

Mate Drinking and Risk of Lung Cancer in Males: A Case-Control Study from Uruguay¹

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Abstract

During the period from January 1988 to December 1994, a case-control study that included 497 cases of lung cancer and 497 controls was carried out at the Instituto de Oncología, Montevideo, Uruguay, to evaluate the relationship between the drinking of *mate* (a local tea prepared with infusions of the herb *Ilex paraguariensis*) and the risk of lung cancer in men. *Mate* drinking has been associated with risk of most upper-aerodigestive tract cancers. After adjusting for major covariates, including pack-years of cigarette smoking, the amount of *mate* was associated with a 1.6-fold increase in risk for heavy drinkers, compared with light drinkers, with a significant dose-response pattern. When the analysis was performed by cell type, small cell lung cancer showed a significant increase in relative risk for *mate* amount (odds ratio, 2.9; 95% confidence interval, 1.3-6.2) and *mate* duration (odds ratio, 3.6; 95% confidence interval, 1.3-9.9). On the other hand, pulmonary adenocarcinoma was not associated with *mate* drinking. Possible reasons for these results are discussed, and areas for future research are suggested.

Introduction

Lung cancer is the leading neoplastic cause of death among Uruguayan males, with an age-adjusted mortality rate of 56.8 per 100,000 persons for the whole country and an age-adjusted incidence rate of 83.3 for 1987 in the capital city of Montevideo (1). It is well known that tobacco smoking is causally associated with more than 80% of the lung cancer cases. Furthermore, the risk of lung cancer increases with all types of tobacco products (2). Other risk factors have been incriminated in the etiological process of lung cancer. Among them, occupational and dietary exposures, such as high consumption of cholesterol and saturated fat and low consumption of vegetables and carotenoids, have been associated with increasing risks of lung

cancer (3-6). Recently, alcohol consumption has been reported as a risk factor for lung cancer (7-9).

Mate, the infusion of the herb *Ilex paraguariensis*, is a hot tea frequently consumed in Uruguay, Southern Brazil, Paraguay, and Argentina. Recently, Victoria *et al.* (10) carried out a survey on patterns of *mate* drinking in the city of Pelotas, Brazil, according to which the prevalence of *mate* drinkers was very high (66.4%). An even higher prevalence (78%) was observed in an Uruguayan survey (11). *Mate* drinking and cigarette smoking are correlated. Current smokers and heavy drinkers of *mate* comprised 39.1% of the population surveyed, significantly higher than the proportion of nonsmokers who were heavy *mate* drinkers (23.0%). Previous epidemiological studies have found a positive association between *mate* drinking and cancer of the esophagus, oral cavity, pharynx, larynx, stomach, and bladder (12-24). This study was designed to evaluate whether a similar association exists between *mate* drinking and lung cancer risk.

Subjects and Methods

During the period from January 1988 to December 1994, all patients ages 25-84 with incident cases of lung cancer admitted for diagnosis and/or treatment in the Instituto Nacional de Oncología of Montevideo, Uruguay, were selected for this study. In total, there were 550 cases occurring in men and 42 in women. The study was restricted to males because of the small number of females. Three patients were unable to complete the questionnaire because of advanced disease. One additional case was excluded because of a diagnosis of rhabdomyosarcoma, and 49 cases were not histologically confirmed, yielding to a study population of 497 patients with lung cancer. Squamous cell carcinoma composed the largest group (238 cases; 47.9%), followed by adenocarcinoma (123 cases; 24.7%) and small cell cancer (84 cases; 16.9%). In the same period, 1995 male patients afflicted with other cancers or nonneoplastic conditions were also admitted to the Instituto Nacional de Oncología. From this potential source of controls, 58 (2.9%) were excluded because of terminal illness, 613 (30.7%) because of a diagnosis of *mate*-related cancer (oral, pharyngeal, esophageal, gastric, and bladder cancer), 174 (8.7%) because of cancer of uncertain primary site, 291 (14.6%) because of nonneoplastic *mate*-related diseases (laryngitis, esophagitis, gastritis, and peptic ulcer), 308 (15.4%) because they were younger than 25 or older than 84 years, and 5 (0.3%) because they were living abroad. Of the remaining 546 patients, 497 were frequency matched with the cases on age (grouped in quinquennia), residence (Montevideo, southern counties, and northern counties), and urban/rural status. Prostate cancer was the most frequent diagnosis (100 patients; 20.1%), followed by nonneoplastic conditions (83 patients; 16.7%), nonmelanoma skin cancer (69 patients; 13.9%), and colorectal cancer (68 patients; 13.7%; Table 1). Both cases and controls were interviewed by three trained social workers who were unaware of the hypothesis to be tested and of any previous exposure of the patients. The questionnaire

