Maté Consumption and the Risk of Squamous Cell Esophageal Cancer in Uruguay[1]

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Abstract

A retrospective hospital-based case-control study was carried out at the Oncology Institute of Montevideo, Uruguay, to investigate the role of maté consumption in esophageal cancer risk. The study included 344 cases with squamous cell carcinoma of the esophagus and 469 controls recruited between January 1988 and August 2000. Maté consumption was significantly associated with an increased risk of developing esophageal cancer and showed a clear dose response, with a relative risk of 2.84 [95% confidence interval (CI), 1.41–5.73] for those drinking more than 1 liter/day of maté as compared with nondrinkers. Subjects who self-reported drinking maté at a very hot temperature had an almost 2-fold increase in risk [odds ratio (OR), 1.87; 95% CI, 1.17–3.00] compared with those drinking warm to hot maté, after adjusting for cumulative consumption of maté. Maté amount and temperature were observed to have independent effects and, although no departure from multiplicativity was observed between the two covariates, those drinking more than 1 liter/day of maté at a very hot temperature had a 3-fold increase in risk (OR, 2.95; 95% CI, 1.30–6.74) compared with those drinking less than 0.5 liter/day of maté at a warm to hot temperature. Subjects with high cumulative exposure to maté in the presence of low alcohol and tobacco exposures presented a lower-risk estimate (OR, 1.52; 95% CI, 0.88–2.62), whereas those with high cumulative exposures to maté, alcohol, and tobacco presented a 7-fold increase in esophageal cancer risk (OR, 7.10; 95% CI, 3.75–13.46). The population-attributable fraction as a result of maté consumption was calculated to be 53%, of which the sole effect of amount and temperature was 14.8 and 12.6% respectively, and 14.9% was attributable to high maté consumption at high temperature.

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Introduction

Esophageal cancer is a malignancy that exhibits a wide diversity in geographical incidence and mortality worldwide (1). Areas with high incidence rates include parts of South America, southeastern Africa, and the so-called esophageal cancer belt in Asia, which stretches from the Caspian provinces of Iran through the central Asian republics to northern China (2). There is a geographical cluster of high-incidence areas in South America, which includes northeastern Argentina, southern Brazil, Paraguay, and Uruguay (1).

Data from the Cancer Registry at the Oncology Institute of Montevideo, Uruguay, have revealed age-standardized incidence rates of esophageal cancer of 11.9 and 3.4 per 100,000 for men and women, respectively (3). However, in the northeastern region bordering with Brazil, the age-standardized incidence rates are reported to be 55.8 and 14.7 per 100,000 for men and women, respectively (4). The most important histological type in this region is squamous cell carcinoma (5). Results from studies conducted in Uruguay and Brazil have identified alcohol drinking and tobacco smoking as important risk factors for esophageal cancer (6, 7). However, risk is further aggravated by diets deficient in fruits and vegetables (8, 9), by high consumption of red meat (4), and by other environmental and lifestyle exposures (10, 11). In addition, factors producing chronic injury to the esophagus, such as rough foods and hot beverages, can contribute to the burden of esophageal cancer by increasing susceptibility to carcinogens (7).

The drinking of maté, a tea-like infusion of the herb *Ilex paraguariensis* (Aquifoliaceae) which is cultivated on a commercial scale, is particularly prevalent in southern Brazil and in Uruguay. A striking ecological correlation was observed between the distribution of maté drinking and the high rates of esophageal cancer, leading to the hypothesis that maté drinking may be an etiological factor for esophageal cancer (12). Studies in Brazil (6), Uruguay (7, 13) and Argentina (14), however, have yielded inconsistent results. In a pooled analysis of data from five studies conducted in Argentina, Brazil, Paraguay, and Uruguay (15, 16), the main risk factors for esophageal cancer were tobacco and alcohol consumption. However, after adjustment for the strong effects of these exposures, heavy maté drinking (>1 liter/day) and self-reported very hot maté drinking were significant risk factors in men and women.

To elucidate the relationship between maté drinking and esophageal cancer risk, a retrospective hospital-based case-control study was undertaken in Uruguay to investigate the role of maté consumption, and in particular, the effect of quantity and temperature, in the risk of developing esophageal cancer.

