Non-alcoholic beverages and risk of bladder cancer in Uruguay

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Abstract

Background: Bladder cancer is the fourth most frequent malignancy among Uruguayan men. A previous study from Uruguay suggested a high risk of bladder cancer associated with maté drinking. We conducted an additional case-control study in order to further explore the role of non-alcoholic beverages in bladder carcinogenesis.

Methods: In the time period 1996–2000, 255 incident cases with transitional cell carcinoma of the bladder and 501 patients treated in the same hospitals and in the same time period were frequency matched on age, sex, and residence. Both cases and controls were face-to-face interviewed on occupation, tobacco smoking, alcohol drinking and intake of maté, coffee, tea, and soft drinks. Statistical analysis was carried out by unconditional multiple logistic regression.

Results: Ever maté drinking was positively associated with bladder cancer (odds ratio [OR] 2.2, 95% confidence interval [CI] 1.2–3.9) and the risk increased for increasing duration and amount of maté drinking. Both coffee and tea were strongly associated with bladder cancer risk (OR for coffee drinking 1.6, 95% CI 1.2–2.3; OR for tea drinking 2.3, 95% CI 1.5–3.4). These results were confirmed in a separate analysis of never-smokers.

Conclusion: Our results suggest that drinking of maté, coffee and tea may be risk factors for bladder carcinoma in Uruguay.

Background

Bladder cancer is the fourth most frequent malignancy among Uruguan men, with age-standardized incidence rate of 19.7 per 100,000 [1]. In international comparisons between registries of the Americas, incidence among Uruguyan men is second only to that among White men in the United States [1].

A previous study from Uruguay reported an increased risk of bladder cancer associated with maté drinking, a local herbal tea derived from the plant known as Ilex para-
guaraniensis [2]. This non-alcoholic beverage has been considered as a risk factor for esophageal cancer [7,8]. According to the International Agency for Research on Cancer maté drinking is a probable carcinogen to humans (Group 2A) possibly acting through thermal injury on esophageal mucosa [9]. In effect, maté is drunk usually very hot, but the effect of maté drinking on the bladder mucosa cannot be explained by temperature. It is possible that maté could contain some carcinogens, not yet discovered. On the other hand, since maté drinking is correlated with tobacco smoking, it is difficult to discard residual confounding by smoking.

Also coffee and tea drinking has been suspected as bladder carcinogens, but the current evidence of such effect is controversial [9]. For this reason we have decided to conduct a case-control study on the role of non-alcoholic beverages in the etiology of bladder cancer in the population of Uruguay characterized by high rates of bladder cancer.

Methods
Selection of cases
In the time period 1996–2000, 261 newly diagnosed and microscopically confirmed consecutive cases of patients afflicted by transitional cell carcinoma of the bladder were identified in the four major hospitals of Montevideo (Cancer Institute, Pasteur, Clinicas and Maciel). Six patients refused the interview, leaving a final total of 255 cases (response rate 97.7 %). Most patients were males (225 patients) and there were only 30 females. All cases were interviewed within one month of their diagnosis.

Selection of controls
In the same time period and in the same hospitals, seven hundred patients with diseases not related with tobacco smoking, alcohol drinking and without recent changes in their diet were considered eligible for this study. Thirty-one patients refused the interview, leaving a final total of 669 potential controls (response rate 95.6 %). Five hundred and one patients were included as controls in the present study. They were randomly selected from amongst those fulfilling the matching criteria (age [5-year groups], sex, residence [Montevideo, other counties]). It is important to emphasize that cases and controls do not overlap with those included in the previous Uruguayan study on bladder cancer and maté drinking [2]. On the other hand, there was some overlapping with a second study on bladder cancer conducted in Uruguay [3]. The controls presented the following diseases: abdominal herna (120 patients, 23.8 %), eye disorders (100, 20.0 %), diseases of the skin (58, 11.6 %), urinary stones (41, 8.2 %), acute appendicitis (38, 7.6 %), injuries (38, 7.6 %), varicose veins (32, 6.4 %), hydatid cyst (27, 5.4 %), prostate hypertrophy (25, 5.0 %) and blood disorders (22, 4.4 %).