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Table 1 Distribution of cases and controls by sociodemographic variables

Variable	Cases		Controls	
	No.	%	No.	%
Age				
25-34	6	1.2	6	1.2
35-44	32	6.4	32	6.4
45-54	80	16.1	80	16.1
55-64	167	33.6	167	33.6
65-74	155	31.2	155	31.2
75-84	57	11.5	57	11.5
Residence				
Montevideo	241	48.5	241	48.5
Southern counties	190	38.2	189	38.0
Northern counties	66	13.3	67	13.5
Urban/rural status				
Urban	373	75.1	373	75.1
Rural	124	24.9	124	24.9
Education, yr				
0-3	190	38.2	184	37.0
4-5	138	27.8	122	24.6
≥6	169	34.0	191	38.4
No. of subjects	497	100	497	100

included, among other variables, information concerning demographic variables, education, income, and occupation; a complete tobacco history; a food frequency form; and information on *mate* drinking (age started, age quit, daily amount ingested, and temperature) and was administered to all patients shortly after admission. The daily consumption of *mate* was measured in liters of water used for the preparation of the infusion (the unit commonly referred to by the patients). Although information on the temperature of *mate* was previously validated, this study does not include any attempt to validate the exposure levels. Because the *mate* drinker tries to obtain a steady concentration of the infusion, the amount of water broadly reflects the amount of substance ingested. The food frequency form included queries concerning alcohol intake (type of beverage discriminated as beer, wine, and hard liquor). Alcohol consumption was measured in ml of ethanol/day. In addition, there were questions concerning seven broad groups of foods (fresh, barbecued, preserved, and salted meat; dairy products; raw vegetables; and fresh fruits), consumption of which was reported as frequency per unit of time (day, week, month, and year), and intake was computed as annual consumption.

Data analysis. Univariate estimates of relative risk, approximated by the OR³, were obtained by exponentiating the coefficients of exposure variables in a logistic regression model. Unconditional logistic regression was used to obtain multivariate estimates for each study variable (25). Because there was evidence of differences between nondrinkers and drinkers of *mate*, ORs were estimated using two different reference categories: nondrinkers (OR1) and low-exposure drinkers (OR2). Dose-response analyses for OR2 excluded nondrinkers from the calculations. Different models were fitted, using the adjusting variables as categorical or continuous. The matching variables were included in all models. Decisions on which covariates to include in the final models were based on: (a) biological plausibility; and (b) whether the regression coefficient of the primary independent variable (*mate* drinking) changed by 10% or more after addition of the potentially confounding variable. The final models included pack-years of cigarette smoking and total alcohol consumption as continuous vari-

Table 2 ORs of lung cancer associated with tobacco use: all cell types^a

Variable	Category	Cases/controls	OR	95% CI
Amount (cigarettes/day) ^b	Never smokers	27/163	1.0	
	1-10	38/84	2.9	1.6-5.0
	11-20	155/119	8.4	5.2-13.6
	21-40	161/100	10.4	6.4-16.9
	≥41	116/31	23.7	13.4-42.1
Duration (yr) ^c	Never smokers	27/163	1.0	
	1-29	43/55	3.4	1.7-6.8
	30-39	78/78	5.2	2.9-8.9
	40-49	171/93	10.4	6.4-16.9
	≥50	178/108	10.8	6.6-17.6
Pack-years ^d	Never smokers	27/163	1.0	
	1-29	79/124	3.8	2.3-6.3
	30-50	114/89	7.6	4.6-12.6
	51-85	136/64	12.7	7.7-21.1
	≥86	141/57	14.9	8.9-24.8
Cessation ^e	Never smokers	27/163	1.0	
	≥10	17/36	2.8	1.4-5.7
	5-9	27/27	6.2	3.2-12.2
	1-4	64/45	9.0	5.2-15.9
	Current smoker	362/226	10.9	6.9-17.1
Type of tobacco	Never smokers	27/163	1.0	
	Blond	169/173	6.1	3.8-9.8
	Mixed	85/39	13.6	7.7-23.9
	Black	216/122	10.9	6.8-17.4
Hand-rolling	Never smokers	27/163	1.0	
	Manufactured	108/113	6.1	3.7-10.0
	Rolled	362/221	10.2	6.5-15.9
Filter use	Never smokers	27/163	1.0	
	Filter	178/156	7.3	4.6-11.8
	Plain	292/178	10.1	6.4-15.6

^a Adjusted for age, residence, urban/rural status, and education.