Material and Methods

Selection of Cases. At the Oncology Institute of Montevideo, all patients who were newly diagnosed with histopathologically confirmed squamous cell carcinoma of the esophagus between January 1988 and August 2000, and who were ages 35–85

years, were considered eligible for inclusion in our study. Cases were ascertained from the medical records of the Oncology Institute Cancer Registry. Patients were required to be of sufficiently good physical and mental health to be able to give reliable answers to the routine questionnaire. Recruitment into the study further required that patients had lived in Uruguay for at least 10 years and had received a diagnosis of squamous cell esophageal carcinoma within the previous 4 months. A total of 355 patients were identified, with the largest proportion (32%) originating from Montevideo, and the remaining cases were from 20 other counties. The response rate of cases was 96.9%, resulting in 344 patients (259 men and 85 women) being included in the study.

Selection of Controls. In the same Institute and during the same time period, 505 patients, with conditions unrelated to tobacco smoking and alcohol drinking, without recent changes in diet, and ages also between 35 and 85 years, were recruited as potential controls. At least one control was selected and frequency matched to each male case, and for each female case, at least two controls were selected. The main diagnostic categories of the controls are listed in Table 1; ~30% of them had an undefined or unknown disease. The response rate of controls was 92.8%, resulting in the inclusion of 469 controls (294 men and 175 women).

Interviews and Data Collection. All of the patients admitted to the Oncology Institute were routinely interviewed, before the work-up diagnostic evaluation, by two trained social workers who were unaware of the hypothesis being tested. The interviewers used a routine questionnaire designed to elicit information on: (*a*) demographic and socioeconomic characteristics (residence, income, education, family size, and occupation); (*b*) family history of cancer in first-degree relatives; (*c*) self-reported height and weight 5 years before the interview; (*d*) history of maté drinking (amount consumed, age started, age quit, duration of consumption, maté temperature during consumption); (*e*) history of alcohol drinking (type of alcoholic beverage and amount of each beverage consumed, duration of consumption, total alcohol consumption); and (*f*) history of tobacco smoking (age started, age quit, smoking duration, number of cigarettes per day, type of tobacco, type of cigarette). The interviewers also used a food-frequency questionnaire that assessed the dietary habits of selected food items 5 years before the interview. Total alcohol consumption, in milliliters of ethanol per day, was calculated as the sum of the different alcoholic beverage types, *i.e.*, beer, wine, and hard liquor. The questionnaire and the interviewers did not change throughout the study.

Statistical Analysis. The association between the different covariates and esophageal cancer was studied using unconditional multiple logistic regression models (17). ORs,[3] as an approximation of relative risk, and their 95% CIs were obtained using the STATA statistical software package (STATA Corp., College Station, Texas). All logistic regression models included age (categorical), sex, urban/rural status, and years of education (categorical). No adjustment for ethnicity was performed because, essentially, the whole Uruguayan population is Caucasian. Duration of maté consumption was calculated up to 1 year before the interview, and time since quitting maté drinking was calculated for all of those who quit drinking at least 2 years before the interview. Those subjects who quit within 2 years of the interview were considered as current drinkers in the analysis. In addition, lifetime consumption of maté and of alcohol (liter-years) and lifetime habit of smoking (pack-years) were calculated. Cut points for categories of food consumption were based on the distribution of the controls. Regression models for maté consumption were adjusted for tobacco smoking and alcohol drinking. For polychotomous exposure variables, tests for linear trend were performed, using the midpoint of each category of the variable in the model as a continuous variable so as to obtain the *P* for linear trend. Effect modification between exposure variables was assessed by including, in the fully adjusted model, the main terms for each variable and the corresponding interaction term. Tests for effect modification were performed between maté consumption and temperature, and the interaction between cumulative exposures to maté, alcohol, and tobacco was assessed. Departure from the multiplicative model was determined by assessing the likelihood ratio test statistic. An α of 0.05 was used as the indicator of statistical significance and, accordingly, 95% CIs were reported. All *P*s were derived from two-sided statistical tests.

