

Cancer and *yerba mate* consumption: a review of possible associations

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ABSTRACT **Objective.** To identify any possible link between mate consumption and cancer, mainly of the esophagus, larynx, and oral cavity.

Methods. A review of literature, published through August 2008, pertaining to the carcinogenic risk of mate consumption was undertaken by searching the two databases, MEDLINE and TOXLINE, for relevant articles. The bibliographies of the articles were examined for additional relevant sources. In addition, a search on the name of each author having published on the topic was conducted. The epidemiological studies are presented by cancer site; experimental works are examined in dedicated sections; and the discussion combines epidemiological and experimental evidence.

Results. Almost all epidemiological studies shared similar methodology: hospital-based, case-control studies where participants were personally interviewed on the main risk factors, using similar questionnaires. Several studies found an association between the temperature of the mate infusion and oral, esophageal, and/or laryngeal cancer risks; while a few focused on carcinogenic contaminants introduced during the industrial processing of the leaves. The cancer most frequently mentioned in association with hot mate with bombilla (drunk through a metal straw) was the esophagus. Size, exposure assessment, methods of analysis, and quality were different among the studies reviewed. The results varied greatly. The higher risk estimate (odds ratio = 34.6) was found for women who drank 1 L or more daily; for men it was only 4.8. Risk increased with duration, daily quantity, and temperature at drinking. The synergic action between mate, alcohol, and tobacco was a clear result in several studies, and in some, nutritional deficiencies and poor oral hygiene played a role. No increased risk was associated with cold mate beverages.

Conclusions. The role of hot mate in increasing the risk of cancer of esophagus, larynx, and oral cavity seems to be supported by several epidemiological studies. The temperature could act by damaging the mucosa or accelerating metabolic reactions, including those with carcinogenic substances in tobacco and alcohol. However, there is no sound population-based case-control study on mate consumption as a risk factor for cancer. This, coupled with the range of results on mate risk, make assessing the etiological fraction difficult. More research needs to be done before a definitive statement can be made regarding cancer risk associated with any of the various forms of mate consumption. Future research should include population-based studies; collection of data on consumption of tobacco, alcohol, hot drinks, fresh fruit, and vegetables; and, a method to precisely measure volume and temperature of mate intake.

Key words Laryngeal neoplasms, esophageal neoplasms, pharyngeal neoplasms, *Ilex paraguayensis*, review literature, Argentina, Brazil, Paraguay, Uruguay.

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Mate is a beverage made from the leaves of a perennial shrub-tree (*Ilex paraguayensis*)

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native to Argentina, Brazil, Paraguay, and Uruguay. The Spanish word *mate* refers to the dried leaves (also called *yerba mate*), as well as the cup from which the beverage is drunk, traditionally a small, hollow gourd. *Mate* is consumed in vari-

ous ways, but the most popular method is by placing the *yerba mate* in the cup (the aforementioned gourd, or a metal, silver, or ceramic vessel shaped like small jug), pouring boiling water into it, and sipping the infused liquid through a metal straw called a *bombilla* (little pump). The *bombilla* acts as a filter—the end that goes into the liquid has a bulb pierced with small holes that prevents the leaves from going up the straw. Hot water is added to the *mate* mainly in Argentina, Brazil, and Uruguay; this type of preparation is called *mate con bombilla*. On the other hand, *mate* can also be a cold beverage (*tereré*), a habit common in Paraguay. Sugar or an artificial sweetener may also be added, though in Brazil, the *mate* is traditionally drunk without sugar (*cimarrão*). The number of times that additional boiling water is poured into the same serving of *yerba mate* differs according to individual preference. In addition, *mate* may be prepared and drunk like a common tea (*mate cocido*). Grocery stores in these countries carry commercial *mate* products with differing amounts of twigs/stems and a variety of flavors, e.g., orange peel.

A flowchart of the industrial processing of *Ilex paraguariensis* leaves and a description of the main compounds found in *mate* can be found in a recent paper by Heck and Mejia (1). A report of the National Institute for Yerba Mate in Argentina provides details of the plant and its cultivation, the production processes, the chemical composition of the resulting commercial products, and the various consumption habits (2). Although *mate* is predominantly a South American habit, commercial products are entering the markets in countries outside the continent.

In 1991, the International Agency for Research of Cancer (IARC) evaluated the carcinogenic risk of *mate* and concluded that: (a) there is “limited evidence for carcinogenicity of hot *mate* drinking in humans;” (b) “no data available on the drinking of cold *mate*,” and, (c) “no data on its carcinogenicity in experimental animals” (3). Overall, IARC classified drinking hot *mate* as “probably carcinogenic to humans (Group 2A)” and *mate* as “not classifiable as to its carcinogenicity to humans (Group 3).” Most of the studies on which the IARC evaluation was based were similar in methodology and shared part of the enrolled subjects and some of the researchers. As of August 2008, the IARC has not released an updated evaluation; however some new studies have been published, showing

heterogeneous results. Incidence rates for cancer of the esophagus, larynx, and oral cavity—the cancers mostly related to *mate* ingestion—vary among Latin American countries. Examples are provided in Figure 1 and are compared with the corresponding data for North America (4).

The main objective of this study was to systematically and analytically review the literature published to date to identify any possible link between *mate* consumption and cancer, mainly of the esophagus, larynx, and oral cavity.

