Fluid intake and bladder cancer. A case control study

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To examine the relation of the total intake of fluids and the types of beverages to the risk of bladder cancer, we conducted a hospital based case-control study with 130 newly diagnosed bladder cancer patients and the same number of matched controls. Information of total fluid intake was derived from the reported frequency of consumption of the different types of beverages on the food frequency questionnaire. Univariate and multivariate logistic regression analyses were performed in statistical analysis. There was no statistically significant difference between the cases and the controls in total daily fluid intake. Multivariate logistic regression model showed consumption of: soda (OR=8.32; 95% CI=3.18–21.76), coffee (OR=1.46; 95% CI=1.05–2.01) and spirits (OR=1.15; 95% CI=1.04–1.28) as statistically significant risk factors, while mineral water (OR=0.52; 95% CI=0.34–0.79), skim milk (OR=0.38; 95% CI=0.16–0.91), yogurt (OR=0.34; 95% CI=0.12–0.97) and frequency of daily urination (OR=0.27; 95% CI=0.18–0.41) were statistically significant protective variables. In our study no statistically significant association was observed for total fluid intake. The findings suggest consumption of soda, coffee and spirits were indicated as a risk factors for bladder cancer, while mineral water, skim milk, yogurt and frequency of urination as protective factors for bladder cancer.

Key words: Bladder cancer, case-control study, fluid intake.

The data on fluid intake in relation to the risk of bladder cancer are inconclusive. The associations for total fluid intake observed in epidemiological studies may be attributable to intake of specific beverages, including chlorinated tap water [4, 25], coffee [9], or beer and coffee [11]. It remains unclear whether it is fluid volume as such responsible for increased risk of bladder cancer, or factors inherent to specific, commonly consumed beverages.

The objective of our study was to examine the relation of the total fluid intake and the types of beverages to the risk of bladder cancer.

Patients and methods

The study group was composed of 130 consecutive newly diagnosed bladder cancer patients (diagnosis old up to 2 years) from the Clinical Center of Serbia in Belgrade and from the Clinical Center in Kragujevac in central Serbia. The study took place from June 1997 to March 1999. The diagnosis of bladder cancer was based on clinical signs and pathohistological findings.

For each case, one control was chosen. The controls were patients from the same institutions, but without urinary malignant diseases or other diseases which may lead to permanent change in diet, individually matched to patients by sex, age (± 2 years) and place of residence (rural, urban). After appropriate medical work-up, the subjects of the control group were diagnosed as: presbyopia – 47, cataract – 17, eye-trauma – 5, myopia – 1, conjunctivitis – 1, degenerative rheumatism – 34, inflammatory rheumatism – 10, sarcoidosis – 2, heart attack – 2, chronic bronchitis – 2, asthma – 1, pneumonia – 1, lung cancer – 1, lung fibrosis – 1, hernia inguinalis – 2 and 3 subjects received no medical diagnosis.

A structured questionnaire was used to obtain information on sociodemographic factors and general characteristics habits, such as smoking, related personal and family history, frequency of daily urination etc.

To assess the average daily fluid intake we used a food frequency questionnaire similar to the one used by VLAJINAC et al [26]. Participants were asked how often (daily/weekly/monthly/yearly) they used each of the beverages. The referential period covered 10 years before the disease onset. If significant changes in the diet had happened during the observed period, dietary habits before the change were recorded. The information on frequency and serving size was combined to give each participant a score in milliliters. Total fluid intake was composed of water, milk, yogurt, tea, coffee, mineral water, different kinds of juices, sodas and alcoholic beverages. It was calculated by adding together fluids from all sources, expressed as milliliters per day.

Univariate and multivariate logistic regression analyses were used for statistical analysis. All variables that independently contributed to risk for bladder cancer were included in multiple logistic regression analysis. Health condition of the subjects (ill, healthy) was taken into account as a dependent variable. The adequacy of the logistic model was estimated with probability $p \leq 0.1$ and the significance of independent variables with probability $p < 0.05$. All odds ratios were adjusted for smoking.