^b $\chi^2 = 190.0$; $P < 0.001$.

^c $\chi^2 = 144.7$; $P < 0.001$.

^d $\chi^2 = 169.9$; $P < 0.001$.

^e $\chi^2 = 150.2$; $P < 0.001$.

ables. A second model with smoking intensity and duration instead of pack-years yielded similar results. Interactions between *mate* drinking and tobacco variables were evaluated. All estimations were performed using the GLIM program (26).

Results

As expected, the distribution of cases and controls was similar in age, residence, and urban/rural status (Table 1). Intensity of smoking, measured in lifetime average consumption of cigarettes/day, showed a strong dose-response pattern with an OR of 23.7 for heavy smokers (Table 2). Also, smoking duration displayed a monotonic gradient of increasing risks, with a highly significant test for linear trend ($P < 0.001$). Ex-smokers showed a 60% reduction in risk compared to current smokers, and lifelong filter usage was associated with a relative risk of 0.7 compared to unfiltered cigarette use. Heavy smokers with a pack-year history of 86 or more had an approximately 15-fold increased risk of lung cancer.

Alcohol consumption was associated with an increased risk of lung cancer (OR, 2.0; 95% CI, 1.3-3.2) and demon-

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

Table 3 ORs of lung cancer associated with mate drinking; all cell types^a

Variable	Cases/ controls	OR1	95% CI ^b	OR2	95% CI ^c
<i>Mate</i> status					
Never drinkers	21/53	1.0			
Ever drinkers	476 /444	2.4	1.3–4.3		
Amount (liters/day)					
Never drinkers	21/53	1.0		0.5	0.3–0.9
0.1–0.99	101 /137	1.9	1.0–3.7	1.0	
1.0–1.99	223 /211	2.6	1.4–4.7	1.3	0.9–1.9
≥2.0	152 /96	2.9	1.5–5.4	1.6	1.1–2.4
<i>P</i> value for linear trend			<i>P</i> < 0.001		<i>P</i> = 0.02 ^d
Duration (yr)					
Never drinkers	21/53	1.0		0.4	0.2–0.8
1–39	134 /138	2.3	1.2–4.3	1.0	
40–49	121 /113	2.1	1.1–4.1	1.0	0.7–1.5
≥50	221 /193	2.9	1.5–5.5	1.4	0.8–2.2
<i>P</i> value for linear trend			<i>P</i> = 0.005		<i>P</i> = 0.14 ^d
<i>Mate</i> -yr					
Never drinkers	21/53	1.0		0.5	0.3–0.9
1–36	131 /177	2.0	1.1–3.7	1.0	
37–60	164 /143	2.7	1.5–5.1	1.3	0.9–1.9
≥61	181 /124	2.8	1.5–5.3	1.5	1.0–2.1
<i>P</i> value for linear trend			<i>P</i> = 0.001		<i>P</i> = 0.02 ^d

^a Adjusted for age, residence, urban/rural status, education, pack-yr, and total alcohol consumption.

^b Reference category, nondrinkers.

^c Reference category, lowest exposure among drinkers.

^d χ^2 is restricted to *mate* drinkers.

strated a significant dose-response pattern, after adjusting for tobacco smoking (*P* = 0.02).

Relative risks of lung cancer (all cell types combined) for *mate* variables are shown in Table 3. As noted previously, two sets of ORs were computed using different referent categories: nondrinkers (OR1) and low-exposure drinkers (OR2). Results for those exposed to the beverage and using the low-exposure category as the referent category are, in general, more conservative. Those who were ever *mate* drinkers showed an increased relative risk of lung cancer of 2.4 (95% CI, 1.4–4.4) after adjusting for age, residence, education, pack-years of tobacco smoking, and alcohol drinking. The amount consumed (measured in liters/day) was significantly associated with lung cancer risk (χ^2 for linear trend, 5.93; *P* = 0.02), with an OR of 1.6 for heavy drinkers after adjusting for potential confounders. *Mate* duration (years of consumption) was associated with a smaller increase in risk and a nonsignificant dose-response. No effect was observed with the reported temperature of *mate*. Finally, the cumulative exposure *mate*-years was associated with a monotonic gradient of increased risks, which was statistically significant.