MATERIALS AND METHODS

A review of literature pertaining to the carcinogenic risk of *mate* consumption was undertaken by searching the two databases, MEDLINE and TOXLINE, with key words and the strings “*mate* & cancer” and “*yerba mate* & tumors” for relevant articles. The bibliographies of the articles were examined for additional relevant sources. In addition, a search on the name of each author having published on the topic was conducted.

All of the resulting epidemiological works published by indexed journals were considered for the review. Of the clinical and the toxicological studies (conducted on humans, in experimental mammals, and in vitro), those that offered an explanation of the epidemiological findings were retained.

Though the epidemiological articles were a non-negligible number, the decision to override the conditions for a formal meta-analysis was made because (a) not all the studies were independent, some being an extension of, combined with, or new analysis of a previous study; (b) the studies varied greatly in terms of design, methods, and techniques of exposure assessment; and, (c) the size of some case-control studies was limited. Therefore, we proceeded with a traditional review, considering the following for each article:

- Population targeted
- Time-period covered
- Study design
- Sample size
- Method of exposure assessment
- Statistical analysis
- Results and their statistical significance
- Sources of possible bias
- Analysis and discussion elements

This review presents the epidemiological studies by cancer site (esophagus; oral cavity, oropharynx, and larynx;

bladder; other cancers). Experimental works are examined in dedicated sections. The discussion combines epidemiological and experimental evidence.

RESULTS

Epidemiological studies

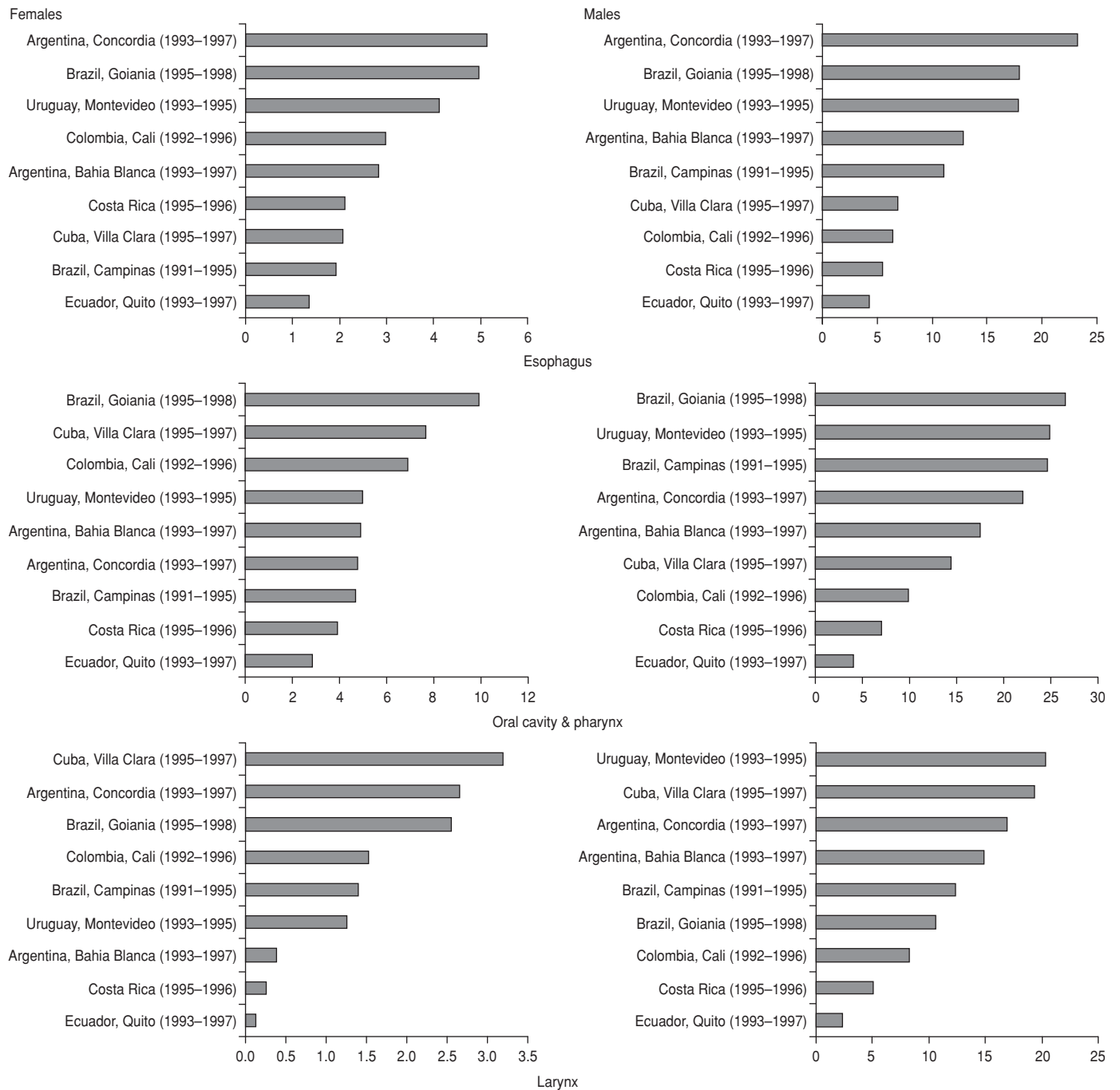
In terms of study design, most of the studies evaluated were hospital-based case-control studies with customized questionnaires used by trained interviewers. Epidemiological studies are presented by tumor site and results are summarized in Tables 1, 2, and 3.

