Artificial sweetener consumption and urinary tract tumors in Cordoba, Argentina

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ABSTRACT

Objective. To determine the role of the habitual use of the most common artificial sweeteners (AS) in the development of urinary tract tumors (UTT) in Argentina.

Methods. Case-control study of 197 patients with histologically confirmed UTT of transitional varieties, and 397 controls with acute, non-neoplastic, and non-urinary tract diseases, admitted to the same hospitals in Córdoba (Argentina) between 1999 and 2006. All subjects were interviewed about their use of AS and their exposure to other known or suspected risk factors for UTT.

Results. Fifty-one UTT patients (26%) and 87 controls (22%) used AS. The risk of UTT was significantly increased in long-term (≥ 10 years) AS users compared with none-AS users. The OR (95% CI) for long-term consumers was 2.18 (1.22–3.89) and for short-term users was 1.10 (0.61–2.00) after adjustment for age, gender, BMI, social status. and years of tobacco use.

Conclusion. Regular use of AS for 10 years or more was positively associated with UTT.

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Introduction

Bladder cancer mortality is the 7th highest cause of death for males in Argentina (WHO, 2001), and the 10th highest in the Córdoba region of this country (Matos et al., 2003). There are many studies showing that diet has an influence on this disease (Hebert and Miller, 1994). That bladder carcinogenesis can be influenced by diet is not surprising since urinary tract surfaces are in close contact with many potentially mutagenic compounds contained in foods and their metabolites before being excreted through urine (Pelucchi et al., 2006).

An investigation carried out in another Argentinean city (La Plata) 20 years ago failed to find an association with saccharin use (Iscovich et al., 1987). However, a positive association was found more recently in a case-control study in the United States, where an examination of 1860 bladder cancer cases and 3934 population-based controls showed that heavy artificial sweetener use was associated with higher-grade, poorly differentiated tumors (Sturgeon et al., 1994).

New generations of AS products, mainly cyclamate and aspartame, were introduced more recently to the market. Due to their mixed formulations it has been difficult to examine the risk of bladder cancer for each individual substance (Weihrauch and Diehl, 2004), and thus far epidemiological studies have not found any evidence of carcinogenic risk for AS (Moller-Jensen et al., 1983; Wakai et al., 1993).

In Argentina, 14% of the population regularly use AS instead of sugar to sweeten drinks and foods, with saccharin and cyclamate being the most frequently consumed AS. A smaller percentage of Argentineans use aspartame and acesulfame-K (SAGPyA, 2000). Moreover, significant percentages of the Argentinean and Uruguayan populations have the habit of drinking 1000 to 2000 ml/daily, or even more, of a hot infusion made of "*Ilex paraguariensis*" leaves, called *mate* (Sewram et al., 2003; Bates et al., 2007). Some studies carried out in Uruguay have found that *mate* drinking is likely to increase the risk of bladder cancer (De Stefani et al., 1991, 2007). Since AS are used mostly for sweetening infusions, it can be inferred that some of the *mate* consumers use high amounts of AS.

Evidently the issue of the potential bladder cancer risk of AS has not been clearly resolved. We conducted a case-control study in Córdoba, Argentina to further address this issue.

Materials and methods

This case-control study was carried out between 1999 and 2006 in Córdoba, a city of 1,300,000 inhabitants in Argentina.

The cases were subjects with incident, histopathologically confirmed urinary tract tumors (UTT) of transitional-cell types from renal pelvises, ureters, and/or bladder who had been admitted to 10 public and private hospitals, including the largest public hospitals in Córdoba and nearby cities of the Greater Córdoba region. All patients were residents in the province of Córdoba and had signed their informed consent before participating in the study. Overall, 197 patients with UTT were interviewed. These represented almost 80% of all incident cases recorded in the patient histories of all experienced urologists of Córdoba ($n=250$), which were employed instead of the Official Tumor Register system because it is still in an early stage of development.

The controls were 397 subjects from the same catchment area as the cases. These were taken from the hospital admission registry at the same time as diagnoses of the cases were made. The controls had no previous history of cancer and were admitted for acute, non-

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Table 1
Distribution of urinary tract tumor (UTT) cases and controls according to demographic characteristics. Córdoba, Argentina 1999–2006

Demographic characteristic		Cases n = 197		Controls n = 397	
		n	%	n	%
Age (years)					
<50		20	10	59	15
50–55		25	13	56	14
56–65		60	30	121	31
66–70		34	17	61	15
71–75		29	15	57	14
>75		29	15	43	11
Gender					
Male		156	79	267	67
Female		41	21	130	33
BMI					
≤24.9		61	31	149	38
25–29.9		94	48	167	42
≥30		42	21	81	20
Tobacco smoking					
Non-smoker		33	17	149	38
Smoker		164	83	248	62
Years of tobacco use	1–10	20	13	70	29
	11–20	30	18	58	23
	21–30	39	24	49	20
	31–40	37	22	38	15
	≥41	38	23	33	13
Cigarettes *per* day	1–10	67	41	130	52
	11–20	59	36	77	31
	≥21	38	23	41	17
Social status					
Very low		39	20	78	20
Low		21	11	38	10
Medium		64	32	105	26
Medium–high		67	34	158	40
High		6	3	18	4
Artificial sweetener (AS) consumption					
No		146	74	310	78
Yes		51	26	87	22
AS type	SCC[a]	40	78	71	82
	AAK[b]	11	22	16	18
Years of AS consumption	1–9 (short-term consumers)	21	41	55	63
	≥10 (long-term consumers)	30	59	32	37
Mate use					
No		46	23	89	22
Yes		151	77	308	78