The relative risks of squamous cell lung cancer for *mate* variables are shown in Table 4. The amount of *mate* consumed was associated with a significant increase of 1.8-fold for heavy drinkers, and the *P* value for linear trend was statistically significant (*P* = 0.02). Years of *mate* use among those exposed to the beverage were not associated with significant increase in risk, whereas the cumulative exposure (*mate*/years) displayed an 80% increase in risk for heavy drinkers. The relative risks for small cell lung cancer are shown in Table 5. Amount of *mate* was associated with an OR of 2.9 for drinkers of ≥2 liters/day (*P* = 0.007). Years of *mate* use was associated with an increased risk of 3.6 (95% CI, 1.3–9.9), and the cumulative

Table 4 ORs of squamous cell lung cancer associated with mate drinking^a

Variable	Cases/ controls	OR1 ^b	95% CI	OR2 ^c	95% CI
<i>Mate</i> status					
Never drinkers	21/53	1.0			
Ever drinkers	228/444	2.2	1.0–4.7		
Amount (liters/day)					
Never drinkers	10/53	1.0		0.8	0.3–1.7
0.1–0.99	49/137	1.7	0.7–3.9	1.0	
1.0–1.99	105/211	2.3	1.0–5.0	1.4	0.9–2.1
≥2.0	74/96	2.6	1.1–6.0	1.8	1.1–2.9
<i>P</i> value for linear trend			<i>P</i> = 0.009		<i>P</i> = 0.02 ^d
Duration (yr)					
Never drinkers	10/53	1.0		0.6	0.3–1.5
1–39	54/138	1.8	0.8–4.3	1.0	
40–49	64/113	2.2	0.9–4.9	1.1	0.7–1.9
≥50	110/193	2.5	1.1–5.7	1.3	0.7–2.4
<i>P</i> value for linear trend			<i>P</i> = 0.03		<i>P</i> = 0.31 ^d
<i>Mate</i> -yr					
Never drinkers	10/53	1.0	–	0.5	0.3–0.9
1–36	57/177	1.6	0.7–3.7	1.0	–
37–60	73/143	2.3	1.0–5.2	1.3	0.9–1.9
≥61	98/124	2.8	1.3–6.3	1.8	1.2–2.8
<i>P</i> value for linear trend			<i>P</i> = 0.002		<i>P</i> = 0.006 ^d

^a Adjusted for age, residence, urban/rural status, education, pack-yr, and total alcohol consumption.

^b Reference category, nondrinkers.

^c Reference category, lowest exposure among drinkers.

^d χ^2 is restricted to *mate* drinkers.

exposure was also significant. Adenocarcinoma of the lung was not associated with *mate* drinking (Table 6).

Joint effects of tobacco smoking (in pack-years) and *mate* drinking (in liters/day) are shown in Table 7. After dichotomization of both exposures at the median values for cases and controls combined, joint exposure of heavy smokers and heavy drinkers of *mate* was associated with an increased risk of 6.5, following a supraadditive pattern.

Discussion

Lung cancer in Uruguayan men is strongly associated with tobacco smoking. Both intensity and duration of tobacco smoking showed independent effects. Of particular interest was the increased risk associated with smoking black tobacco and hand-rolled cigarettes.

The present study is, to our knowledge, the first one to consider the relationship between *mate* drinking and lung cancer risk. The results suggest that there is an effect of *mate*, independent of tobacco use, that is best shown by the daily amount of the beverage consumed. Moreover, the effect appears to be more evident in squamous cell and small cell cancers (Kreyberg I group).

Because the first short-term tests were unable to find mutagenic activity in *mate* extracts,⁴ the increased ORs observed in digestive cancers have been attributed tentatively to thermal injury resulting from the hot temperature at which *mate* is usually drunk (13–15, 27). The IARC monograph has classified hot *mate* drinking as probably carcinogenic to humans (Group 2A) and recommends, before reaching a more conclusive result, resolution of the following issues: (a) recall bias (*i.e.*,

⁴ H. Yamasaki and H. Bartsch, personal communication.