Esophageal cancer. This was the cancer most frequently mentioned in association with *mate* consumption. One of the first papers published on patients with esophageal cancer was a hospital-based case-control study carried out in Uruguay in 1985 (5). The methodology applied was partially modified in following studies, to which some of the same authors contributed. A high odds ratio (OR), with a statistically significant confidence interval (95%CI), was found for women who reported drinking 1 L or more *mate* per day (34.6; 95%CI: 4.9–246.5), while for men consuming the same amount, the risk was only 4.8 (95% CI: 1.9–12.1). The authors suggest a synergic action between *mate* consumption and smoking.

Following this study, the IARC coordinated some additional studies in various countries in the Southern Hemisphere and found different results (6–8). One of these studies postulated an interesting hypothesis for explaining the greater effect of *mate* on smokers of dark tobacco, than on smokers of blond tobacco (7). The authors suggested that the root cause could be socioeconomic differences between the two types of smokers—in general, smokers at the lower socioeconomic levels smoke dark tobacco. They also eat diets poorer in fruits and vegetables, which have been recognized to protect against esophageal cancer. The study found no consistent relationship between effects and the temperature at which the individuals reported drinking the *mate*.

Some years later, De Stefani et al. carried out a study to assess the effect of certain dietary factors on the etiology of esophagus carcinoma, finding a statistically significant risk of about 2 for salted and stewed meat (9). The authors suggested that this effect, as would also be the case with *mate*, could be due to the

FIGURE 1. Incidence rates of cancer of the esophagus, oral cavity, or larynx, adjusted by age (world standard population), and expressed as the number of new cases per 100 000 individuals from 20–85 or more years of age (4)



high temperature at which these foods are consumed. In a detailed study on the *mate* drinking habit and esophageal cancer occurrence, it was found that the risk increased with the duration of the habit, the daily quantity ingested, and the temperature of the drink (self-reported as “warm,” “hot,” or “very hot”) (10). The authors noted that the temperature rating could have been affected by subjectivity. The risk for drinkers of more than 1 L of “very hot” *mate* per day was 2.95.

A more recent retrospective study was performed enrolling all esophageal cancer cases diagnosed at the Montevideo Cancer Institute in 1988–2000 (10). An association between *mate* consumption and esophageal cancer was found, signaling two independent factors: the temperature and the daily quantity of the *mate* drunk. The risk found for the individuals with higher accumulated exposure to *mate* was lower if they were less exposed to alcohol and tobacco (OR 1.52; 95%CI:

0.88–2.62 versus OR 7.1; 95%CI: 3.75–13.00 if more exposed).

Of the series of studies conducted in Uruguay (5, 7, 9–11), it is interesting to single out the one based on data of esophagus cancer patients who were not smokers or consumers of alcohol, thus excluding the two most important confounding factors: tobacco and alcohol consumption (11). The authors described a model where daily consumption (OR 2.20, 95%CI: 1.02–4.91, for 1 L or more

TABLE 1. Summary of studies on mate intake and esophageal cancer in South America, by year of publication

Country	Year	Number of cases/controls	Sex	Mate intake			OR ^a	95% CI	Reference number
				Unit quantity	Frequency	Temperature			
Uruguay	1985	175/313	Males	L/day	0		1		4
					< 0.5		1.1	0.2–5.0	
					0.5–0.99		3.1	1.2–7.8	
					≥ 1		4.8	1.9–12.1	
		40/66	Females		0		1 ^b		
					0.001–0.499		2.1	0.1–31.7	
					0.5–0.999		12.5	2.0–80.1	
					≥ 1.000		34.6	4.9–246.5	
Brazil	1987	171/342	Both		Less than daily		1	0.87–2.5	5
					Daily		1.47		
Uruguay	1990	261/522	Both	L/day	0		1		6
					0.01–0.49		2.52	0.8–8.4	
					0.5–1.49		3.60	1.3–9.9	
					1.50–2.49		6.07	2.1–17.3	
				≥ 2.5		12.21	3.8–39.6		
Argentina	1994	131/262	Both			Warm ^c	1		7
						Hot/very hot	1.7	1.0–2.9	
Paraguay	1995	127/370	Both		Mate and mate cocido	Warm/hot ^c	1		13
						Very hot	2.4	1.3–4.3	
		101/298	Both		Mate cocido	Warm/hot ^c	1		3.2–13.2
						Very hot	6.5		
Argentina, Brazil Paraguay, Uruguay	2000	759/1 538	Both		Mate	Cold/warm	1		14
						Hot	1.11	0.84–1.47	
						Very hot	1.89	1.24–2.86	
					L/day	0–0.50		1 ^d	
				0.51–1.00		0.95	0.75–1.20		
				1.01–1.50		1.40	0.99–1.98		
				> 1.50		1.58	1.17–2.17		
		689/1 466				Never very hot	1		
						Always very hot	2.07	1.55–2.76	
Uruguay	2003	344/469	Both	L/day		Warm, hot	1		9
						Very hot	2.95	1.30–6.71	
Uruguay	2004	73/219 ^e	Both	L/day	0–0.49		1		10
					0.50–0.99		1.60	0.67–3.58	
					≥ 1		2.20	1.02–4.91	

^a Odds ratio adjusted by age, alcohol, and tobacco.

^b Without adjusting for tobacco and alcohol.

^c Quantity independent.

^d Joint effect of amount and temperature.

^e Non-smokers, non-drinkers.

per day), duration of habit (OR 2.49, 95%CI: 1.15–5.40, for 60 or more years of habit), and intensity of habit (OR 1.91, 95%CI: 1.06–3.45 for more than 37 L per year) were the most relevant factors linked to risk.