Definition of high-risk occupations
The following occupations were considered high-risk jobs: dyestuff workers, dye users, rubber workers, leather workers, painters, truck drivers, metal workers, printers, textiles, butchers, construction workers and roofers, based on results of preliminary analyses of occupational risk factors of bladder cancer in this study population.

Statistical analysis
Relative risks, approximated by the odds ratios (OR’s) and corresponding 95 percent confidence intervals (95 % CI’s) were estimated by unconditional multiple logistic regression [11]. The basic model included the following terms: age (categorical, 6 strata), sex, residence (categorical), urban/rural status (categorical), education (categorical, 3 strata), family history of bladder cancer among first degree relatives (no/yes), body mass index (categorical), employment in high-risk occupations (no/yes) and tobacco smoking (smoking status, number of cigarettes smoked per day, years since quitting and age at start smoking), maté drinking (categorical), coffee drinking (categorical), tea drinking (categorical) and milk intake (categorical).
The analyses were repeated after stratification for smoking status. Tests for linear trend were performed after entering categorical variables as ordinal (continuous) in the same model. Departure from the multiplicative model was determined by assessing the likelihood ratio test statistic. An alpha level of 0.05 was used as the indicator of statistical significance. All p-values were derived from two-sided statistical tests. All the calculations were done with the STATA programme [12].

The study was approved by the ethics committee of the International Agency for Research on Cancer. Participants signed an informed consent form to participate in the study.

Results

The distribution of cases and controls by sociodemographic variables, potential confounders and tobacco smoking is shown in Table 1. As a result of the matched design, the distribution by age and sex were similar, while a higher proportion of cases than controls lived outside Montevideo. The proportion of rural cases was significantly higher compared with controls, and cases were more educated and earned higher incomes than controls. There was a significantly higher proportion of cases with family history of bladder cancer compared with controls (OR 5.0, 95 % CI 1.7–4.3). Both series of patients displayed similar BMI. Cases worked more frequently in high-risk occupations compared with controls (OR 1.4, 95 % CI 0.9–2.1). Finally, cases were more frequently smokers compared with controls (OR 1.9, 95 % CI 1.2–2.9).

Odds ratios of bladder cancer for maté drinking are shown in Table 2. Former drinkers displayed higher risks compared with current drinkers. It is important to note that only 13 cases and 17 controls were ex-drinkers. Ever (i.e., current or former) drinkers of maté experienced an OR of 2.2 (95 % CI 1.2–3.9). Amount of maté drunk per week was positively associated with bladder cancer risk (OR for heavy drinkers 3.7, 95 % CI 1.9–7.1, p-value for trend < 0.01). There was also a dose-response relationship between years of drinking maté and bladder cancer risk (OR for long-term drinkers 3.0, 95 % CI 1.5–6.0, p-value for trend < 0.01). Cumulative exposure to maté, measured in liter-years, was directly associated with a three-fold increase in risk and those exposed to very hot maté displayed an OR of 4.9 (95 % CI 2.2–11) (reference category: never drinkers).

Odds ratios of bladder carcinoma for consumption of coffee, tea and soft drinks are shown in Table 3. Coffee consumption was directly associated with bladder cancer risk. This applies to former and current drinkers of both pure coffee and coffee with milk. Although drinking of coffee with milk was apparently associated with a higher risk of bladder cancer than drinking of black coffee, the difference was not statistically significant. Also, tea drinking was directly associated with risk of bladder cancer. The increase in risk was similar for amount of pure tea and for tea with milk (OR 6.5, 95 % CI 2.0–21, p-value for trend = 0.002). Finally, drinking of soft drinks was not associated with risk of bladder cancer.

