Mate Drinking, Alcohol, Tobacco, Diet, and Esophageal Cancer in Uruguay

Eduardo De Stefani, Nubia Muñoz, Jacques Estève, Alberto Vasallo, Cesar G. Victora, and Sibylle Teuchmann

ABSTRACT

A case-control study was conducted in Uruguay to investigate the role of mate drinking, alcohol, tobacco, and certain dietary factors in the etiology of esophageal cancer. The study included 261 patients with squamous cell carcinoma of the esophagus and 522 hospital controls matched by sex and age. A strong association with a clear dose-response relationship was observed with the amount of mate drunk daily and duration of the habit. The relative risk for those drinking over 2.5 liters of mate per day was 12.2 (95% confidence interval, 3.8-39.6) after adjusting for the effects of age, area of residence, alcohol, and tobacco. Strong associations were also observed with tobacco smoking and alcohol drinking which appear to act in a multiplicative way. The relative risk for those who smoke and drink heavily compared to that of light smokers and drinkers was 22.6. The risk associated with black tobacco was about three times higher than that associated with blond tobacco. A clear protective effect was found for the consumption of fruits and vegetables but a dose-response relationship was present only for fruits. Finally, an increased risk was also found for those eating barbecued meat daily.

INTRODUCTION

Esophageal cancer is characterized by worldwide geographical variation in incidence and mortality rates, even within small areas (1). In South America, the highest rates have been reported in Uruguay, a small country which shows large variation in the rates of esophageal cancer. The mortality rates for males range from 40 per 10^5 in the northeast region, which borders Brazil, to 10 per 10^5 in the capital city of Montevideo (2). The death rates are lower for females, with a male/female ratio of 3.8 for the whole country.

Cancer of the esophagus can be divided into those cancers essentially due to alcohol and tobacco and those in which these two factors do not appear to play an important part. The joint effect of tobacco and alcohol exposures accounts for about 80% of the etiology of the disease in North America (3), South America (2, 4), Europe (5), South Africa (6), and some Asian countries (7).

On the other hand, in areas with extremely high incidence such as Iran and China, alcohol and tobacco appear to play a minor role (8, 9) and the main risk factors remain to be identified. There is evidence suggesting that opium tar may be the major cause in Iran (10), and N-nitroso compounds have been proposed as possible etiological candidates but convincing evidence is still lacking in China (11).

Factors producing chronic injury to the esophagus, such as rough foods, hot beverages, and certain vitamin deficiencies, may increase susceptibility to carcinogens.

Esophageal thermal injury resulting from drinking hot beverages is a very difficult issue to study epidemiologically because of the widespread consumption of these drinks and the unreliability of data on temperature obtained through interviews.

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High risk areas in South America (southern region of Brazil, Uruguay, and Argentina) offer a unique opportunity to study this problem. This is due to the fact that their populations share the habit of drinking large quantities of a local tea, known by the folk name of mate. This beverage, an infusion of the herb Ilex paraguayensis, is drunk very hot through a metal straw. Despite the fact that the prevalence rate of exposure is over 80%, there remains a well-defined nonexposed group. A previous case-control study in Uruguay, in which routinely collected information on mate drinking was extracted from the clinical records of patients with esophageal cancer and other cancers, showed a strong association with mate drinking (RR = 4.7, 95% CI = 1.9-12.1), after adjusting for the effects of age and alcohol and tobacco consumption (2).

Although a subsequent case-control study in southern Brazil did not show a strong association between mate drinking and esophageal cancer, the moderate increase in risk and the high prevalence of mate drinking in this population could account for a considerable proportion of esophageal cancers occurring (4).

This case-control study was designed to obtain further information on the hypothesis that mate ingestion is associated with the risk of developing esophageal cancer.

SUBJECTS AND METHODS

The basic protocol utilized in the Brazilian study (4) was used in this study. The Brazilian questionnaire was adapted to the local situation of Uruguay, especially in relation to type of tobacco and diet.