Table 1 Diagnostic categories among control patients

ICD-9[a]	Diagnosis	*n*	%
210–229	Benign neoplasms	56	11.9
240–279	Endocrine, metabolic, and immunity disorders	7	1.5
280–289	Diseases of the blood and blood-forming organs	10	2.1
345	Epilepsy	1	0.2
363–374	Disorders of the eye and adnexa	4	0.9
382–388	Diseases of the ear and mastoid process	2	0.4
454	Varicose veins of lower extremities	1	0.2
486	Pneumonia (organism unspecified)	3	0.6
523–529	Diseases of oral cavity, salivary glands, and jaws	26	5.6
550–551	Hernia of abdominal cavity	3	0.6
555–558	Noninfectious enteritis and colitis	2	0.4
562–569	Other diseases of intestines and peritoneum	2	0.4
592–599	Other diseases of the urinary system	9	1.9
600–608	Diseases of male genital organs	53	11.3
610–611	Disorders of breast	36	7.7
614–616	Inflammatory disease of female pelvic organs	3	0.6
617–627	Other disorders of female genital tract	8	1.7
682–709	Diseases of the skin and subcutaneous tissue	44	9.4
713–719	Arthropathies and related disorders	6	1.3
721–724	Dorsopathies	6	1.3
726–729	Rheumatism (excluding the back)	2	0.4
730–739	Osteopathies, chondropathies, and acquired musculoskeletal deformities	10	2.1
752–759	Congenital anomalies	2	0.4
777	Perinatal disorders of digestive system	18	3.8
782–789	Symptoms of ill-defined conditions	7	1.5
799	Other ill-defined and unknown causes of morbidity and mortality	140	29.9
802–872	Injury	4	0.9
927–959	Late effects of injuries, poisonings, toxic effects, and other external causes	4	0.9

[a] ICD, International Classification of Diseases.

Results

Data from 344 cases and 469 controls were analyzed in our study. The control:case ratio was 1.1 for men and 2.1 for women. The prevalence of maté drinking, alcohol drinking, and tobacco smoking among the cases was 96, 65, and 79%, respectively, and among the controls, it was 86, 42, and 61%, respectively. Categorical data, which included the study characteristics and the distribution of cases and controls according to sociodemographic and selected exposure variables, were summarized using frequency tables (Table 2). Cases smoked tobacco and consumed alcohol in a greater proportion and were more likely to come from rural areas with less education than were the control group.

[3] The abbreviations used are: OR, odds ratio; CI, confidence interval.

Table 2 Study characteristics and distribution of cases and control according to sociodemographic and selected exposure variables

Variable categories	Cases (344)	Controls (469)	χ^2 *P*
	n (%)	*n* (%)	
Age (yr)			
≤40	2 (0.6)	18 (3.8)	
41–55	46 (13.4)	101 (21.6)	
56–70	165 (48.0)	197 (42.0)	
≥70	131 (38.1)	153 (32.6)	
Sex			
Males	259 (75.3)	294 (62.7)	
Females	85 (24.7)	175 (37.3)	
Residence			
Urban, Montevideo	46 (13.4)	149 (31.9)	
Urban, other cities	188 (54.7)	234 (50.0)	
Rural	110 (32.0)	85 (18.2)	<0.0001
Data unknown		1	
Years of study			
None	42 (12.3)	38 (8.1)	
1–4	208 (60.8)	203 (43.3)	
5–8	84 (24.6)	167 (35.6)	
≥9	8 (2.3)	61 (13.0)	<0.0001
Data unknown	2		
Smoking status			
Nonsmoker	73 (21.2)	181 (38.6)	
Exsmoker	83 (24.1)	126 (26.9)	
Current smoker	188 (54.7)	162 (34.5)	<0.0001
Type of tobacco			
Nonsmokers	73 (21.3)	181 (38.6)	
Blond	92 (26.8)	190 (40.5)	
Black	151 (44.0)	73 (15.6)	
Mixed	27 (7.9)	25 (5.3)	<0.0001
Data unknown	1		
Total alcohol (ml/day)			
Nondrinker	120 (34.9)	270 (57.6)	
1–60	58 (16.9)	93 (19.8)	
61–180	82 (23.8)	66 (14.1)	
≥181	84 (24.4)	40 (8.5)	<0.0001
All fruits and vegetables (servings/year)			
<105	106 (30.8)	105 (22.4)	
105–416	165 (48.0)	228 (48.7)	
≥417	73 (21.2)	135 (28.9)	0.007
Data unknown		1	