Coffee drinking was positively correlated with tea drinking (coefficient 0.09, p = 0.02), while maté drinking was negatively correlated with drinking of coffee (coefficient -0.07, p = 0.07) and tea (-0.11, p = 0.002).

Table 4 presents results on drinking of maté, coffee and tea separately for ever- and never-smokers. In the case of coffee drinking, the results were similar in the two groups, although the precision of risk estimates in never smokers was reduced by the relatively small number of subjects. In the case of drinking of maté and tea, an effect was suggested also in never smokers, although of lesser magnitude than among smokers. Overall these results suggest that the increased risk of bladder cancer for intake of non-alcoholic beverages do not appear to be completely explained by smoking.

Discussion

The most important finding of our study was the significant increase in risk of bladder cancer associated with maté consumption. Most previous studies on maté drinking and human cancer [7-9,13-15] were conducted in cancer sites on which maté ingestion may be in direct contact with the epithelium. This fact reinforces the hypothesis that maté drinking acts by thermal injury. A complementary mechanistic hypothesis is that maté could contain chemical carcinogens. An unpublished chemical analysis (R.D. Adams and D. Hoffmann, personal communication) failed to obtain evidences of the presence of N-Nitroso compounds. On the other hand, one study reported the presence of large amounts of benzo [a]pyrene in eight commercial samples of maté leaf bought in Germany; however, the beverage resulting from infusion of the leaves contained only 0.02–0.12 micrograms/liter [16]. Other chemical studies suggested that maté could have carcinogenic effects due to its contents in tannins [17,18]. Experimental studies in rats and mice showed that caffeic acid (a metabolite of chlorogenic acid which is abundant in maté leaves) has carcinogenic effects on the kidney [19]. Experimental studies in Brazil suggested that maté displayed mutagenic and clastogenic activities in cell cultures [20,21]. Finally, in an experimental study in animals, Roffo [22] was able to produce squamous cell carcinomas of the skin after painting this organ with "tar" from maté. Recently, Fagundes and colleagues (personal communication) studied the urine in maté

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drinkers and found evidences of high levels of PAH derived from tobacco and maté.

Since there exist the possibility that maté could contain chemicals with carcinogenic activity, it was suggested that epidemiologic studies on maté drinking and cancer sites not related with maté temperature in humans could be a useful model to test this possibility. Up to date five such studies were conducted. Three case-control studies conducted in Uruguay [2,23,24] displayed significant positive associations between maté drinking and lung, renal cell and bladder cancers. One additional case-control from Argentina study was characterized by a strong direct association between coffee consumption and bladder cancer, but no effect of maté drinking [25]. Finally, in a recent case-control study conducted in Córdoba, Argentina, maté was associated with bladder cancer risk [26]. No data were previously reported on effect of temperature of maté on bladder cancer risk.

Thus, it remains the strong possibility that maté drinking could be carcinogenic to cancer sites not related with direct contact with the beverage. In other words, our findings of a strong direct association between maté drinking and bladder cancer risk are partially supported by previous chemical, experimental and epidemiological studies in cancer of the bladder and of other organs.

Another possibility is related with residual confounding of maté drinking by tobacco smoking. In the present study, the analysis of maté drinking was adjusted for smoking status, cigarettes per day and years since quit.

