RESEARCH ARTICLE

Diet Patterns and Risk of Squamous Cell Oesophageal Carcinoma: A Case-control Study in Uruguay

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Abstract

Background: Oesophageal cancer presents high incidence rates in the so-called Brazilian-Uruguayan belt. Materials and Methods: The present study included 1,170 participants (234 cases and 936 controls) which were analyzed by unconditional multiple logistic regression in order to examine risk of oesophageal squamous cell carcinoma (OESCC) associated with several food groups. Results: Boiled red meat (OR 2.59, 95%CI 1.69-3.97), lamb meat (OR 1.64, 95%CI 1.07-2.51), processed meat (OR 1.49, 95%CI 1.01-2.21), whole milk (OR 1.78, 1.19-1.68), fresh vegetables and fruits (OR 0.42, 95%CI 0.27-0.63), mate consumption (OR 2.04, 95%CI 1.32-3.16), and black tea (OR 0.10, 95%CI 0.04-0.28) were significantly associated with risk of OESCC. Conclusions: Hot beverages (mate) and hot foods (boiled meat) appear to be important determinants in the risk of OESCC, allowing the penetration of carcinogens in tobacco and alcohol into the oesophageal mucosa.

Keywords: Brazilian-Uruguayan belt - hot beverages - hot foods - mate drinks - black tea

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Introduction

Oesophageal cancer is a frequent malignancy in Uruguay, mainly in the northern counties, with age-standardised incidence rates of 55.8 for 100,000 men and 14.7 for 100,000 women (Vassallo et al., 1998; Barrios et al., 2010). This belt, similar to the Asian belt, includes the north-east counties of Uruguay and the southern areas of Brazil. The inhabitants of this high-risk area have the common habit of drinking large amounts of hot mate (a local beverage derived from the herb called Ilex paraguariensis) (Heck et al., 2007). Although it has been postulated that the noxious effects of mate are due to the hot temperature of the beverage (IARC, 1991), recent studies conducted in Brazil by local researchers and other researchers from the National Cancer Institutes of USA have suggested that mate drinks are rich in benzo(a)pyrene, a potent carcinogen (Fagundes et al., 2006; Kamangar et al., 2008). Therefore there is room for future studies on the relationship between oesophageal carcinoma and the habit of drinking hot mate.

In spite of the high rates observed in the Brazilian-Uruguayan belt, squamous cell cancer of the oesophagus has declined in the last decades (Barrios et al., 2010). Although the reasons for this decline are mostly unknown, the smoking of hand-rolled cigarettes filled with black tobacco and the consumption of salted meat, a kind of processed meat, have also declined lately, suggesting a potential relationship between the aforementioned habits and the incidence rate of squamous cell oesophageal cancer. Both are considered as a source of carcinogens for the oesophageal mucosa.

Moreover, the Uruguayan population has the first place in the world in beef consumption, surpassing countries which are heavy producers of beef, like Argentina, Australia, and New Zealand (Matos et al., 2002). Although the role of beef in the aetiology of oesophageal cancer is unclear because of conflicting evidence, several studies have suggested that red meat is positively associated with the risk of oesophageal cancer (Launoy et al., 1998; De Stefani et al., 1999; Bosetti et al., 2000; Cross et al., 2011; De Stefani et al., 2012).

For these reasons we decided to conduct a case-control study in Uruguay in order to clarify the role of several food items in the aetiology of this deadly malignancy. It should be emphasised that most Uruguayan cases are squamous cell carcinomas, with the adenocarcinoma of the distal oesophagus and gastric cardia being less frequent .

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Materials and Methods

Selection of cases

In the time period 1996-2005 all the newly diagnosed and microscopically confirmed squamous cell cancer of the oesophagus were considered eligible for the study. A total of 240 cases were eligible and 6 patients refused the interview, leaving 234 cases for inclusion in the study (response rate: 97.5%). All the cases were admitted to the four major public health hospitals, with patients belonging to the low socioeconomic strata of the Uruguayan population. Furthermore, 78.6% of the cases were males (184 cases), whilst the females amounted to 21.4% of the total number (50 cases) .