A study conducted in the southern part of Brazil (6), found that there was a 50% increase in risk of esophageal cancer among the daily drinkers of *mate con bombilla*, but maybe because of the confounding effects of smoking and place of residence, the risk was not statistically

significant (OR 1.47; 95%CI: 0.87–2.5). The main risk factors for esophageal cancer in this geographic area were alcohol consumption, smoking habits, residing in a rural area, and a diet poor in fruit.

In a molecular epidemiological study also conducted in the south of Brazil, TP53 mutations different from those of the worldwide database were found in subjects with squamous cell carcinoma of the esophagus. The authors postulated that the presence of these mutational differences could be explained,

at least partially, by the presence of a chronic inflammatory process due to mucosal irritation caused by the very hot *mate* commonly drunk in this area (12).

A pilot survey was carried out in healthy males to investigate the effects of hot beverages on the human esophagus (13). The histological exams performed on the esophageal mucosa of daily drinkers of hot *mate*, as well as non-drinkers, showed almost twice the number of esophagitis in drinkers. It has been postulated that the cause of the damage

TABLE 2. Summary of studies on mate intake and oral and oropharyngeal cancer in South America

Country	Year of publication	Number of cases/controls	Mate intake		OR ^a	95%CI	Reference number
			Unit	Quantity			
Uruguay	1988	108/286 ^b	L/day	< 1	1		26
				1–1.99	2.5	1.1–5.7	
				≥ 2	5.2	2.1–13.1	
Brazil	1989	232/464 ^c	Mates/month	< 1	1		30
				1–30	1.6	0.8–3.3	
				> 30	1.6	0.8–3.3	
Uruguay	1991	57/353 ^d	L/day	< 1	1		27
				1–1.99	0.9	0.4–2.1	
				≥ 2	2.5	1.2–5.6	
Brazil	1994	378/756 ^e	Mates/day	Non-drinker	1		24
				Drinker	1.61	1.2–2.2	
		160/338 ^f		Non-drinker	1		
				Drinker	1.88	1.1–3.3	

^a Odds ratio adjusted by age, alcohol, and tobacco.

^b Oropharynx, males.

^c Oral cavity, both sexes.

^d Tongue, males.

^e All upper aerodigestive tract, both sexes.

^f Mouth, both sexes.

TABLE 3. Summary of studies on mate intake and laryngeal cancer in South America

Country	Year of publication	Number of cases/controls	Mate intake		OR ^a	95%CI	Reference number
			Unit	Quantity			
Uruguay	1987	107/290	L/day	0–0.49	1		26
				0.50–0.99	3.2	0.9–10.3	
				1.00–1.49	2.6	0.8–8.2	
				≥ 1.50	4.9	1.7–14.3	
				0–0.49	1		
> 0.49	3.4	1.8–6.6					
Brazil	1994	97/194	Mates/day	No	1		25
				Yes	2.24	1.15–4.50	

^a Odds ratio adjusted by age, alcohol, and tobacco.

was the thermal action of the beverage. The need for additional studies on a greater number of healthy individuals to validate these findings was suggested, but no such further studies have been published to date.

In Argentina, a hospital-based case-control study was conducted by Castelletto et al. (8), using a design similar to those used in Uruguay and Brazil (6, 7, 11). This study found an increased risk associated with tobacco and alcohol consumption, but not with mate drinking in general. However, after dividing the mate drinkers into two groups according to their individual perception of the temperature at which they drink their mate (warm vs. hot/very hot), and after adjusting for the effect of other factors, the

authors found that the risk was higher for the group drinking it hot/very hot (OR 1.7; 95%CI: 1.0–2.9).

A similar study was conducted in Paraguay considering the possible effects of both mate cocido (prepared as tea) drunk hot and mate con bombilla drunk hot or cold (14). One of the difficulties encountered in the analysis was that more than 88% of the respondents reported being drinkers of hot mate, and that the habit of drinking cold mate was also rather widespread; therefore, there were too few respondents who drank mate only hot or only cold. Because this hospital-based case-control study, excluded subjects with diseases potentially associated with tobacco and alcohol from the control group, a greater propor-

tion of mestizos and tobacco and alcohol consumers were among the cases. Regardless, the authors were able to identify an increased risk of esophageal cancer among consumers of very hot mate (OR 2.4; 95%CI: 1.3–4.3), independent of habit duration.

In 2000, a pooled analysis of the studies carried out in Latin American countries (15) was published, including 830 cases and 1 779 controls. This analysis confirmed that alcohol and tobacco were the most influential factors in esophageal cancer; it also suggested that there is an increased risk associated with daily mate intake, especially when drunk hot. The same study quantified the risk due to the consumption of other hot drinks, finding that the risk increased rapidly among those that declared drinking tea or coffee with milk at very high temperatures. No excess risk was found for drinkers of very hot coffee alone. The authors suggested that this disparity in the results was probably linked to the lower volume of the hot liquid intake when the coffee is drunk alone. As early as 1972, a relationship was identified between an increase in the intraesophageal temperature and the coffee volume (16).

A detailed study (17) on the possible contribution of temperature of an infusion to the carcinogenic process showed that, for more than 70% of subjects, a thermometer immersed just prior to ingestion ranged from 51°C–78°C. The study also showed that the temperature reported by the subject had only limited correspondence with the temperature indicated by the thermometer.