### Table 1: Distribution of controls and cases by sociodemographic variables and selected risk factors

| Variable                        | Category       | Cases Number | %     | Controls Number | %     | OR   | 95% CI   |
|---------------------------------|----------------|--------------|-------|-----------------|-------|------|----------|
| Age (years)                     |                |              |       |                 |       |      |          |
|                                 | 30–39          | 2            | 0.8   | 4               | 0.8   | NA   |          |
|                                 | 40–49          | 14           | 5.5   | 28              | 5.6   |      |          |
|                                 | 50–59          | 37           | 14.5  | 74              | 14.8  |      |          |
|                                 | 60–69          | 91           | 35.7  | 182             | 36.3  |      |          |
|                                 | 70–79          | 86           | 33.7  | 175             | 34.9  |      |          |
|                                 | 80–89          | 25           | 9.8   | 38              | 7.6   |      |          |
| Sex                             | Males          | 225          | 88.2  | 441             | 88.0  | NA   |          |
|                                 | Females        | 30           | 11.8  | 60              | 12.0  |      |          |
| Residence                       | Montevideo     | 116          | 45.5  | 254             | 50.7  | NA   |          |
|                                 | Other counties | 139          | 54.5  | 247             | 49.3  |      |          |
| Urban/rural status              | Urban          | 192          | 75.3  | 416             | 83.0  | 1.00 |          |
|                                 | Rural          | 63           | 24.7  | 85              | 17.0  | 1.31 | 0.80–2.14 |
| Education (years)               | 0–2            | 57           | 22.3  | 140             | 27.9  | 1.00 |          |
|                                 | 3–5            | 106          | 41.6  | 175             | 34.9  | 1.42 | 0.93–2.17 |
|                                 | 6+             | 92           | 36.1  | 186             | 37.2  | 1.24 | 0.79–1.95 |
| Income (US dollars per month)   | <=142          | 93           | 36.5  | 225             | 44.9  | 1.00 |          |
|                                 | 143+           | 113          | 44.3  | 194             | 38.7  | 1.51 | 1.05–2.17 |
|                                 | Missing        | 49           | 19.2  | 82              | 16.4  | 1.50 | 0.94–2.40 |
| Family history of bladder cancer| No             | 244          | 95.7  | 495             | 98.8  | 1.00 |          |
|                                 | Yes            | 11           | 4.3   | 6               | 1.2   | 4.97 | 1.73–14.27 |
| Body Mass Index                 | <=22.8         | 59           | 23.1  | 127             | 25.3  | 1.00 |          |
|                                 | 22.9–25.1      | 65           | 25.5  | 126             | 25.1  | 1.13 | 0.72–1.79 |
|                                 | 25.2–27.1      | 53           | 20.8  | 120             | 23.9  | 0.92 | 0.57–1.49 |
|                                 | 27.2+          | 78           | 30.6  | 128             | 25.7  | 1.33 | 0.84–2.10 |
| Occupation                      | Low risk       | 175          | 68.6  | 385             | 76.9  | 1.00 |          |
|                                 | High risk      | 80           | 31.4  | 116             | 23.1  | 1.41 | 0.92–2.15 |
| Years of smoking                | Never smokers  | 48           | 18.8  | 136             | 27.1  | 1.0  | Reference |
|                                 | 1–29           | 32           | 12.5  | 60              | 12.0  | 1.55 | 0.85–2.82 |
|                                 | 30–39          | 31           | 12.2  | 70              | 14.0  | 1.34 | 0.73–2.46 |
|                                 | 40–49          | 54           | 21.2  | 109             | 21.8  | 1.61 | 0.94–2.74 |
|                                 | 50+            | 90           | 35.3  | 126             | 25.1  | 2.39 | 1.46–3.90 |
| N patients                      |                | 255          | 100.0 | 501             | 100.0 |      |          |

NA, not applicable (matching variable)

OR, odds ratio adjusted for age, sex, residence, urban/rural status, education, family history of bladder cancer among first-degree relatives, body mass index, occupation, smoking status, years since quit, number of cigarettes smoked per day, maté drinking, coffee drinking, tea drinking, soft drinks and milk intake.

CI, confidence interval.
Moreover, since there were a sizeable number of never smokers, this allowed to estimate the effect of maté drinking among this subset. Although results among never smokers were less precise than those obtained in the whole study population, the increased risk for heavy drinking of maté obtained in this subgroup detracts from the hypothesis of confounding by tobacco smoking.