Selection of controls

In the same hospitals and in the same time period, patients afflicted by non-neoplastic conditions, not aetiologically related to smoking nor alcohol drinking, were considered eligible for the study. From an initial number of 1,537 patients, 45 refused the interview, leaving a final total of 1,492 controls (response rate: 97.1%). They were categorised by gender into 1,072 men and 420 females. From this pool of controls, we randomly selected 936 patients, frequency matched to the cases on age (in decennia), sex, and residence (Montevideo, other counties). They presented the following conditions: abdominal hernia (248 patients, 26.5%), eye disorders (168, 17.9%), prostate hypertrophy (146, 15.6%), fractures (75, 8.0%), benign breast diseases (75, 8.0%), diseases of the skin (48, 5.1%), varicose veins (37, 4.0%), acute appendicitis (36, 3.9%), hydatid cyst (32, 3.5%), injuries (30, 3.2%), blood disorders (21, 2.2%), and urinary stones (20, 2.1%).

Inteviews and questionnaire

Cases and controls were interviewed by two trained social workers, unawere of the objectives of the study. The interviews were performed face-to-face in the hospitals and proxy interviews were not allowed. The participants were administered a structured questionnaire which included the following sections: sociodemographics (age, residence, education, monthly income), a complete occupational history based on the last four jobs and its duration, self-reported height and weight five years before the date of the interview, a complete smoking history (age at start, age of quit, number of cigarettes smoked per day, type of cigarette, type of tobacco, inhalation practices), a complete history of alcohol drinking (age at start, age of quit, number of glasses drinked per day or week, type of alcoholic beverage), a complete history of non-alcoholic beverages (coffee, tea, mate), menstrual and reproductive events, and a food frequency questionnaire (FFQ) on 64 food items. This FFQ was considered representative of the Uruguayan diet and allowed the estimation of total amount of energy intake. Although the FFQ was not validated, it was tested for reproducibility with good results (Ronco et al., 2006).

Statistical analysis

Relative risks, approximated by the odds ratios, were estimated by unconditional multiple logistic regression (Rothman et al., 2008). We fitted the following model: age (continuous), sex, residence (Montevideo, other counties), education (categorical, 3 strata), income (categorical, 3 strata), body mass index (continuous), smoking status (categorical, 3 strata), smoking cessation (categorical, 4 strata), number of cigarettes smoked per day among current smokers (categorical, 5 strata), alcohol drinking (categorical, 5 strata), mate consumption (categorical, 4 strata), and total energy intake (continuous). The items to be studied were those included in the aforementioned model, either as categorical or continuous. In the case of meat, each type of meat was further adjusted for the other types of meat, in order to capture the total ingestion of this item. All the calculations were performed with the Stata software, release 12.1 (StataCorp, 2012).

Results

The distribution of sociodemographic variables and main risk factors for oesophageal cancer is shown in Table 1. As a result of the matched design of the study, age, sex, and residence were identical among both groups of participants. Also education, monthly income and hospital distribution were rather similar. On the other hand, cases smoked more frequently than controls and drunk significantly more alcohol and mate compared with the controls.

The effects of different types of meat are shown in Table 2. The highest risk was associated with boiled meat consumption (OR 2.59, 95%CI 1.69-3.97, p value for trend

Table 1. Distribution of Cases and Controls by Sociodemographic Variables and Main Risk Factors