Temperature of infusion and esophageal cancer risk has also been studied in other continents, specifically with respect to tea consumption. A Japanese cohort study followed 220 272 men from 1966–1981 (18). During that period, there were 440 deaths due to esophageal cancer, and a relative risk of 1.6 was found for hot green tea drinkers vs. those drinking tea at a moderate temperature. A low intake of green or yellow vegetables was also associated with an increased risk.

Several subsequent studies have investigated the role of fruit and vegetable consumption and the risk of esophageal, oral, and oropharyngeal tumors. The protective effect of a diet rich in fruits and vegetables has been evidenced by several population groups with very different dietary habits (19–21).

The role of thermal irritation due to very hot tea consumption, together with

the promoting effect of tannins and the nutritional deficiencies, has also been found to be associated with the development of esophageal cancer in the coastal Caspian area of Iran (22). The Caspian area is known to have a high incidence of this cancer. However, the results of this study, undertaken with information from the 1968–1997 period, could have been affected by opium intake and consumption of bread contaminated with silica fibers. In China, the consumption of beverages and soups at high temperatures has also been found to be associated with an increased risk (2–3 times) of esophageal cancer (23).

Oral cavity, oropharynx, and larynx cancer. Tobacco and alcohol are well established as important etiological factors in these cancers also; but other factors, including viruses, could play an independent role or act as modifiers in the carcinogenic process. The HPV16 (a common type of papilloma virus found in genital mucosa) has been recently postulated as a risk factor (24).

Concerning beverages intake, Pintos et al. (25) analyzed the answers to a questionnaire administered to hospital cases and controls, finding some excess risk of developing oral and laryngeal cancer for *mate* drinkers, but not for tea or coffee drinkers. In the discussion, it was mentioned that the results could reflect the presence of confounding factors; for example, those individuals drinking larger quantities might tend to say they drank it less hot. In this study, the intake was quantified by the number of *mates*, instead of daily volume.

In a hospital-based case-control study (26), those drinking 1.5 L or more of very hot *mate* per day had nearly 5 times the risk for laryngeal cancer, after adjusting for alcohol and tobacco consumption (OR 4.9; 95%CI: 1.7–14.3). There were no differential effects, whether the lesions were glottic or supraglottic. Phenolic compounds present in the *mate* were postulated to play a carcinogenic role, and the *mate* itself was postulated to be a solvent of the carcinogenic compounds contained in tobacco. Using the same methodology, the same authors studied the risk factors for oropharyngeal tumors, finding black tobacco, alcohol (wine and liquor), and *mate* consumption to be independent and statistically significant factors (27).

Another study in Uruguay (28) found an increased risk for tongue cancer of 2.5 (95%CI: 1.2–5.6), adjusted for tobacco,

alcohol, and diet, among those drinking 2 L or more of *mate* per day (with no mention of the temperature of the drink or the habit duration).

A review published in 2001 has evaluated the incidence and mortality rates according to risk factors for mouth cancers in Latin America (29), paying particular attention to dietary factors such as red meat, particularly barbecued meat, and hot drinks. In the case of Brazil, Wunsh-Filho stated that in addition to alcohol and tobacco consumptions, conditions present among low-income populations—nutritional deficiencies and poor oral hygiene—may play a part in an increase risk for oral cavity and pharyngeal cancers (30). Franco et al., again in Brazil, found that, after adjusting for alcohol and tobacco, the risk of oral cancer doubled for people who brushed their teeth infrequently versus those brushing daily (31).

In two other reviews, *mate* consumption was suggested to play a role in the development of oral and oropharyngeal cancers, although the exact process was not identified (32, 33).

Cancer of the bladder. The thermal injury hypothesis would not explain a higher risk of malignant tumors in organs that do not come into direct contact with the hot beverage. In a study aimed at assessing the role of different types of tobacco on bladder cancer (34), an increased risk was found relative to daily *mate* intake with a multiplicative association regarding number of cigarettes smoked. No excess of risk was reported for habit duration or age at onset. However, it was not possible to rule out some bias, for example, by including patients with other tumors as controls, rather than only healthy individuals.

In 2007, there was a new analysis (35) of a study published previously that had aimed to identify the possible effects of arsenic exposure on bladder cancer occurrence in Argentina (36). The research consisted of a case-control study, with hospitalized bladder cancer patients, residents of a geographic area where arsenic was present in the water. The consumption of *mate cocido*, as well as *mate con bombilla*, was studied during three periods of the subjects' lives: at the time of the survey, at 20 years prior to it, and at 40 years prior. It was found that there was no significant increased risk for *mate cocido* consumption. However, there was a 4-fold increased risk for smokers and alcohol drinkers (OR 3.77; 95%CI: 1.17–

12.1) who were drinkers of *mate con bombilla* at least 20 years prior to the study.

Another study, carried out in Argentina (37) in 1983–1985, evaluated the effect of the tobacco habit and exposure to certain occupational hazards on the occurrence of bladder cancer; *mate* intake, taken into account as a possible risk factor, did not increase the risk.

Other cancers. The effect of *mate* was also considered in a case-control study carried out in Uruguay on patients with kidney cancer (38). It was found that there was a 3-fold increased risk, adjusted for other factors, for individuals that reported drinking 2 L or more of *mate* per day. The authors postulated that the presence of caffeic acid and/or the diuretic effect of *mate* could be associated with increased risk.