Concerning the effect of other non-alcoholic beverages, both coffee and tea drinking were directly associated with bladder cancer risk, mainly when coffee is ingested with milk. The latter result was unexpected and can be due to chance or residual confounding. It might also indicate the presence of bladder carcinogens in black tea. Previous studies on tea intake and bladder cancer risk yielded controversial results. At least one prospective study [27] and two case-control studies [28,29] reported significant increases in risk of bladder cancer, whereas the remaining studies failed to show an association between tea consumption and bladder cancer risk [30]. Thus, there is no consistent evidence of a carcinogenic effect of tea on bladder mucosa. The possibility of residual confounding from smoking is very difficult to exclude since the OR's for tea drinking among never smokers was not clearly elevated, although the number of tea drinkers was rather small. Chance remains an additional possible explanation of these findings.

We did not ask about intake of water. However, this would create a bias only if drinking of water were associated with bladder cancer risk and is correlated to drinking of the beverages under study. Indeed, low overall fluid intake (represented mainly by water) has been suggested as a possible risk factor for bladder cancer [31], but this would act as a positive confounder in our study only if high intake of maté, coffee or tea would associated with low overall fluid intake. The lack of information on source of drinking water and potential exposure to drinking water contaminants such as chlorination by-products and nitrates is an additional limitation of our study.

The present study, as other hospital-based case-control studies, is subjected to several limitations. Selection bias is almost impossible to rule out. We tried to minimize this bias by frequency matching controls and cases on age, sex and residence. Although matching for the latter variable was not complete, we adjusted for it in all analyses. Furthermore, we have adjusted the risk estimates for possible determinants of selection of cases and controls, such as urban/rural status and education.

### Table 2: Odds ratios of bladder cancer for maté drinking

| Category                  | Cases/Controls | OR   | 95 % CI |
|---------------------------|----------------|------|---------|
| Maté drinking             |                |      |         |
| Never drinkers            | 18/71          | 1.0  |         |
| Former drinkers           | 13/17          | 3.1  | 1.2–8.1 |
| Current drinkers          | 224/413        | 2.2  | 1.2–3.9 |
| Ever drinkers             | 237/430        | 2.2  | 1.2–3.9 |
| Amount of drinking        |                |      |         |
| (liters/day)              |                |      |         |
| Never drinkers            | 18/71          | 1.0  |         |
| 0.1–0.9                   | 31/89          | 1.3  | 0.6–2.7 |
| 1.0–1.9                   | 125/248        | 2.1  | 1.2–3.9 |
| 2.0+                      | 81/93          | 3.7  | 1.9–7.1 |
| p-value for trend         |                | <0.01|         |
| Duration of drinking      |                |      |         |
| (years)                   |                |      |         |
| Never drinkers            | 18/71          | 1.0  |         |
| 1–49                      | 84/180         | 1.7  | 0.9–3.3 |
| 50–59                     | 85/155         | 2.4  | 1.3–4.5 |
| 60+                       | 68/95          | 3.0  | 1.5–6.0 |
| p-value for trend         |                | <0.01|         |
| Cumulative consumption    |                |      |         |
| (liters/day × years)      |                |      |         |
| Never drinkers            | 18/71          | 1.0  |         |
| 1–47                      | 66/156         | 1.7  | 0.9–3.3 |
| 48–69                     | 77/149         | 2.1  | 1.1–3.9 |
| 70+                       | 94/127         | 3.2  | 1.7–6.0 |
| p-value for trend         |                | <0.01|         |
| Temperature               |                |      |         |
| Never drinkers            | 18/71          | 1.0  |         |
| Warm                      | 11/20          | 2.1  | 0.8–5.4 |
| Hot                       | 191/383        | 2.1  | 1.2–3.7 |
| Very hot                  | 35/27          | 4.9  | 2.2–11  |

OR, odds ratio adjusted for age, sex, residence, urban/rural status, education, family history of bladder cancer among first-degree relatives, body mass index, occupation, smoking status, years since quitting, number of cigarettes smoked per day, coffee drinking, tea drinking, soft drink intake, and milk intake. CI, confidence interval.
### Table 3: Odds ratios of bladder cancer for coffee, tea and soft drinks consumption