Results

According to our results bladder cancer affected primarily men (79.2%). Patients' ages varied from 26 to 81 years (median 64.9 years). Most of cases were urban dwellers (66.1%). There were no significant differences between cases and controls either in marital status or in education level. Transitional cell carcinoma was the most common histologic type, occurring in 121 (93%) of the patients (gradus II – 69 patients, gradus I – 25 patients, gradus III – 12 patients, gradus II/III – 7 patients and gradus I/II – 8 patients); they were predominantly characterized by a papillary pattern of growth. Eight patients had carcinoma planocellulare (gradus II – 7 patients, gradus I – 1 patient), and one patient had adenocarcinoma (gradus II).

Cigarette smoking was strongly associated with the risk of bladder cancer (OR=2.37). The age starting of smoking showed an inverse association with bladder cancer, yielding decreasing risk for older age (OR=0.90; 95% CI=0.85–0.96). The risk estimate increased with an increasing number of cigarettes smoked per day (OR=1.06; 95% CI=1.03–1.10) and number of years of smoking nonfiltered cigarettes (OR=1.07; 95% CI=1.02–1.13) (data non shown).

Table 1 shows the mean amount of every consumed beverage, total fluid intake and number of consumers from both groups. The cases were more prevalent consumers than the controls for tea, beer, wine, spirits, whole milk and soda, but controls were more prevalent consumers of skim milk, yogurt, juices, mineral and tap water.

The results of univariate logistic regression analysis are presented in Table 2. Consumption of coffee, beer, spirits, soda and whole milk were significantly related to bladder cancer, while consumption of skim milk, yogurt, juices, mineral water, tap water and frequency of daily urination showed an inverse association with bladder cancer. In addition to data given in Table 2, mean number of urination per day was 3.49 for cases, and 5.17 for controls. There was no statistically significant association between wine, tea and total fluids consumption and bladder cancer.

Table 1. Types and mean amounts of consumed beverages among cases and controls

Beverage (ml/day)	Number of cases/controls	Mean amount (cases)	Mean amount (controls)
Tea[$]	41/36	38.13	27.00
Coffee[$$]	119/119	175.57	132.64
Beer[#]	61/40	94.85	17.58
Wine[##]	46/29	20.22	3.37
Spirit[+]	76/75	15.66	5.93
Whole milk	90/57	52.02	17.91
Skim milk	70/105	26.92	63.92
Yogurt	98/112	54.71	58.34
Soda[*]	72/27	17.72	1.84
Mineral water	74/105	16.60	48.92
Fruit juice[**]	58/95	11.60	31.32
Water	123/130	1372.20	1497.63
Total fluids	130/130	1896.20	1906.40

[$]Different kinds made from domestic flowers (camomile, mint, dog-rose); [$$]regular (ground) coffee; [#]Light beer; [##]White and red wine; [+]Plum brandy, vodka; [*]This category comprised cola and noncola sodas (regular, low-calorie, caffeinated and noncaffeinated sodas); [**]Orange, apple, grapefruit, tomato and other juices were included.

In order to estimate independent unconfounded effect of the potential risk factors, we used multivariate conditional logistic regression analysis. Only statistically significant variables were entered into the model. According to the data presented in Table 3 we observed a significant increased risk of bladder cancer associated with consumption of soda (OR=8.32), coffee (OR=1.46) and spirit (OR=1.15), irrespectively of tobacco use. More frequently daily urination contributed to a lower risk (OR=0.27) as did the consumption of mineral water (OR=0.52), skim milk (OR=0.38), and yogurt (OR=0.34).

Discussion

Several epidemiological studies of bladder cancer have examined total fluid intake. Three case-control studies [7, 20, 22] and one cohort study [15] have reported no statistically significant relationships between total fluid intake and the risk of bladder cancer. A study in New Orleans reported no major differences in the frequency distribution of total fluid consumption for cases compared with controls [7]. Another study in USA (Utah) reported a smoking-adjusted

Table 2. Univariate logistic regression estimates of odds ratio for bladder cancer associated with daily intake of fluids and specific beverages