Table 3 shows the estimated effects of maté consumption on esophageal cancer risk. All of the aspects of maté drinking have been found to be significantly related to risk. Ever drinkers of maté were observed to have a 2-fold increase in risk compared with nondrinkers (OR, 2.26; 95% CI, 1.19–4.27). The cumulative (lifetime) consumption of maté also presented an increased risk with increasing exposure. There was a significant trend among maté drinkers ($P = 0.009$), particularly among those with a lifetime consumption >8000 liter-years. If one accounts for change in the reference category, the relative risk estimate did not change after further adjustment for maté temperature. An effect of the amount of maté consumed was evident, even after further adjustment for maté temperature and duration of maté consumption. Compared with nondrinkers, subjects who self-reported drinking maté at warm to hot temperatures had a 2-fold increased risk, and consumers of very hot maté had an almost 4-fold increased risk. After further adjustment for lifetime consumption, consumers of very hot maté presented an almost 2-fold increase in risk (OR, 1.87; 95% CI, 1.17–3.00) as compared with consumers of maté at lower temperature. Duration of maté consumption was calculated up to 1 year before the interview, and an increase in the risk estimate was observed with increasing years of maté consumption ($P = 0.005$). The trend remained significant ($P = 0.04$) even after additional adjustments for maté amount and temperature. A decrease in risk was observed with years since quitting, although this analysis was hampered by the small number of quitters.

On stratification of the data by gender, women ever having consumed maté presented a 1.5 times greater risk (OR, 2.83; 95% CI, 0.79–10.13) compared with men (OR, 1.97; 95% CI, 0.93–4.16). The risk estimates also increased in both sexes with increasing cumulative exposure, with men in the highest exposure category (>24,000 liter-years) presenting a 2-fold increased risk (OR, 2.43; 95% CI, 1.07–5.50), whereas women presented a 5-fold increase in risk (OR, 4.96; 95% CI, 1.22–20.18). Compared with nondrinkers, men self-reporting drinking maté at a very hot temperature had a 3-fold increased risk (OR, 3.13; 95% CI, 1.29–7.59), whereas women presented a 6-fold increase in risk (OR, 6.52; 95% CI, 1.49–28.46). These results suggest that the association between maté exposure and esophageal cancer is stronger in women than in men.

Maté amount and temperature were found to have independent effects on risk, even after adjusting for each other. Hence, the interaction between these two variables was subsequently explored by fitting appropriate logistic regression models with interaction terms for these variables, so as to estimate the effect of the amount in each stratum of temperature and the effect of temperature in each stratum of amount (Table 4). The interaction between the two variables was not statistically significant ($P = 0.7$), indicating no departure from the multiplicative model; however, the results suggested a competitive effect of maté amount and temperature, because the effect of amount is apparent only for those drinking at a mild temperature, while the effect of temperature remained consistent for both light and heavy drinkers.

The combined effect of lifetime exposure to maté, alcohol, and tobacco was assessed by fitting a multivariate model, adjusted for age, sex, urban/rural status, and years of education, which included the main-effect terms at each level characterized by "high" or "low" exposure, as well as the interaction terms between the different exposure variables (Table 5). The interaction terms were not statistically significant (overall *P*, 0.96) and are not presented in the Table. The low exposure category for the three variables was used as the reference category. The OR for high consumption of maté with low exposures to alcohol and tobacco was 1.68 (95% CI, 0.88–2.62), that for high tobacco consumption with low exposures to maté and alcohol was 2.36 (95% CI, 1.23–4.53), and that for high alcohol consumption in the presence of low exposures to maté and tobacco was 2.54 (95% CI, 0.93–6.95). The OR for high cumulative exposures of all three agents was 7.10 (95% CI, 3.75–13.46).

Discussion

In line with previous epidemiological studies in Uruguay (7, 18), our study once again shows that maté consumption is associated with an elevated risk of esophageal cancer. An almost 3-fold increase in risk was observed among those drinking more than 1 liter/day of maté, after adjustment for the effects of age, sex, urban/rural status, education, tobacco smoking, and alcohol drinking. A previous study conducted by Vassallo *et al.* (18) showed that heavy maté consumption (≥1.0 liter/day) in men was associated with a 5-fold increase in esophageal cancer risk (OR, 4.8; 95% CI, 1.9–12.1) after adjusting for age, tobacco, and alcohol. Women who were exposed to this amount of maté presented a thirty five-fold increased risk (OR, 34.6; 95% CI, 4.9–246.5) after adjusting for age. Subsequently, De Stefani *et al.* (7) found that the relative risk of those drinking >2.5 liters of maté per day was 12.2