#### Coffee

| Category                        | Cases/Controls | OR  | 95 % CI       |
|---------------------------------|----------------|-----|---------------|
| **Drinking status**             |                |     |               |
| Never drinkers                  | 135/332        | 1.0 |               |
| Former drinkers                 | 9/13           | 1.4 | 0.6–3.6       |
| Current drinkers                | 111/156        | 1.7 | 1.2–2.3       |
| Ever drinkers                   | 120/169        | 1.6 | 1.2–2.3       |
| **Amount (pure coffee)**        |                |     |               |
| Never drinkers                  | 135/332        | 1.0 |               |
| 1–6 cups/week                   | 22/28          | 1.6 | 0.8–3.1       |
| 7+ cups/week                    | 15/21          | 2.0 | 0.9–4.4       |
| **Amount (coffee with milk)**   |                |     |               |
| Never drinkers                  | 135/332        | 1.0 |               |
| 1–6 cups/week                   | 70/112         | 1.5 | 1.0–2.2       |
| 7+ cups/week                    | 24/24          | 1.9 | 1.0–3.7       |
| **Amount (total coffee)**       |                |     |               |
| Never drinkers                  | 135/332        | 1.0 |               |
| 1–6 cups/week                   | 84/133         | 1.5 | 1.1–2.2       |
| 7+ cups/week                    | 36/36          | 2.1 | 1.2–3.6       |

* p-value for trend

#### Tea

| Category                        | Cases/Controls | OR  | 95 % CI       |
|---------------------------------|----------------|-----|---------------|
| **Drinking status**             |                |     |               |
| Never drinkers                  | 180/419        | 1.0 |               |
| Former drinkers                 | 1/2            | 1.5 | 0.1–19        |
| Current drinkers                | 74/80          | 2.3 | 1.6–3.4       |
| Ever drinkers                   | 75/82          | 2.3 | 1.5–3.4       |
| **Amount (pure tea)**           |                |     |               |
| Never drinkers                  | 180/419        | 1.0 |               |
| 1–6 cups/week                   | 21/111         | 4.4 | 2.0–10        |
| 7+ cups/week                    | 20/32          | 1.5 | 0.8–2.8       |
| **Amount (tea with milk)**      |                |     |               |
| Never drinkers                  | 180/419        | 1.0 |               |
| 1–6 cups/week                   | 28/40          | 1.7 | 1.0–3.0       |
| 7+ cups/week                    | 10/5           | 6.5 | 2.0–21        |
| **Amount (total tea)**          |                |     |               |
| Never drinkers                  | 180/419        | 1.0 |               |
| 1–6 cups/week                   | 59/72          | 2.1 | 1.4–3.1       |
| 7+ cups/week                    | 16/10          | 4.1 | 1.7–9.9       |

* p-value for trend

#### Soft drinks

| Category                        | Cases/Controls | OR  | 95 % CI       |
|---------------------------------|----------------|-----|---------------|
| **Amount**                      |                |     |               |
| Never drinkers                  | 138/289        | 1.0 |               |
| 1–104 bottles/years             | 65/121         | 1.1 | 0.7–1.6       |
| 105+ bottles/years              | 52/91          | 1.1 | 0.7–1.7       |
| **p-value for trend**           |                | 0.62|               |

OR, odds ratio adjusted for age, sex, residence, urban/rural status, education, family history of bladder cancer among first-degree relatives, body mass index, occupation, smoking status, years since quitting, number of cigarettes smoked per day, *maté* drinking, soft drink intake, milk intake, and, when appropriate, coffee drinking and tea drinking.