In the study period from July 1985 to September 1988, 283 cases with clinical and/or radiological diagnosis of esophageal cancer were admitted to the four main hospitals in Montevideo. These centers have a catchment area which covers 45% of the population of Montevideo and about 55% of the rest of the country. Patients treated in these hospitals are covered by Social Security medical care and have rather low incomes. Conditions for eligibility were: (a) to have histological diagnosis of squamous cell carcinoma; (b) to have been diagnosed within the previous 4 months; (c) to have lived in the country for at least 5 years; (d) to have been diagnosed at least 5 years; (e) to have been in sufficiently good physical and mental health to give reliable answers to the questionnaire. Proxy interviews were not accepted. Cases were ascertained shortly after clinical diagnosis through the hospital cancer registries operating in the participating centers.

None of the patients refused to be interviewed and 15 patients were excluded, 12 because no histological confirmation was available and three because of a diagnosis of adenocarcinoma. Of the remaining 268 patients, seven could not be interviewed due to terminal illness. The remaining 261 patients were included in the study. For each case, two controls matched by age (±5 years) were interviewed. Conditions for eligibility were: (a) to be admitted to the same hospital; (b) not to have a diagnosis of tobacco and/or alcohol-related diseases; (c) to live in the country or for at least 5 years. The main diagnostic categories among the controls are listed in Table 1.

The questionnaires were completed by four trained social workers. Information was collected on socioeconomic status (education, income, and occupation); on the lifetime habits of drinking mate, coffee, and tea (quantity, duration, and temperature); alcohol drinking (dose, expressed in milliliters of alcohol, duration, and type of alcoholic beverage); and tobacco smoking (type of tobacco, duration, intensity, and cessation periods). Dietary habits were assessed in two time periods:

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the period just before the onset of symptoms and 10 years before admission to the hospital. A food frequency questionnaire was used to assess the consumption of the various food items. The same 10 food groups used in the Brazilian questionnaire were included, i.e., fresh vegetables, fresh fruits, fats, and dairy products.

The statistical analysis was done by linear logistic modelling (12) using the unconditional method with the GLIM software (13). An unconditional analysis was done because it is generally accepted that in a matched study, this analysis can be performed if appropriate adjustment is made for the matching variables that in this study were sex, age, and residence when a common relative risk for male and female was estimated. Adjustment for residence was made because it is known that the rates for esophageal cancer are higher in rural than urban areas in Uruguay. Trend tests were performed by adjusting a linear model using the numbers of the categories as covariate and the risk increases significantly after an average consumption of 50 ml of pure alcohol per day in males and earlier in females. Among the latter, however, the estimates are unstable due to the small number of drinkers. The trend tests for testing the effect of alcohol and tobacco are nevertheless highly significant ($\chi^2$ with one degree of freedom are respectively, 4.9 and 5.5), and the interaction between tobacco, alcohol, and sex was not significant but the CIs were very wide. As only two female drinkers were included in the study, the effects of their smoking habits could not be evaluated separately from the smoking habits of non-drinkers. The results obtained with the unconditional analysis were practically identical to those obtained with the unconditional one. Relative risk estimates were approximated by odds ratios adjusted simultaneously for all relevant categorized cofactors. The statistical analysis for the main risk factors yielded similar results for both subgroups and in addition the $\chi^2$ tests for heterogeneity were nonsignificant. Thus both subgroups were combined in the final analysis.

**RESULTS**

A total of 261 cases (199 males, 62 females) and 522 controls were included in the study. Their distribution by age, sex, residence, education (years of schooling), income, and some risk factors is given in Table 2. Cases, especially males, are more often rural and have lower socioeconomic status than controls. The association of these variables with esophageal cancer was evaluated as follows.

Effects of Alcohol and Cigarette Consumption. Tobacco smokers and alcohol drinkers were defined as those who smoked or drank alcoholic beverages, for at least 1 year, independently of the amount. Cases and controls were classified according to the lifetime consumption of cigarettes and alcoholic beverages, duration and daily consumption.