The same authors, using the same questionnaire, found an association between lung cancer risk and *mate* consumption (both quantity and habit duration as risk factors) (39). The effect was more evident in the small cell and squamous cell type lung cancer patients than in adenocarcinoma lung cancer patients. In this study, the presence of Benzopyrene (BP), a carcinogenic polycyclic aromatic hydrocarbon (PAH) in *mate* was postulated to be a possible action mechanism.

In 1974–1975, an ecological study (40) was conducted in several cities in Brazil to assess the association between cancer mortality and dietary factors. An association was found between *chimarrão* (unsweetened *mate*) and esophageal, colon, and lung cancer mortality; however, the results may be influenced by ecological bias.

Studies on the prevalence of consumption

A survey of 719 randomly-selected households in the south of Brazil collected data on the prevalence of different modalities of *mate* drinking (41). A questionnaire was administered to 1 388 participants, 33.6% of whom were not drinkers of *mate*. In the homes in which at least one *mate* drinker was present, one subject was asked to complete a more detailed questionnaire. A higher frequency of consumption and a higher temperature of ingestion were found in men (an average of 71.1°C in men vs. 67.6°C in women, $P < 0.001$). The survey also found a higher daily volume drunk among individuals who were also alcohol drinkers or cigarette smokers.

A small, descriptive study conducted in northeastern Argentina (42), where *mate* drinking is very prevalent, collected the clinical histories of 117 cases of esophageal cancer, with little data on *mate* consumption. This study cannot be used to estimate either the prevalence (since cases were recruited on a hospital basis) or the relative risk (since no control group was included).

Other studies

Clinical/experimental (in vivo: humans and animals). The possible genotoxic activity of *mate* was studied in samples drawn from the esophageal mucosa; the patients were interviewed on their habits after the endoscopy (43). The findings indicated a higher frequency of micronucleus among the tobacco smokers and *mate* drinkers; however, the significance of the micronucleus in tumor occurrence has still to be understood.

Commercial forms of *yerba mate* could contain PAH due to the drying process (1, 2). As early as 1941, research by Dr. Angel Roffo referred to the tar content of *yerba mate* extracts and the occurrence of skin tumors in experimental animals painted with a *yerba mate* mixture (44).

In another study, a metabolite of BP, 1-hydroxypyrene glucuronide, was found in urine samples of healthy individuals (45). Its concentration varied according to cigarette and *mate* consumption and with the exposure to *asados* (open fire used for barbecuing meat). This observation led the authors to conclude that the population could be exposed to certain levels of PAHs through tobacco smoking, as well as *mate* drinking and inhaling *asado* smoke. The presence of different genotypes was strongly associated with the levels of BP metabolite, 1-hydroxypyrene glucuronide (46), in urine.

In 1985, the presence of BP was assessed in samples of commercial brands of *yerba mate* (47). Concentrations of BP as high as 461 µg/1 Kg dry *mate* were found; lower concentrations were found in the prepared beverage.

Zuin et al. reported an effective and simple procedure to analyze PAHs in *mate* infusions. The method found 15 PAHs in 11 *mate* brands available on the market in Brazil (48).

In 2008, a study measured PAHs in *mate* brands on the market in Brazil (49). The researchers found that *mate* leaves contained PAH concentration ranging from 2–11 times that of green tea leaves.

High mass fractions of carcinogenic PAHs were found, not only in dry leaves, but also in hot and cold *mate* infusions. The PAH measurements were of good quality and the estimation of its intake mimicked real-life consumption.

Preliminary results of a study carried out on esophageal cancer patients highlighted the presence of polymorphisms in enzymes of the P450 cytochrome group in the esophageal mucosa (50). Some of these polymorphisms were different from the ones found previously in other populations. These enzymes are involved in the metabolism of polycyclic aromatic hydrocarbons and nitrosamines, both substances capable of promoting esophageal tumors in animals. The enzymatic polymorphisms together with certain mutations encountered could explain some of the differences in the risk of esophageal cancer among different populations groups.

To understand the possible injuries due to *mate* intake, apart from those that could be ascribed to temperature, a study was carried out on experimental animals, exposing rats to *mate* drinking for the remainder of their lives (51). The *mate* infusion was administered at room temperature, after having been prepared with hot water. A histological examination of the upper aero-tract, stomach, esophagus, duodenum, pancreas, bladder, and kidney was conducted five months into the experiment. Significant differences were found, especially in the incidence of tracheitis and bronchiolitis, between the groups that drank *mate* and the controls that drank only water. There was only one occurrence of a tumor, a mediastinal mesothelioma. This study indicated that, at least for this animal model, continuous *mate* consumption during a large part of its life, could affect the upper aerodigestive tract, but was not causing tumors in the esophagus, oral cavity, bladder, or kidneys.

The effect of drinking hot water was studied in an interesting experimental model (52). It found that, for F344 rats, drinking tea had a protective effect against esophageal carcinogenesis induced by N-nitrosomethylbenzylamine. This protective effect of substances present in tea was inhibited by the action of hot water (over 55°C), and it was concluded that, in this model, drinking hot water increased the risk of esophageal cancer.