CI, confidence interval.
Misclassification bias is also difficult to exclude. It is important to note that the role of nonalcoholic beverages in bladder cancer risk is unknown, both by the general population, the hospital population and the interviewers. Thus, it is rather unlikely that differential or nondifferential exposure to 
 maté drinking has occurred in our study. Furthermore, although current intake of non-alcoholic beverages among controls might have been modified by their disease, we consider unlikely that the use of hospital controls has created a bias in the prevalence of lifetime exposure. A further limitation is the relatively small sample size of the study, which reduced the power of detecting interactions between risk factors (e.g., differences in 
 maté-related OR according to smoking status) and differences according to subtle differences in exposure (e.g., whether the effect of coffee with milk is really different from that of black coffee, as suggested by our results). On the other hand our study has strengths. Perhaps the more important strength is related with the high response rate in both series of patients (cases and controls). Another strength is the absence of proxy interviews. Finally, the sizeable number of never smokers, which allowed to estimate OR’s of 
 maté drinking among these subset of patients, is a strength of the study.

### Table 4: Odds ratios of bladder cancer for drinking of 
maté, coffee, tea, by smoking status

| Category | Never smokers | Ever smokers |
|----------|---------------|--------------|
| Maté drinking (liters/day × years) | | |
| Category | Cases/Controls | OR | 95% CI | Cases/Controls | OR | 95% CI |
| Never drinkers | 10/30 | 1.0 | | 8/41 | 1.0 | |
| 1–47 | 12/48 | 0.95 | 0.32–2.86 | 54/108 | 2.51 | 1.06–5.95 |
| 48–69 | 16/38 | 1.35 | 0.46–3.95 | 61/109 | 2.97 | 1.25–7.03 |
| 70+ | 10/20 | 2.31 | 0.65–8.23 | 84/107 | 4.30 | 1.82–10.1 |
| p-value for trend | 0.2 | | <0.01 | |

| Category | Cases/Controls | OR | 95% CI | Cases/Controls | OR | 95% CI |
|----------|---------------|----|-------|---------------|----|-------|
| Coffee drinking (total coffee, cups/week) | | | |
| Never drinkers | 26/91 | 1.0 | | 109/241 | 1.0 | |
| 1–6 | 17/36 | 2.22 | 0.97–5.12 | 67/97 | 1.33 | 0.88–2.00 |
| 7+ | 5/9 | 2.02 | 0.54–7.54 | 31/27 | 2.04 | 1.12–3.72 |
| p-value for trend | 0.08 | | 0.01 | |

| Category | Cases/Controls | OR | 95% CI | Cases/Controls | OR | 95% CI |
|----------|---------------|----|-------|---------------|----|-------|
| Tea drinking (total tea, cups/week) | | | |
| Never drinkers | 34/111 | 1.0 | | 146/308 | 1.0 | |
| 1–6 | 11/20 | 2.22 | 0.84–5.83 | 48/52 | 1.91 | 1.20–3.04 |
| 7+ | 3/5 | 1.52 | 0.27–8.59 | 13/5 | 5.90 | 1.97–17.6 |
| p-value for trend | 0.2 | | <0.01 | |

OR, odds ratio adjusted for age, sex, residence, urban/rural status, education, family history of bladder cancer among first-degree relatives, body mass index, occupation, soft drink intake, and milk intake, and, when appropriate, 
 maté drinking, coffee drinking, and tea drinking. CI, confidence interval.

Conclusion
The present study replicates previous findings from Uruguay suggesting a role of 
 maté in bladder carcinogenesis. Also, the effect of 
 maté drinking among never smokers suggest that this beverage is an independent factor. Future studies should confirm or reject the hypothesis of a role of 
 maté in bladder carcinoma. If these findings are confirmed, 
 maté drinking is likely to contribute to the high risk of bladder cancer in Uruguay and other South American countries in which the habit is widespread.

Competing interests
The author(s) declare that they have no competing interests.

Authors’ contributions
EDS, PB, PC and PBr designed the study; EDS, HDP, ALR, GA and MM collected the data; EDS, PB and GF analyzed the data; EDS and PB drafted the manuscript. All authors reviewed and approved the manuscript.

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