The distribution of alcohol and cigarette consumption being very different in males and females, the evaluation of these risk factors has been done separately for each sex. Table 3 shows the relative risks and their CIs for various levels of consumption.
with years since quitting: the RR values adjusted for age, were found to modify significantly the risk. The assessment of categories), and duration (five categories), no effect of age at whereas wine and hard liquor increased the risk by the same effect between beverages. Beer did not contribute to the risk, given by the sum of the three types of alcoholic beverages, the drinkers. On the other hand, heavy drinkers tend to drink more beer and wine and less spirits than heavy distribution differs between cases and controls. Light drinkers of type of alcohol consumed by the study subjects changes with non-drinkers and occasional drinkers 0.48 (0.29-0.81) (P = 0.001).

Influence of the Type of Alcoholic Beverage. The distribution of type of alcohol consumed by the study subjects changes with their total consumption of alcohol; as a consequence, this distribution differs between cases and controls. Light drinkers tend to drink more beer and wine and less spirits than heavy drinkers. On the other hand, heavy drinkers tend to drink more spirits than light drinkers. Since total alcohol consumption is given by the sum of the three types of alcoholic beverages, the average linear increase for each of them separately was calcu male exdrinkers (P = 0.01) and there was a significant trend with years since quitting: the RR values adjusted for age, residence, and amount of cigarettes per day, with the regular drinkers as reference category, were as follows: 1-9 years since quitting 0.78 (95% CI, 0.48-1.26), >10 years 0.46 (0.23-0.92), number for each milliliter of pure alcohol added. Therefore, in addition, 64% of cases and 40% of controls smoked black black tobacco only. This difference was highly significant after controlling for daily dose of alcohol and tobacco. The risk for those who have smoked mainly black tobacco compared to that of those who smoked mainly blond tobacco was 2.6 (95% CI, 1.7-3.9). For mixed smokers, mainly black tobacco smokers were those who have smoked more black tobacco than blond tobacco over their life-span. Moreover, the effect of type of tobacco combines multiplicatively with duration of smoking (Table 5).

Among male smoker patients, 19% used filter cigarettes against 28% among controls. This apparent protective effect of filters was however no longer significant after adjustment for alcohol, cigarette consumption, and type of tobacco: the use of filter cigarettes was in fact similar in cases and controls after stratification by type of tobacco.

No cases or controls used pipes or cigars.

Dietary Factors. In the following analyses, all risk evaluations were made after adjustment for age, sex, region, alcohol, duration of cigarette smoking, and type of tobacco smoked. The current and past frequencies of consumption of the 10 food groups were compared between cases and controls and no significant differences were found. Therefore the current consumption was used in the analysis. The 10 food groups were fresh meat, preserved meat, barbecued meat, fat, dairy products, eggs, cereals, potatoes, vegetables, and fresh fruits. Table 6 reports the results for those food groups which have been suspected of influencing the risk of esophageal cancer. A clear protective effect and a significant dose-response relationship was found with the consumption of fresh fruits. A reduction in risk was also observed with the consumption of vegetables but without significant dose response. A significant increase in risk

### Table 3 Relative risk for cigarette and alcohol consumption adjusted for each other and for age and residence (confidence interval in parentheses)

