for only 2%. Besides the underlying mechanisms discussed in the bacterial cystitis, egg deposits cause urinary bladder stasis, and parasitic antigens are immunosuppressive.^{4,25,32}

Also papillomavirus (HPV) and polyomavirus (BKV and JVC) are associated with increased risk of BC, but the scientific evidence for this is less.^{5,25,33} High carcinogenic risk papillomavirus transfer to mucosal cells E6 and E7 genes, which encode oncoproteins that disrupt the cell cycle, the maintenance of telomerase and regulation of apoptosis. HPV-infected immunosuppressed patients provide more convincing data. Some meta-analysis find increases 2.3–2.8 times higher to submit BC in this group of patients.²⁵ A recent meta-analysis documented a significantly increased risk of bladder cancer associated with HPV positivity overall (OR 2.84 [95% CI 1.39–5.80]); other factors influencing this increase were: the type of HPV, the region of study, DNA sample of the HPV and the detection method. The 5 most common types of HPV identified, in decreasing order of prevalence, were HPV-16, HPV-18, HPV-33, HPV-31 and HPV-5234.³⁴

Lithiasis

The urinary tract lithiasis, regardless of their association with local infections, increases the risk of BC. The most extensive study carried out up to date was conducted in a cohort of 61,144 patients hospitalized with kidney or ureteral stones and 25-years follow-up. A

statistically significant increase in patients both with and without secondary infection was found.³⁵ Case-control studies have been less convincing.

Neoplasias

Some studies in survivors of the renal pelvis carcinoma have greater RR of subsequently developing BC.^{36,37} The risk is inversely proportional to the time since diagnosis of kidney cancer, suggesting that the same RFs, such as smoking, are involved in the two locations.

Higher risks have been also described after diagnoses of renal parenchyma, prostate, testes and even in non-melanocytic skin cancers.^{4,37,38} If we do not consider tobacco as common RF with renal parenchymal tumors and prostate cancer, the plausible hypotheses of the association are based on the effects of treatment, greater evolutionary control and other unknown effects.

Bladder stasis and urinary pH

Urine is the major route of elimination of soluble carcinogens, so the retention time increases contact with the bladder mucosa and may be associated with an increased risk of BC.^{8,9} Experimental and ecological studies attest that relationship. In humans only a case-control study with positive results has been published.³⁹

Studies in vitro and in experimentation animals show that acid urine rapidly hydrolyze glucuronide conjugates of 4-aminobiphenyl and their nitro-hydroxylated derivative, and metabolize into active forms which produce injuries and forming adducts in the DNA of the bladder mucosa. In a recent study⁴⁰ conducted in Spain with 1219 patients and 1271 hospital controls urinary pH, smoking and the risk of BC were analyzed. The study documented that pH 6.0 was associated with increased risk of BC with OR = 1.5 (IC 95%: 1.2–1.9). CI: 1.2–1.9). When comparing the BC risk with smoking intensity, the risk was higher in active smokers with acid urine (OR = 8.8, 11.5 and 23.8) while the risk in smokers with basic urine (OR = 4.3, 7.7 and 5.8)); the data relate to consumers of 1–19, 20–29 and ≥ 30 cigarettes/day, respectively. These data suggest that urine pH is an important RF of BC.

Finals remarks

Exposure to smoke of tobacco combustion is associated in both sexes with 50% of the BC and becomes the main RF of this neoplasm. For this reason we present the following comments. First, we must think about the importance of urologists in the primary prevention of BC, for recommending smoking cessation to smokers presenting any kind of disease.¹⁰ Second, we have to assess their importance in tertiary prevention of BC, ordening to survivors of BC, who are active or passive smokers, to stop smoking, in order to decrease the likelihood of local recurrence.^{8–10} Third, it is important to emphasize the natural resilience of the bladder mucosa cell to the carcinogenic actions of numerous chemical substances that are contained in the combustion of tobacco.¹⁰ Fourth, it is necessary to highlight the synergistic action of carcinogens that reach the bladder uroepithelium via the blood and urinary tract.⁸

Among the remaining RF analyzed, urologists should advise all BC survivor relevant dietary modifications in order to increase plant-food intakes and to decrease animal-food ones, as well as to increase total fluid intake, mainly non-chlorinated water, and to avoid using hair dyes.

Lastly, all the survivors of malignancies, both urological and any other location, who have been treated with CFM, MFIs and ionizing radiation, should be candidates for secondary prevention of BC.

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Table 1

Major non-occupational environmental RF associated with BC.

Smoking
Dietary factors
<i>Water pollutants</i>
Arsenic
By-products of water chlorination
Hexavalent chromium
<i>Liquid intake</i>
<i>Intake of coffee, alcohol, tea and mate</i>
<i>Artificial Sweeteners</i>
<i>Fruits and vegetables</i>
<i>Other dietary factors</i>
Medicines/drugs
<i>Analgesics</i>
<i>Phenobarbital</i>
<i>Antineoplastic</i>
Alkylating agents
Chlornaphazine
<i>Other drugs</i>
Ionizing radiation
Hair dyes
Urologic diseases
<i>Urinary tract infections</i>
<i>Lithiasis</i>
<i>Neoplasias</i>
<i>Bladder stasis and urinary pH</i>

Table 2

Human carcinogens contained in tobacco smoke, classified by chemical groups and highlighting the most representative.^{8,9}

Chemical group	No. of carcinogens	Representative carcinogens
Polycyclic aromatic hydrocarbons and heterocyclic analogs	15	Benzo(a)pyrene (BaP) Dibenzo(a,h) anthracene
N-nitrosamines	8	4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) N'-nitrosonornicotine (NNN)
Aromatics amines	12	4-Aminobiphenyl 2-naphthylamine
Aldehydes	2	Formaldehyde acetaldehyde
Phenols	2	Catechol caffeic acid
Volatile hydrocarbons	3	Benzene 1,3-Butadiene Isoprene
Other organics	12	Ethylene oxide Acrylonitrile
Inorganic compounds	8	Cadmium Polonio-210

Table 3

Dietary risk factors associated with bladder carcinoma.^{4,5,15–23}

Nutrients	Association
<i>Vit. A, carotenoids, retinoids</i>	Dubious (possibly ↓ risk)
<i>Selenium</i>	Dubious (possibly ↓ risk)
<i>Vit. E</i>	Dubious (possibly ↓ risk)
<i>Vit. C</i>	Dubious (possibly ↓ risk)
<i>Multivitamin</i>	Dubious (possibly ↓ risk)
<i>Meat products</i>	Increases risk
<i>Fats</i>	Increases risk
<i>Fruits</i>	Decrease risk
<i>Vegetables</i>	Decrease risk
<i>Soy</i>	Dubious (possibly ↓ risk)
<i>Water</i>	
Overall liquid	Dubious (possibly ↓ risk)
Arsenic	Increases risk
By-products of water chlorination	Increases risk
Hexavalent chromium	Increases risk
<i>Alcohol</i>	
Coffee	Increases risk
Tea	?
Mate	Increases risk
Artificial sweeteners	