Variable	Coefficient	Standard error	p-value	Adjusted* odds ratio	95% CI**
Water(ml/day)	–0.632	0.220	0.0041	0.53	0.35–0.82
Coffee (ml/day)	0.439	0.115	0.0001	1.55	1.24–1.94
Beer (ml/day)	0.135	0.061	0.0267	1.14	1.02–1.29
Wine (ml/day)	0.110	0.087	0.2050	1.12	0.94–1.32
Spirit (ml/day)	0.191	0.043	0.0000	1.21	1.12–1.32
Whole milk (ml/day)	1.058	0.260	0.0000	2.88	1.73–4.79
Skim milk (ml/day)	–1.281	0.284	0.0000	0.28	0.16–0.48
Yogurt (ml/day)	–0.709	0.326	0.0294	0.49	0.26–0.93
Soda (ml/day)	1.555	0.279	0.0000	4.73	2.74–8.18
Fruit juice (ml/day)	–1.215	0.265	0.0000	0.30	0.18–0.50
Tea (ml/day)	–0.092	0.105	0.3820	0.91	0.74–1.12
Mineral water (ml/day)	–0.609	0.125	0.0000	0.54	0.43–0.69
Total fluids	–0.036	0.230	0.8765	0.96	0.61–1.52
Frequency of daily urination	–1.514	0.178	0.0000	0.22	0.15–0.31

*For smoking, **confidence interval

Table 3. Fluid intake as risk factors for bladder cancer – multivariate logistic regression model

Variable	Coefficient	Standard error	p-value	Adjusted* odds ratio	95% CI**
Soda (ml/day)	2.119	0.490	0.0000	8.32	3.18–21.76
Coffee (ml/day)	0.376	0.165	0.0224	1.46	1.05–2.01
Spirit (ml/day)	0.144	0.053	0.0069	1.15	1.04–1.28
Mineral water	–0.658	0.216	0.0023	0.52	0.34–0.79
Skim milk (ml/day)	–0.958	0.443	0.0306	0.38	0.16–0.91
Yogurt (ml/day)	–1.073	0.531	0.0432	0.34	0.12–0.97
Frequency of daily urination	–1.305	0.205	0.0000	0.27	0.18–0.41

*For smoking, **confidence interval

odds ratio of 1.4 (95% CI: 0.9–2.1) for more than 653 oz of total fluid intake per day compared to 289 oz or less [22]. A study in Canada, reported an odds ratio of 1.0 (95% CI: 0.9–1.1) and 1.3 (95% CI: 0.98–1.6) for a 1 liter/day increase of total fluid for men and women, respectively [20]. Our study found no difference in total daily fluid consumption between bladder cancer patients and controls, when adjusted for smoking.

According to a case control study conducted in Western New York [25], total fluid consumption was found to be a strong risk factor for bladder cancer when a number of potential confounding risk factors were controlled for. In several others case-control studies an increase of risk was seen with higher total fluid or beverage consumption in at least one subgroup. In a Danish study [9], a greater increase in risk was seen for men than women, with smoking adjusted odds ratios of 3.3 (95% CI: 1.4–7.4) and 1.8 (95% CI: 0.4–7.4), respectively, for 4 liters of total fluid/day or more compared with less than 1 liter of total fluid/day. A study in the USA also reported a statistically significant increase of risk with larger total beverage consumption; and this association appeared to be mainly attributable to the intake of chlorinated tap water [4]. In Germany, analyzing the daily total fluid intake, significantly increased smoking-adjusted relative risks were found with increasing total liquid consumption in men, yielding an OR of 4.9 associated with drinking more than 3 liters of total fluid per day [11].

Different hypotheses have been put forward to explain the increase of risk with higher total fluid intake. A potential mechanism relates to the "urogenous contact hypothesis" which implicates prolonged contact of the urinary bladder epithelium with carcinogenic substances in the urine [2]. Vena and colleagues have proposed that increased fluid intake does not lead to dilution of carcinogens in the urine, but actually provides a mechanism that would increase tissue contact of the stretched bladder lining with the carcinogens in the urine [25].

Two studies found that high fluid intake was associated with decreased risk of bladder cancer [14, 18]. Michaud and colleagues [14] examined the relation between total fluid intake and the risk of bladder cancer over a period of 10 years among almost 50,000 participants in the prospective

Health Professionals Follow-up Study. They found that men who drank the most fluids (12 or more cups per day) had a 51 percent lower incidence of developing bladder cancer than men who drank the least (less than 5 cups). An increase in total fluid intake may reduce contact time between carcinogens and urothelium by diluting urinary metabolites and increasing the frequency of voiding. This is in accordance with our finding that total fluid intake and frequency of urination are inversely associated with the bladder cancer risk, although we did not find statistically significant association for fluid intake. However, the study by MICHAUD et al had not been sensitive enough to determine whether water quality, especially chlorination, played a role in cancer risk [10]. In a case control study conducted in Germany a significantly decreased odds ratio of 0.34 (95% CI: 0.11–0.99) was found in women for a daily fluid intake of more than two liters [18].