<table>
<thead>
<tr>
<th>Cigarettes (per day)</th>
<th>No. cases</th>
<th>No. controls</th>
<th>Adjusted RR</th>
<th>No. cases</th>
<th>No. controls</th>
<th>Adjusted RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>7</td>
<td>56</td>
<td>1</td>
<td>41</td>
<td>105</td>
<td>1</td>
</tr>
<tr>
<td>1-7</td>
<td>14</td>
<td>54</td>
<td>1.93 (0.7-5.4)</td>
<td>11</td>
<td>11</td>
<td>2.27 (0.9-6.0)</td>
</tr>
<tr>
<td>8-14</td>
<td>28</td>
<td>75</td>
<td>2.66 (1.1-6.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15-24</td>
<td>62</td>
<td>101</td>
<td>4.26 (1.7-10.4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25+</td>
<td>88</td>
<td>112</td>
<td>4.62 (1.9-11.1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol (ml per day)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>26</td>
<td>100</td>
<td>1</td>
<td>38</td>
<td>88</td>
<td>1</td>
</tr>
<tr>
<td>1-24</td>
<td>16</td>
<td>61</td>
<td>0.85 (0.4-1.8)</td>
<td>12</td>
<td>24</td>
<td>1.04 (0.4-2.4)</td>
</tr>
<tr>
<td>25-49</td>
<td>12</td>
<td>51</td>
<td>0.71 (0.3-1.6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50-149</td>
<td>50</td>
<td>117</td>
<td>1.37 (0.8-2.4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>150-249</td>
<td>46</td>
<td>38</td>
<td>3.57 (1.9-6.7)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>250+</td>
<td>49</td>
<td>31</td>
<td>5.27 (2.7-10.2)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 4 Age and residence-adjusted relative risks for the joint effect of alcohol and tobacco consumption

<table>
<thead>
<tr>
<th>Alcohol (ml per day)</th>
<th>Cigarettes per day</th>
<th>Total (RR for alcohol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-49</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>50-149</td>
<td>2.7</td>
<td>6.5</td>
</tr>
<tr>
<td>150-249</td>
<td>3.9</td>
<td>21.5</td>
</tr>
<tr>
<td>250-349</td>
<td>10.4</td>
<td>30.0</td>
</tr>
<tr>
<td>350+</td>
<td>22.7</td>
<td>22.6</td>
</tr>
<tr>
<td>Total (RR for cigarette)</td>
<td>1</td>
<td>3.1</td>
</tr>
</tbody>
</table>

Table 5 Age, residence, and alcohol adjusted relative risks (95% CI)* for duration of smoking and type of tobacco (males only)

<table>
<thead>
<tr>
<th>Duration of cigarette smoking (years)</th>
<th>Type of tobacco</th>
<th>Duration (years) adjusted for type of tobacco</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-24</td>
<td>Mainly blond</td>
<td>3.2</td>
</tr>
<tr>
<td>25-44</td>
<td>Mainly black</td>
<td>8.1</td>
</tr>
<tr>
<td>45+</td>
<td></td>
<td>2.5 (1.1-5.7)</td>
</tr>
<tr>
<td>Type of tobacco adjusted for duration</td>
<td>4.4</td>
<td>9.0</td>
</tr>
<tr>
<td></td>
<td>3.3 (1.5-7.3)</td>
<td></td>
</tr>
</tbody>
</table>

* The estimation was carried out within the set of male smoker cases and controls.

* The χ^2 for interaction between the two factors is 1.15 with 2 df.
for those who eat barbecued meat daily was observed but without a significant dose-response relationship. However, the increase in risk for those who eat barbecued meat daily persisted after adjusting for meat consumption. No clear effect for fresh meat and fat and no significant associations with the other food groups were observed.

**Mate Drinking.** Mate drinking is very common in Uruguay. Only 9% of controls and 2% of cases were nondrinkers. There was a clear dose-effect relationship between amount of mate drunk each day and the risk of esophageal cancer (Table 7). There was also a less convincing but significant relation with duration of use. The slope of the dose-effect relationship was the same for both sexes in each alcohol consumption category and in all smoking categories. There was, however, a significant absence of effect among blond tobacco smokers (x² = 8.3 on 2 df). There was no significant interaction with any other available factor. The slope of the dose-effect plot was larger among the rural population, but not significantly so.

**Interaction for Tobacco Smoking, Alcohol, and Mate Drinking.** Interaction terms for tobacco smoking, alcohol, and mate drinking, and socioeconomic status were calculated and found nonsignificant as expected from the size of the study.