[a] Saccharine/cyclamate.
[b] Aspartame/acesulfame-K.

neoplasic and non-urinary tract diseases (51% for osteoarticular disorders; 19% for routine check-ups; 7% for emergencies such as infections, injuries, acute abdominal pain, intoxication and migraine; 3.5% for cardiovascular diseases; 3% for respiratory diseases; 3% for hernia; and the rest for other causes such as minor surgery, skin diseases, and varicose veins). Patients with digestive tract diseases or with long-term modifications of their diet were excluded from being controls. In order to avoid bias in the results, chronic diabetics who were high AS users were also excluded. The case:control ratio was approximately 1:2.

Nutritionists, who were centrally trained and routinely supervised, interviewed all the subjects. A food frequency questionnaire (FFQ), originally developed to study the risk of colorectal cancer (Muñoz et al., 1998; Navarro et al., 2003, 2004) in our population, was modified accordingly and then implemented. This FFQ was validated, and then used to estimate typical food intake (Navarro et al., 2001). For each food item, patients were asked to estimate the frequency of intake over the 5 years before diagnosis or hospitalization. The FFQ was supported by a validated photographic atlas (Navarro et al., 2000).

Other epidemiological information collected at the interview included date of birth, residential history, educational attainment, occupational history, smoking habits (years of tobacco use and cigarettes per day, personal medical history, and family history of cancer. Body mass index (BMI=weight/height^2) was derived from self-reported data. Due to the fact that these data could be either under- or overestimated, weight was checked using the patient charts.

Study subjects were also requested to recall their habitual use of AS in the five years leading up to the interview. First, they were asked if they had ever consumed AS; if the answer was affirmative, information was requested about the brand name of the AS consumed and the duration in years of consumption. Depending on the use indicated, they were then classified as non-AS consumers, AS short-term consumers (1 to 9 years) or AS long-term consumers (10 or more years). AS varieties were – according to the type offered for sale at the time that subjects were asked to recall – classified into two subgroups: saccharine/cyclamate (SCC) and aspartame/acesulfame-K (AAK).

The study was conducted according to all international ethical norms for research in human populations and was approved by the Committee of Ethics in Health Research of the province of Córdoba and by each individual Ethics Committee of the main hospitals.

Statistical analyses

Crude, stratified, and Mantel–Haenszel (MH) adjusted odds ratios (OR) and their 95% confidence intervals (CI) to assess the strength of the association between AS use (including *mate* consumption) and the risk of UTT were obtained using multiple logistic regression (Breslow and Day, 1980; Mc Cullagh and Nelder, 1989). The MH analyses were adjusted for gender, BMI using cut-off points established by the WHO (results were similar with BMI treated as continuous, hence are not shown), social status, and years of tobacco use.

Results

The demographic characteristics of the case-control study sample are summarized in Table 1. As expected, according to the incidence rates estimated by the IARC (International Agency for Research on

Table 2
Odds ratios (OR) of artificial sweetener (AS) consumption stratified by confounding variables. Córdoba, Argentina 1999–2006

	AS consumption				OR[a]	95% CI[a]	OR$_{MH}$[b]	95% CI[b]
	Never (0 years)		Ever (≥1 years)					
	Cases (n=146)	Controls (n=310)	Cases (n=51)	Controls (n=87)				
Age								
<55	35	87	10	28	1.07	0.47–2.45	0.77	0.52–1.15
55–65	50	102	18	34	0.89	0.46–1.73		
>65	61	121	23	25	0.55	0.29–1.04		
Gender								
Male	117	230	39	37	0.48	0.29–0.80	0.67	0.44–1.02
Female	29	80	12	50	1.41	0.66–3.03		
Tobacco use (years)								
0	21	115	12	35	0.53	0.24–1.18	0.65	0.41–0.98
1–10	13	46	7	21	0.83	0.29–2.38		
11–20	24	45	6	13	1.16	0.39–3.43		
21–30	29	42	10	7	0.48	0.16–1.42		
≥30	59	62	16	11	0.54	0.21–1.30		
Social Status								
Very low / Low	38	82	24	33	0.61	0.32–1.18	0.81	0.54–1.22
Médium	47	80	17	25	0.86	0.42–1.76		
Medium high/ High	61	148	10	29	1.12	0.51–2.46		
BMI								
≤24.9	52	120	10	30	1.23	0.56–2.72	0.79	0.53–1.18
25–29.9	68	134	26	32	0.62	0.34–1.12		
≥30	26	56	15	25	0.76	0.34–1.67		

[a] Crude OR with 95% confidence interval.
[b] Mantel–Haenszel OR with 95% confidence interval.