Experimental, in vitro. The impact of heat on the esophageal epithelium was

studied on sections of rabbit esophagus mounted on culture chambers that imitate the conditions of *in vivo* hot intakes (53). The study showed that, although the oral cavity partially modulates the temperature of the liquid that arrives to the esophagus, the structure and the functions of the esophageal epithelium can be damaged by heat stress. A study on genotoxicity using *Saccharomyces cerevisiae* model (54) found that the treatment of the cultures with *mate* infusion at 30°C was only capable of inducing a very low mutagenic effect. The highest mutagenic effect found for this model was obtained by hyperthermia (54°C). This effect was also dependant on time of exposure. The hot caffeine was also observed to be mutagenic to the system. The mutagenic effect was lower than hyperthermia alone, but higher than the one observed due to the action of *mate* at 54°C. The authors suggested that the hot caffeine and *mate* infusions could decrease the mutagenic effect of the hyperthermia by leading the lesions induced in the DNA into an error-free repair system.

Aqueous extracts of *Ilex paraguariensis* were observed (55) to be genotoxic for *Escherichia coli* and *Salmonella typhimurium*, but the addition of S9 microsomal fraction, capable of intervening in various metabolic steps, counteracted the genotoxic activity. The *mate* extracts also produced an increased number of chromosomal aberrations in human lymphocytes. On the other hand, the capacity of *mate* extracts to inhibit cellular proliferation through its content in flavonoids has also been suggested (56). The flavonoids, among which chlorogenic acid is the most important in *mate* extracts, were able to inhibit the proliferation of a human oral carcinoma cell line through the inhibition of topoisomerase II. The total content of flavonoids varied among the commercial brands studied, and no correlation was found between their quantity and the degree of inhibition of topoisomerase in cell cultures.

DISCUSSION AND CONCLUSIONS

Mate drinking is very common in some parts of South America, and several studies in Argentina, Brazil, and Uruguay have examined the possible role of *mate* in cancer of the esophagus, larynx, and oropharynx (6–8, 10, 14, 15). Many publications are analyses of epidemiological studies carried out in Uru-

guay, beginning in 1985. The same group of authors, with occasional contributions of investigators from other countries, participated in the studies.

In general, almost all epidemiological studies included in this review shared similar methodology: hospital-based, case-control studies where participants were personally interviewed on the main risk factors, using similar questionnaires. Controls were recruited from among hospital patients suffering from diseases apparently not related with the risk factors in question. Choosing to use hospitalized controls could be a cause of confounding in the results. From a methodological point of view, it would have been more appropriate to use subjects from the general population in the control groups, but this would probably have added a significant complexity to the logistics of the studies.

The tobacco and alcohol consumption habits, fresh vegetables and fruits intake, and tea, coffee, and mate drinking were shown, in general, to be mutually correlated. Even if the presence of possible biases were controlled at the moment of analysis, the results could be influenced by residual confounding. The synergic action between mate, alcohol, and tobacco was a clear result in several studies.

An important source of inaccuracy regarding the volume of *mate* consumed might be simply the challenge of remembering how much one has drunk, especially if estimating over the course of a lifetime. Moreover, in different studies, *mate* consumption was expressed in different units, adding to the difficulty of drawing accurate comparisons among them.

Many of the studies used a general questionnaire designed to find associations between dietary and occupational factors and cancer. If a questionnaire specific to *mate* consumption were used, estimates of the risks might be more accurate. New studies using questionnaires focused on *mate* consumption are recommended to achieve more precise results.

It is unlikely that the participants' responses regarding the habit of drinking *mate* (essentially the quantity and temperature) were influenced by prior knowledge of its health effects—public awareness of the issue is low. Past studies referencing the issue of hot *mate*, especially those linking it to cancer, were not widely disseminated. However, future studies should take into account that awareness of the possible association of

hot *mate* with the risk of tumors is increasing and responses may be biased in the future.

In most publications reviewed, there is a lack of data regarding the socioeconomic level of individuals interviewed. However, it was found that for esophageal cancer, the socioeconomic level was inversely related to risk and directly linked to alcohol consumption, nutritional deficiencies, tobacco habit, poor oral hygiene, and infections associated with some types of agents (20).

In interpreting the epidemiological results, the mechanisms mentioned were the temperature of consumption and/or the chemical content of the *mate* itself. The risk for esophageal cancer due to hot *mate* consumption—as *mate con bombilla* or *mate cocido*—and the absence of effect from cold *mate* (5, 7, 13–15) sustain the hypothesis of a thermal action as the cause of the increased risk. This hypothesis agrees with observations reported from an area in Iran where the incidence of esophageal cancer is high and very hot tea is drunk (22). It has also been postulated that the contact of hot liquids with the esophageal mucosa could increase gastric reflux, causing further damage from gastric acid (22).

Thermal injury caused by hot drinks was very difficult to investigate accurately because, in general, there was no exact, objective measurement of the temperature at which *mate* was drunk. A lack of precise measurement of *mate* temperature on contact with the different tissues could lead to errors and complexity when comparing studies. The temperature of the beverage was, in general, self-evaluated, defined subjectively as “warm,” “hot,” and “very hot,” and these categories presented only limited correlation with thermometer readings (17).

In addition, the quantity of water added to the quantity of leaves when preparing *mate con bombilla* varies from person to person. This presents a problem for inter- and intra-study comparisons. Likewise, since drinking *mate* in South America is often a social activity during which a group of drinkers partake from the same vessel, estimations of volume ingested by the individual can be inaccurate. Moreover, the size of the *mate* vessel can differ, adding to the imprecision.

The thermal injury hypothesis does not validly explain an excess of cancer risk in organs with which the hot beverage does not come into direct contact. In a study where an increased risk of

bladder cancer was found relative to the daily intake of *mate*, the results may have been biased by including patients with other tumors as controls (34).