Table 5 ORs of small cell lung cancer associated with mate drinking^a

Variable	Cases/ controls	OR1 ^b	95% CI	OR2 ^c	95% CI
<i>Mate</i> status					
Never drinkers	1/53	1.0			
Ever drinkers	83/444	6.9	0.9–53.9		
Amount (liters/day)					
Never drinkers	1/53	1.0		0.3	0.1–2.9
0.1–0.99	12/137	3.6	0.4–29.7	1.0	
1.0–1.99	39/211	7.2	0.9–56.4	2.1	1.0–4.4
≥2.0	74/96	9.6	1.2–76.1	2.9	1.3–6.2
<i>P</i> value for linear trend		<i>P</i> < 0.001		<i>P</i> = 0.007 ^d	
Duration (yr)					
Never drinkers	1/53	1.0		0.3	0.1–2.4
1–39	19/138	4.3	0.5–34.7	1.0	
40–49	21/113	7.3	0.9–60.5	1.7	0.8–3.9
≥50	43/193	15.5	1.8–134.5	3.6	1.3–9.9
<i>P</i> value for linear trend		<i>P</i> < 0.001		<i>P</i> = 0.02 ^d	
<i>Mate</i> -yr					
Never drinkers	1/53	1.0		0.2	0.1–1.9
1–36	19/177	4.9	0.6–39.8	1.0	
37–60	21/143	6.8	0.9–54.4	1.3	0.7–2.5
≥61	43/124	9.7	1.2–76.5	1.9	1.0–3.8
<i>P</i> value for linear trend		<i>P</i> = 0.004		<i>P</i> = 0.04 ^d	

^a Adjusted for age, residence, urban/rural status, education, pack-yr, and total alcohol consumption.

^b Reference category, nondrinkers.

^c Reference category, lowest exposure among drinkers.

^d χ^2 is restricted to *mate* drinkers.

awareness that *mate* drinking may increase the risk for cancer could have led to increased reporting of *mate* drinking for cancer cases as compared with controls); (b) confirmation of the *mate*-cancer relationship by other groups of investigators; and (c) exclusion of the possibility of residual confounding by tobacco smoking and alcohol drinking (20). In dealing with a disease like lung cancer with such a strong causative agent as tobacco smoking, careful consideration of bias is central to the evaluation of the results. The problem of residual confounding by tobacco smoking is a major one in lung cancer studies. We treated this potential bias using cumulative exposure of tobacco smoking (pack-years, smoking duration, and smoking intensity) in either continuous or stratified terms, with similar results. Differential reporting by cases and controls is not likely in the present study, because no association between risk of lung cancer and *mate* drinking had been established at the time of the study, and both cases and controls were patients at the Oncology Hospital.

Conflicting results have been reported from Brazil and Argentina on the association of *mate* with other cancers. According to Victora *et al.* (14), daily *mate* drinking was associated with a borderline increase of 1.5-fold in esophageal cancer. Franco *et al.* (18) and Pintos *et al.* (19) reported significant increases in risk of oral and laryngeal cancer in a multicenter Brazilian study. On the other hand, Iscovich *et al.* (22) failed to find any effect of *mate* drinking on bladder cancer in a study conducted in the city of La Plata, Argentina. Recently, Castelletto *et al.* (16) reported an increase in risk of esophageal cancer, associated with hot *mate* drinking, but amount consumed per day was nonsignificant. The same applies to the report from Paraguay (24). It should be noted that Argentinians have a much lower consumption of *mate* than Brazilian and Uruguayan populations. This is clearly shown in that only 4% of the controls in the Castelletto *et al.* study (16) were