Table 3 OR of esophageal cancer for consumption of maté

Variables	Cases		Controls		OR_1[a]	(95% CI)	OR_2[b]	(95% CI)
	n	(%)	*n*	(%)				
Maté drinking								
Never	15	(4.4)	64	(13.7)	1.00[c]			
Ever	327	(95.6)	405	(86.3)	2.26	(1.19–4.27)		
Lifetime consumption (liter-years)								
Nondrinkers	15	(4.4)	64	(13.7)	1.00[c]			
1–8000	31	(9.1)	89	(19.0)	1.43	(0.68–3.01)	1.00[c]	
8001–16000	86	(25.2)	127	(27.1)	2.21	(1.12–4.35)	1.64	(0.95–2.81)
16001–24000	93	(27.3)	104	(22.2)	2.43	(1.22–4.83)	1.70	(0.98–2.95)
≥24001	116	(34.0)	84	(18.0)	3.07	(1.53–6.16)	2.16	(1.23–3.79)
P for trend (drinkers only)						0.009		0.2
Amount consumed (liter/day)								
Nondrinkers	15	(4.4)	64	(13.6)	1.00[c]			
0.01–0.50	73	(21.4)	149	(31.8)	1.69	(0.85–3.35)	1.00[c]	
0.51–1.00	152	(44.4)	172	(36.7)	2.47	(1.28–4.77)	1.49	(1.00–2.23)
1.01	102	(29.8)	84	(17.9)	2.84	(1.41–5.73)	1.62	(1.01–2.62)
P for trend (drinkers only)						0.02		0.3
Temperature								
Nondrinkers	15	(4.8)	64	(14.1)	1.00[c]			
Warm/hot	241	(77.8)	347	(76.4)	2.00	(1.05–3.81)	1.00[c]	
Very hot	54	(17.4)	43	(9.5)	3.98	(1.98–8.44)	1.87	(1.17–3.00)
P for trend (drinkers only)						0.004		
Duration of consumption (yr)								
Nondrinkers	15	(4.4)	67	(14.3)	1.00[c]			
1–35	33	(9.6)	92	(19.7)	1.31	(0.61–2.81)	1.00[c]	
36–49	98	(28.6)	117	(25.0)	2.29	(1.16–4.52)	1.62	(0.91–2.88)
50–58	92	(26.9)	98	(20.9)	2.58	(1.27–5.24)	1.90	(0.96–3.73)
≥59	104	(30.4)	94	(20.1)	4.31	(1.99–9.34)	3.06	(1.35–6.94)
P for trend (drinkers only)						0.005		0.04
Time since quitting (yr)								
Nondrinkers	15	(4.8)	64	(14.1)	1.00[c]			
Current drinkers[d]	280	(89.7)	359	(78.9)	2.31	(1.22–4.37)		
3–10	11	(3.5)	14	(3.1)	1.84	(0.63–5.36)		
≥11+	6	(1.9)	18	(3.9)	1.13	(0.35–3.62)		
P for trend (quitters only)						0.1		

[a] OR_1 adjusted for age, sex, urban/rural status, years of education, number of cigarettes smoked per day, smoking duration, total alcohol per day, and duration of alcohol consumption.
[b] OR_2, analysis restricted to ever maté drinkers, lifetime consumption further adjusted for temperature; amount consumed, maté temperature, and duration of maté consumption further adjusted for each other.
[c] Reference category.
[d] Includes quitters of up to 2 years.

Table 4 OR of esophageal cancer for the joint effects of amount and temperature of maté drinking[a]

Maté drinking temperature	Maté drinking amount (liter/day)		
	0.01–0.50	0.51–1.0	≥1.01
	OR (95% CI) cases/controls	OR (95% CI) cases/controls	OR (95% CI) cases/controls
Warm/hot	1.0 (reference) 60/135	1.60 (1.05–2.44) 115/146	1.80 (1.08–3.00) 65/66
Very hot	2.84 (1.06–7.66) 9/10	2.80 (1.37–5.71) 27/18	2.95 (1.30–6.74) 18/15

[a] ORs adjusted for age, sex, urban/rural status, years of education, number of cigarettes smoked per day, smoking duration, total alcohol per day, and duration of alcohol consumption. *P* for the interaction between maté amount and maté temperature = 0.7.