**Influence of Temperature of Hot Beverages.** The reported temperature of beverages other than mate was not associated with the risk of esophageal cancer. The temperature of mate had a nonsignificant significant effect: the slope of the dose-effect relationship was lower among people who reported hot mate drinking, and higher and identical among those who report warm or very hot. The effect of dose of mate was nevertheless significant in the three categories of drinkers.
and cooked vegetables. No clear effect of fresh meat was found. A protective effect was found in France (26), but an increased risk has been associated with fresh meat in Brazil (4). A clear increase in risk was observed for those eating barbecued food daily compared to those eating them less frequently, even after adjusting for meat consumption. This observation is contrary to the findings of a similar case-control study carried out in a neighboring area (4), but it is consistent with laboratory investigations showing the presence of animal carcinogens and mutagens in barbecued foods formed by the pyrolysis of proteins (27).

The present study was designed to study further the association with mate drinking. A strong association with a clear dose-response relationship was observed with the amount of mate drunk daily. The RR for those drinking over 2.5 liters per day was 12.2 (95% CI, 3.8–39.6), after adjusting for age, tobacco, and alcohol. A less strong and less clear dose-response relationship was observed with duration of the habit. The fact that the mate effect was present among nonsmokers and light smokers, and among smokers of black tobacco but not smokers of blond tobacco, is puzzling. The possibility that blond tobacco smokers were from a higher socioeconomic level and had a higher intake of fruit and vegetables was considered, especially in view of a greater effect of mate drinking among the rural population, but it was not confirmed. The finding of a significant but not consistent effect of the temperature at which mate is drunk is not surprising considering the subjectivity in the perception of temperature. To evaluate the degree of misclassification in the reported temperature at which mate is drunk, a validation study is being carried out in Southern Brazil and in Montevideo.

There are two possible mechanisms through which mate drinking could increase the risk of esophageal cancer. First, the plant extract may contain carcinogenic or promoting substances. This possibility was raised in a previous study carried out in Uruguay (2), but laboratory studies have so far not demonstrated any promoting or mutagenic activity.3 Secondly, hot mate drinking may increase the susceptibility of the esophagus to carcinogens. Several epidemiological studies point towards a possible effect of hot drinks on esophageal cancer incidence. Ecological studies from Japan (28), the Soviet Union (29), and northern Iran (30) have suggested that inhabitants of high risk areas drink larger quantities of hot tea than those of low risk areas. Also in Iran, Singapore, and Puerto Rico case-control studies indicated similar differences (8, 31, 32). A prospective study carried out in Japan (25) also showed a higher risk among those drinking hot green tea.

A possible effect of mate drinking on precancerous lesions of the esophagus has been demonstrated in an endoscopic survey carried out in Rio Grande do Sul (33). In addition, a recent study on chronic esophagitis among young subjects in a high risk population for esophageal cancer in China, the strongest risk factor found for esophagitis was the consumption of beverages at burning hot temperatures.4 Experimental animal data suggest that hot drinks may potentiate the effect of esophageal carcinogens (34). The above observations, and in particular the finding that mate drinking increases the risks of esophagitis, suggest that mate itself may not contain specific carcinogens but that its effect may be due to chronic thermal injury of the esophagus increasing the susceptibility of the esophagus to carcinogens such as those contained in tobacco tar. Results from the previous studies in Uruguay and Brazil and the present one support this possibility.

A direct test of whether mate exerts its effect through direct carcinogens or through chronic thermal injury is being carried out in Paraguay, where the habit of drinking mate is also widespread. There it is mainly drunk cold and the esophageal cancer rates are lower than in Southern Brazil, Uruguay, and northeastern Argentina.

Finally, since this study was hospital based, the possibility of selection bias should be considered. The possibility of this bias among cases cannot be evaluated but it was attempted among controls. The inclusion of patients with other cancers in the control group did not appear to affect the associations detected.

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