Chlorination by-products in drinking water were first associated with bladder cancer risk by ecologic studies [17] and later by case-control studies [6]. In several investigations, detailed information was available on water quality and temporal aspects of exposure. These studies support the association between chlorination by-product levels in drinking water sources and bladder cancer risk. In one cohort study in USA, residents who consumed chlorinated surface water had higher incidence of bladder cancer than those who consumed nonchlorinated deep well water [27]. In the study conducted in ten areas of the United States, risk of bladder cancer increased with intake of beverages made with tap water [4]. This was restricted to subjects with at least 40 years of exposure to chlorinated surface water and was not observed among long-term consumers of nonchlorinated ground water. However establishing a person's exposure to chlorination byproducts is difficult. In studies that have examined persons with long-term exposure to chlorinated water (at least 40 years), the relative risk for bladder cancer, as compared with that among persons with no such exposure, has not exceeded 2.0. In a study in Massachusetts [28], residents of communities supplied with chlorinated drinking water experienced higher bladder cancer mortality than those exposed to water containing lower concentrations of chlorination by-products. Four case-control studies showed no association between chlorinated water and bladder cancer risk [2]. The majority of the study population of the present study, conducted in Serbia, spent 90% of their life using public water supplies, which have been treated with chlorine for disinfection. Our results suggest that high intake of water may decrease the risk of bladder cancer and are in agreement with the finding of some authors [14].

There are many data about coffee consumption and bladder cancer. On the basis of an analysis of case-control studies in European countries, only a very small proportion of cancers of the bladder among nonsmokers could be attributed to coffee drinking [21]. According to the majority of the authors coffee can be a risk factor only if its consumption exceeds five cups per day [2]. We found that coffee consumption was a risk factor for bladder cancer, but the mean number of consumed cups was almost twice less.

Most previous studies have failed to identify a relationship between drinking of beer and bladder cancer occurrence [8, 16, 24]. Some authors [20] reported slightly increased, statistically insignificant association for female beer drinkers. According to German authors [14, 18] elevated risk was observed for higher consumption of beer, and our findings are in agreement with these findings. The results about lack of association between consumption of spirits and bladder cancer occurrence are pretty consistent [3, 14, 16, 24]. Current study has shown statistically significant association between spirits consumption and bladder cancer appearance.

Of three prospective studies that have examined milk consumption, two studies have shown essentially no relationship with bladder cancer [15, 23], whereas the third one, conducted in Hawaii, reported a decreased risk, for consumption of milk more than five times per week compared with less than once [5]. Of four case-control studies that investigated milk consumption, one found statistically significant OR=0.6 for those consuming three or more cups per day [13]. Another study reported an OR of 1.5 for the highest consumption level of milk and dairy products combined [19]; the remaining two studies found no association with milk consumption [12, 20]. We found that milk consumption (whole milk) was risk factor for bladder cancer development. Consumption of skim milk and yogurt were indicated as protective variables. Present investigation showed consumption of mineral water as protective and consumption of sodas as a risk factor for bladder cancer appearance. There is a shortage on literature data for their influence on bladder cancer occurrence and at present we have no adequate explanation for it. Higher intakes of sweetened fruit juice was associated with a decreased risk of bladder cancer [15]. Fruit and vitamin C consumption has often been found to protect against bladder cancer [2]. Our finding that consumption of fruit juices was protective are in accordance with that mentioned above.

Recent epidemiological studies have suggested that tea may be protective against cancers of the urinary tract [1]. We did not find statistically significant association between tea consumption and bladder cancer risk.

Generally, it is not possible in epidemiological studies to determine whether the constituents in specific, commonly consumed beverages are responsible for associations observed for total fluid intake, or whether the most commonly consumed beverages are implicated only because of their impact on the volume of total fluid consumed.

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