(95% CI, 3.8–39.6) after adjustment for the effects of age, area of residence, alcohol, and tobacco. In a pooled analysis of five studies in South America, Castellsagué *et al.* (16) reported an OR of 1.57 (95% CI, 1.22–2.03) for maté amount (>1 liter *versus* <0.5 liter). The possible effect of maté drinking on precancerous lesions of the esophagus has also been shown in an endoscopic survey conducted in Rio Grande do Sul, Brazil (12) in which a two point 2-fold excess (90% CI, 1.1–9.8) of histologically confirmed esophagitis was shown among maté drinkers compared with nondrinkers.

In studying the association between maté drinking and esophageal cancer, one of the challenges lies in disentangling the effects of amount and temperature, in order to assess whether the potential association is related to the plant itself (because of the presence of carcinogenic compounds), to the high temperature at which it is consumed (resulting in thermal injury to the esophagus), or to a combination of these two factors. It has long been suspected that herbs can cause esophageal cancer. Studies undertaken in Curaçao, Venezuela and in South Carolina resulted in the identification of numerous plant products that are consumed in large quantities by local populations in which esophageal cancer is prevalent (19–21). It is possible that exposure to maté may increase the risk of esophageal cancer through the presence of carcinogenic compounds in the beverage. Maté infusion contains tannins in a proportion that ranges from 7 to 14% (22), and experimental studies with tannins have shown the occurrence of malignant fibrous histiocytomas at the inoculation sites, as well as malignant tumors

Table 5 Joint effects of cumulative exposure to maté, alcohol, and tobacco smoking on esophageal cancer risk[a]

Lifetime consumption of maté[b]	Lifetime drinking of alcohol[c]	Lifetime tobacco smoking[d]	No. of cases/controls	OR (95% CI)
Low	Low	Low	43/148	1.00 (reference)
Low	Low	High	32/67	2.36 (1.23–4.53)
Low	High	Low	8/14	2.54 (0.93–6.95)
Low	High	High	45/47	4.06 (2.07–7.96)
High	Low	Low	38/68	1.52 (0.88–2.62)
High	Low	High	51/62	3.12 (1.69–5.78)
High	High	Low	7/6	3.40 (1.00–11.59)
High	High	High	89/46	7.10 (3.75–13.46)

[a] ORs adjusted for design variables age, sex, urban/rural status, and years of education. *P* for the interaction between lifetime exposures to maté, alcohol, and tobacco smoking = 0.96.
[b] Lifetime consumption of maté (liter-years): low, 0–16000; high, ≥16001.
[c] Lifetime consumption of alcohol (liter-years): low, 0–832; high, ≥833.
[d] Lifetime exposure to tobacco smoking (pack-years): low, 0–5840; high, ≥5841.

in rat liver (23–25). In addition, aqueous solutions of maté have also been shown to induce mutagenesis in *Salmonella typhimurium* strains TA97, TA98, TA100, and TA102 (26) and to increase the frequency of chromosomal aberrations in human peripheral lymphocytes (27).

In addition to a possible direct carcinogenic effect of maté, the temperature at which maté is consumed is likely to play an important role in esophageal carcinogenesis. A population-based survey in southern Brazil (28), where the temperature at which maté had been consumed by 1400 adults was measured, showed that the mean temperature just before consumption was 69.5°C. This indicates that the esophageal mucosa may be exposed to temperatures that may cause chronic thermal injury. Our study showed that drinkers of very hot maté presented a 2-fold increase in risk as compared with those consuming warm/hot maté. This result is consistent with several other studies that have suggested a possible effect of hot drinks on esophageal cancer incidence as a result of thermal injury to the organ. In observing such results, one needs to acknowledge that self-reporting of temperature at which maté is consumed may be subject to misclassification. Because there was no objective measurement, subjects may misclassify the "warm/hot" and "very hot" categories. However, it can be postulated that, because the association between hot temperature and esophageal cancer risk is practically unknown in this population, it is unlikely that report bias has occurred. Although we aimed to obtain information on exposures before the onset of symptoms, it is possible that, even in the preclinical stage, cases of esophageal cancer were more sensitive to maté temperature than were controls, resulting in differential misclassification.