Table 3
Crude and adjusted odds ratios (OR) of urinary tract tumors (UTT) by years of artificial sweetener (AS) consumption. Córdoba, Argentina1999–2006

Years of AS consumption	Cases (n)	Controls (n)	OR[a]	95% CI[a]	OR[b]	95% CI[b]	OR[c]	95% CI[c]
0	146	310	1	–	1	–	1	–
1–9	21	55	0.85	0.49–1.46	0.98	0.55–1.73	1.10	0.61–2.00
≥10	30	32	2.00	1.17–3.42	2.00	1.15–3.48	2.18	1.22–3.89

[a] Crude OR with 95% confidence interval.
[b] OR adjusted for age, gender, BMI, and social status.
[c] OR adjusted for age, gender, BMI, and social status, and years of tobacco use.

Cancer) for Argentina in 2001, most cases were males. The majority were also smokers and more than 56 years old.

As shown in our previous studies, most cases and controls were overweight to some extent and the use of AS was more frequent in cases than in controls. The data on AS consumption refer exclusively to their use as an additive in infusions (tea, coffee, *mate*). There were no data concerning the consumption of AS from other sources, such as soft drinks or dietetic foods.

The stratified analyses showed a statistically significant association between UTT and years of AS consumption in years ($p<0.02$), UTT and years of tobacco use ($p<0.0001$), AS use and sex ($p<0.0001$), AS use and BMI ($p<0.01$) and AS use and social status ($p<0.0001$) (Table 2). However, no association between *mate* consumption alone and risk for UTT was observed ($p=.80$, data not shown otherwise).

In the Mantel–Haenszel analyses of AS consumption adjusted for age, gender, BMI, and social status, either with or without adjustment for years of tobacco use, there was no association with UTT risk for short-term AS consumers, but a positive association was found between long-term AS users and the risk of UTT (Table 3).

Discussion

Since the 1970's reports of the potential cancer risks of artificial sweeteners have been widely circulated in the mass media (Weihrauch and Diehl, 2004). The extensive distribution and frequent usage of AS complicate a systematic analysis of their potential risks (Sommer et al., 2004). In fact, to date, research has produced conflicting evidence with respect to the risk of bladder cancer linked to the consumption of AS. To further investigate this issue, we studied 197 cases and 397 controls in Córdoba, Argentina.

In this work, we focused on the use of AS only as sugar substitutes in infusions. This type of AS use was found to be positively associated with UTT risk, but only when consumed regularly for 10 years or more. On the other hand, no association was found for short-term consumers. Coincidently, Sturgeon et al. (1994) also observed a significantly increased risk in heavy AS consumers, with the risk of bladder cancer was not being affected by low AS use.

Nevertheless, some studies carried out in the 1980's and 1990's did not observe an association between AS and UTT (Moller-Jensen et al., 1983; Wakai et al., 1993), including an investigation carried out in another Argentinean city (La Plata) that did not find any link with saccharin use (Iscovich et al., 1987).

The risk of UTT in long-term AS consumers was slightly increased when linked to chronic tobacco use. This is in agreement with previous reports observed in a case-control study in Uruguay, which is to be expected as this population shares similar social habits with Argentineans (De Stefani et al., 1991).

Experimental studies show that sodium saccharin induces calcium phosphate precipitates in rat urine, which causes irritation, hyperplasia and, ultimately, tumors (Cohen et al., 1995; Zurlo and Squire, 1998). Even though it has been argued that this mechanism is related to the particular physiology of the male rat bladder (Cohen et al., 2000), our previous results showed that melamine plus calcium precipitates induce irritation and neoplastic lesions in rat and mice urothelium, respectively (Cremonezzi et al., 2001, 2004). Moreover, a recent experimental study found that female rats fed on a diet supplemented with aspartame developed transitional-cell carcinomas of the renal pelvis and ureter. The authors suggested that calcium in the urinary tract lyths might be the mechanism involved in the induction of these tumors (Soffritti et al., 2006). In addition, a recent study pointed out that infections and stones in the human urinary tract cause chronic irritation of the bladder epithelium, thus increasing bladder cancer risk (Pelucchi et al., 2006).

Conclusion

We agree with Soffritti et al. (2006) that differing results concerning the association of AS use with bladder cancer risk may be due to the difficulties of finding a control group of subjects that had not been previously exposed, even involuntary, to these widely diffused substances. However, experimental data such as those of the latter study are still a useful tool for assisting in the design of public health policies until less equivocal epidemiologic evidence is obtained.

The present case-control study results shed further light on this issue with the finding that regular AS consumption for 10 years or more increased UTT risk. However, further research on the specific uses of AS, particularly as additives in various food and drink products other than just infusions, is needed.

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