Table 6 ORs of lung adenocarcinoma associated with mate drinking^a

Variable	Cases/ controls	OR1 ^b	95% CI	OR2 ^c	95% CI
<i>Mate</i> status					
Never drinkers	10/53	1.0			
Ever drinkers	83/444	1.6	0.7–3.9		
Amount (liters/day)					
Never drinkers	10/53	1.0		1.1	0.4–3.0
0.1–0.99	22/137	1.1	0.4–2.9	1.0	
1.0–1.99	61/211	1.9	0.8–4.6	1.7	0.9–2.9
≥2.0	33/96	1.6	0.6–4.0	1.4	0.7–2.6
<i>P</i> value for linear trend		<i>P</i> = 0.12		<i>P</i> = 0.19 ^d	
Duration (yr)					
Never drinkers	10/53	1.0		0.7	0.3–1.8
1–39	47/138	1.7	0.7–4.4	1.0	
40–49	28/113	1.3	0.5–3.5	0.8	0.4–1.4
≥50	41/193	1.6	0.6–4.3	0.9	0.4–1.9
<i>P</i> value for linear trend		<i>P</i> = 0.48		<i>P</i> = 0.82 ^d	
<i>Mate</i> -yr					
Never drinkers	10/53	1.0	–	0.7	0.3–1.9
1–36	36/177	1.3	0.5–3.3	1.0	–
37–60	48/143	2.2	0.9–5.5	1.7	0.9–2.8
≥61	98/124	1.4	0.5–3.5	1.0	0.6–1.8
<i>P</i> value for linear trend		<i>P</i> = 0.36		<i>P</i> = 0.48 ^d	

^a Adjusted for age, residence, urban/rural status, education, pack-yr, and total alcohol consumption.

^b Reference category, nondrinkers.

^c Reference category, lowest exposure among drinkers.

^d χ^2 is restricted to *mate* drinkers.

Table 7 Age- and residence-adjusted ORs of lung cancer associated with tobacco (pack-yr) and mate consumption

Pack-yr	<i>Mate</i>			
	Cases/controls	0–0.99 ^a	Cases/controls	≥1.0 ^a
0–44	49/139	1.0	118/192	1.7 (1.2–2.6)
≥45	73/51	4.2 (2.6–6.8)	257/115	6.5 (4.4–9.7)

^a Liters/day. 95% CIs in parentheses.

heavy drinkers, compared with 25% of the controls in the present study. Furthermore, the mean daily amount consumption of *mate* is higher in Uruguay (0.95 liters/day) than in Argentina (0.59; Ref. 16). Lung cancer was considered a good model for testing a chemical rather than thermal effect of *mate*.

Because the Cancer Institute treats patients from the whole country, it was decided to finely stratify birthplace and current residence (19 categories for each variable) and to include both in the analysis to control differential referral by county. The results strongly suggest a homogeneous study base (28, 29). The inclusion of cancer controls in this type of study has been the subjects of previous papers (30, 31). In the present study, cancer controls represented 83.3% of all referents (414 patients). Because these patients may have similar errors in recall, this may alleviate some of the problems related with recall bias (32). Moreover, the inclusion of controls with many different sites of cancer minimizes potential bias if any one site turns out to be related to exposure (30–32).

Mate has undergone chemical analyses that identified in it, among other substances, caffeine, theobromine, chlorogenic acids, sucrose, and ascorbic acid (27). Of particular interest was the finding of relative large quantities of benzopyrene in eight com-

mercial samples of *mate* (33). The possible presence of tannins in *mate* has been the subject of conflicting reports (34, 35). Because tannic acid is carcinogenic in rats after its s.c. injection, producing liver tumors and sarcomas, further analysis should be conducted to elucidate its possible presence in *mate* (36). In the only experimental study conducted to date with *mate* extracts, skin painting with tar from the processing of the leaf resulted in skin carcinomas (37). Caffeic acid, a precursor of chlorogenic and iso-chlorogenic acids, is present in *mate* and has been recently considered as possibly carcinogenic to humans (38). Experimental studies using oral administration of caffeic acid in male B6C3F1 mice resulted in an increased incidence of alveolar II-cell tumors (adenomas plus carcinomas) of the lung (8 of 30; $P < 0.05$; Ref. 39). Thus, several chemicals present in *mate* (tannic acid, caffeic acid, and benzopyrene) could be responsible for the increased risk of lung cancer observed in our study. Considering that the average Uruguayan consumes about 8 kg/year of *mate* (i.e., 45 mg of benzopyrene/year) the increased risk of cancer is biologically plausible.⁵ Recently, genotoxic activity of *mate* infusions in short-term tests has been reported (40).

Although we postulate possible mechanistic pathways for a possible association, it should be emphasized that this finding requires further confirmation. Future research should include both experimental carcinogenesis and further epidemiological studies.

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⁵ S. Garcia and P. Moyna, personal communication.

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