Hot maté drinking was a risk factor for esophageal cancer in Paraguay (OR, 2.4; 95% CI, 1.3–4.3) after adjustment for the effects of alcohol consumption and tobacco smoking (29). In Argentina, the effect of drinking maté at hot/very hot temperatures was associated with a 70% increase in risk (OR, 1.7; 95% CI, 1.0–2.9) compared with those drinking warm maté (14). In a pooled analysis of five studies in South America, Castellsagué *et al.* (16) reported an OR of 1.76 (95% CI, 1.27–2.44) for very hot versus lower maté temperature. Consumption of other drinks or soups at high temperatures has also been reported as a risk factor for esophageal cancer in Puerto Rico (30), Singapore (31), Iran (32), and China (33–35).

The population-attributable fraction for maté consumption was calculated from logistic regression data. On the basis of a relative risk of 2.26 (95% CI, 1.19–4.27) for exposure to maté, a population-attributable risk of 53% was obtained (95% CI, 15%–74%). Thus, assuming a causal relationship exists, 53% of the esophageal cancers in the population would have been prevented if this exposure had been removed. The high population-attributable risk for maté consumption is attributable its high prevalence in the population. With emphasis on maté-related variables, the population-attributable fraction for high maté consumption (>1 liter/day) *versus* nondrinkers was calculated as 30%, and high temperature of maté consumption was attributed to 28% of the cases. Because the effects of the two variables overlap, 15% of the cases were attributable to high maté consumption at high temperature.

Our study was hospital based and, hence, may have been subject to various kinds of bias. Selection bias may arise for cases if they are not representative with respect to all of the cases in the population, and this is bound to affect the external validity (generalizability) of the results. The Oncology Institute of Montevideo has a catchment area that covers both the population of Montevideo (45% of patients) and the rest of the country (55% of patients). Selection bias for controls arises if they are not comparable with the cases and would affect the internal validity of the study results. Selection bias would be particularly relevant for hospital-based controls if their referral to participating hospitals differs from that of the cases. We addressed this source of bias by selecting controls from several diagnostic categories. Lack of participation is a further potential source of selection bias; however, it is not likely to have played an important role, because the response rate was high among both cases and controls. Recruitment of cases lasted 12 years, but controls were sampled during the whole study period, thus minimizing the possibility of case-control cross-over.

Errors in measurement may also be introduced as a result of observer (interviewer) or responder (patient) bias. Although it is rather difficult to exclude observer bias, the interviewers were blind to the hypothesis being tested and the interviews were done before diagnosis. Responder bias can manifest as a result of differential recall of information by cases and controls; for instance, cases may be more likely to recall past exposure, especially if its association with the disease is widely known. This type of bias can either exaggerate the degree of effect associated with the exposure or underestimate it. In our study, this form of bias is unlikely to have generated the difference between cases and controls concerning maté consumption, because the patients were interviewed before the work-up diagnostic evaluation, and, therefore, their diagnosis at the time of interview was unknown. Hence, it is unlikely that cases overestimated their exposure to maté. Furthermore, the association of maté drinking with esophageal cancer is not widely known. Hence, if misclassification did occur, it is likely to be nondifferential with regard to case-control status. Thus the

reported risk estimates might be an underestimation of the real underlying effect of maté exposure.

We excluded controls with cancer or with alcohol- and tobacco-related problems. However, ~30% of the controls had ill-defined conditions, and it may have been possible that some of the controls in this category had other cancers or conditions related to tobacco smoking and alcohol drinking. The risk estimates for maté, alcohol, and tobacco consumption did increase slightly when this group of controls was removed from the analysis, indicating that some confounding may have occurred. It is important to note that the extent to which confounding can be controlled for will depend on the accuracy of the data. Nondifferential misclassification of exposure to either alcohol or tobacco will lead to an underestimation of the effect of these factors; hence, the association is likely to persist, even after adjustment, because of residual confounding. Furthermore, we must also recognize that confounding from dietary factors has not been taken into account. Because no disease is known to be associated with maté drinking, we did not perform a maté-related selection of diagnostic categories eligible for controls. However, an association between some of the diseases of the controls and maté drinking may exist without being known: this phenomenon would bias the estimate of the relative risk towards the null.

Our study confirms previous findings in Uruguay on the association between maté drinking and esophageal cancer. The results suggest that two independent and competitive mechanisms could be at play: firstly, a carcinogenic effect of agents present in the herb *I. paraguariensis*, and, secondly, a role of chronic thermal injury to the esophagus as a result of very hot maté consumption. The high attributable risk of esophageal cancer depends mostly on the high prevalence of maté exposure (and would, therefore, be specific to the population exposed), and it does not exclude an important effect of alcohol drinking and tobacco smoking.

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