Different concentrations of PAHs were found in *yerba mate* leaves of different commercial brands, and in cold and hot infusions (48, 49). These results could support the hypothesis that the cancer risk associated with *mate* intake could be related not only to its temperature, but also its level of carcinogenic compounds. The more traditional *mate con bombilla* involves adding water to the same batch of leaves several times and drinking several cups consecutively. This could expose the *mate* drinker to a higher level of PAHs, than they would otherwise be exposed to if the drink were prepared once, as is the case with common tea, and the leaves discarded. It would be interesting to know the PAH levels of the various different brands and consumption habits, as well as the PAH level yielded by different processing techniques employed to dry, roast, and enhance the flavors of the fresh leaves (1, 2). Differences in these processes could produce differing levels of contaminants in the final products. However, the results of the genotoxic studies of *Ilex paraguariensis* extracts were not homogeneous (54–56).

In conclusion, there is no sound population-based case-control study on *mate* consumption as a risk factor for cancer available. This, coupled with the range of results on *mate* risk, make assessing the etiological fraction difficult.

The role that drinking of hot beverages plays on increasing the risk of cancer of the esophagus, larynx, and oral cavity seems to be supported by the results of several epidemiological studies, conducted mainly in South American countries. The temperature might act *per se* damaging the mucosa, or the heat may be accelerating certain metabolic reactions, including enhancing the effect of carcinogens, such as tobacco and alcohol. Thermal injury may be increasing gastric reflux, promoting contact with other irritants and carcinogenic agents. Moreover, contaminants, such as carcinogenic PAHs, present in processed *mate* support the hypothesis that in addition to temperature, carcinogens in processed leaves may be playing a role in cancer risk.

Bibliographic sources were widely and exhaustively searched up to August 2008, taking into account published papers and books from a variety of disciplines. There may have been some com-

munications from scientific meetings that were not included as data sources, but it is unlikely this would produce a bias in our conclusions.

More research needs to be done before a definitive statement can be made regarding cancer risk associated with any

of the various forms of *mate* consumption. Future research should include:

- Population-based studies;
- Collection of data on consumption of tobacco, alcohol, hot drinks, fresh fruit, and vegetables;

- A method to precisely measure volume and temperature of *mate* intake.

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RESUMEN

Cáncer y consumo de yerba mate: revisión de posibles asociaciones

Objetivo. Identificar posibles vínculos entre el consumo de mate y el cáncer, en particular de esófago, laringe y cavidad bucal.

Métodos. Se realizó una revisión de la bibliografía publicada hasta agosto de 2008 sobre el riesgo carcinogénico del consumo de mate en dos bases de datos, MEDLINE y TOXLINE. Se revisaron las referencias bibliográficas de los artículos para encontrar fuentes adicionales y se buscó por cada autor que hubiera publicado sobre el tema. Los estudios epidemiológicos se presentan según la localización del cáncer, los trabajos experimentales se examinan en secciones separadas y en la discusión se combinaron los datos epidemiológicos y experimentales.

Resultados. Casi todos los estudios epidemiológicos siguieron la misma metodología: estudios de casos y controles basados en hospitales donde se entrevistaba personalmente a los participantes acerca de los principales factores de riesgo mediante cuestionarios similares. En algunos estudios se encontró una asociación entre la temperatura de la infusión de mate y el riesgo de cáncer bucal, de esófago y de laringe, mientras que unos pocos se concentraron en los contaminantes carcinogénicos introducidos durante el procesamiento industrial de las hojas. El tipo de cáncer más frecuentemente mencionado en asociación con el mate caliente en bombilla (tomado a través de una cañita metálica) fue el de esófago. El tamaño de la muestra, la evaluación de la exposición, el método de análisis y la calidad variaron de un estudio a otro. Los resultados variaron considerablemente. Se estimó un mayor riesgo (razón de posibilidades = 34,6) en las mujeres que tomaban 1 L diario o más; en los hombres este riesgo fue solo de 4,8. El riesgo aumentó con el tiempo de consumo, la cantidad diaria y la temperatura de la infusión consumida. En algunos estudios se observó una clara sinergia entre el consumo de mate, alcohol y tabaco, mientras que en otros las deficiencias nutricionales y la inadecuada higiene bucal desempeñaron un papel importante. No se observó aumento en el riesgo asociado con el consumo de bebidas frías de mate.

Conclusiones. Varios estudios epidemiológicos parecen respaldar el papel de las bebidas calientes de mate en el aumento del riesgo de cáncer de esófago, laringe y cavidad bucal. La temperatura podría influir al dañar la mucosa o acelerar algunas reacciones metabólicas, entre ellas con algunas sustancias carcinogénicas del tabaco y el alcohol. No obstante, no se encontraron estudios robustos de casos y controles basados en la población sobre el consumo de mate como factor de riesgo de cáncer. Esto, unido a los resultados encontrados sobre el riesgo del consumo de mate, hace difícil estimar su fracción etiológica. Se requieren más investigaciones antes de establecer definitivamente el riesgo de cáncer asociado con alguna de las diversas formas de consumo de mate. Se deben realizar estudios basados en la población, obtener más datos sobre el consumo de tabaco, alcohol, bebidas calientes, frutas frescas y vegetales y se deben emplear métodos que permitan medir con precisión el volumen y la temperatura del mate consumido.

Palabras clave

Neoplasias laríngeas, neoplasias esofágicas, neoplasias faríngeas, *Ilex paraguariensis*, revisión, Argentina, Brasil, Paraguay, Uruguay.