Variable	Category	Cases No (%)	Controls No (%)	Global p value
Age (years)	40-49	19 (8.1)	76 (8.1)	
	50-59	46 (19.7)	184 (19.7)	
	60-69	75 (32.1)	300 (32.1)	
	70-79	71 (30.3)	284 (30.3)	
	80-89	23 (9.8)	92 (9.8)	1.00
Sex	Males	184 (78.6)	736 (78.6)	
	Females	50 (21.4)	200 (21.4)	1.00
Residence	Montevideo	92 (39.3)	368 (39.3)	
	Other counties	162 (60.7)	568 (60.7)	1.00
Education (yrs)	0-3	98 (41.9)	410 (43.8)	
	4-6	104 (44.4)	422 (45.1)	
	7+	32 (13.7)	104 (11.1)	0.54
Monthly income	<=146	92 (39.3)	357 (38.1)	
(US dollars)	147+	87 (37.2)	362 (38.7)	
	Unknown	55 (23.5)	217 (23.2)	0.91
Hospital	Cancer	79 (33.8)	312 (33.3)	
	Pasteur	94 (40.2)	373 (39.9)	
	Clinicas	37 (15.8)	148 (15.8)	
	Maciel	24 (10.2)	103 (11.0)	0.99
Smoking	Never smokers	48 (20.5)	345 (36.9)	
(pack years)	1-20	17 (7.3)	177 (18.9)	
	21-38	41 (17.5)	154 (16.4)	
	39-58	50 (21.4)	144 (15.4)	
	59+	78 (33.3)	116 (12.4)	<0.0001
Alcohol drinking	Never drinkers	73 (31.2)	422 (45.1)	
(ml/ethanol/day)	1-60	45 (19.2)	252 (26.9)	
	61-120	48 (20.5)	134 (14.3)	
	121-240	38 (16.2)	88 (9.4)	
	241+	30 (12.8)	40 (4.3)	<0.0001
Mate years	Never drinkers	11 (4.7)	111 (11.9)	
(liters/year)	1-40	56 (23.9)	294 (31.4)	
	41-63	81 (34.6)	274 (29.3)	
	64+	86 (36.7)	257 (27.5)	<0.0001
No patients		234 (100.0)	936 (100.0)	

<0.0001), followed by total meat (OR 1.81, 95%CI 1.22-2.68), lamb consumption (OR 1.64, 95%CI 1.07-2.51), and processed meat intake (OR 1.49, 95%CI 1.01-2.21). Among the broad group of processed meats, the highest risks were observed for salted meat and hot dogs. Fried beef and fresh fish were inversely associated with the risk of oesophageal cancer (OR for fish intake 0.57, 95%CI 0.37-0.86). Barbecue, poultry, and total white meat were not associated with squamous cell oesophageal cancer.

Odds ratios of oesophageal cancer for dairy foods, eggs, and desserts are shown in Table 3. Only dairy foods and whole milk were positively associated with risk of oesophageal carcinoma (OR for whole milk intake 1.78, 95%CI 1.19-2.69, p value for linear trend=0.004). The remaining food items were not associated with squamous cell oesophageal cancer.

The effect of vegetables and fruits is shown in Table 4. Fresh vegetables and fruits were inversely associated with risk of oesophageal cancer (OR for the highest tertile vs the lowest one 0.42, 95%CI 0.27-0.63, p value for linear trend <0.0001). Also raw vegetables (OR 0.48, 95%CI 0.32-0.70) and citrus fruits (OR 0.48, 95%CI 0.31-0.73) were markedly protective. On the other hand, potato consumption (OR 1.60, 95%CI 1.09-2.35) and low consumption of vegetables and fruits (OR 2.40, 95%CI 1.58-3.64) were positively associated with risk of oesophageal cancer.

Non-alcoholic beverages are shown in Table 5. Coffee was inversely associated with risk of squamous cell oesophageal cancer (OR 0.61, 95%CI 0.88-0.98) and black tea showed a marked reduction in risk of 90%. Finally, mate consumption (mate years) was positively associated with the risk of oesophageal cancer (OR 2.04, 95%CI 1.32-3.16).

The final model, fitted by stepwise forward method, is shown in Table 6. The following variables were retained into the model: black tea, boiled red meat, raw vegetables, hot dogs, fried red meat, lamb consumption, fresh fish, mate years, and citrus fruits. They were adjusted for age, sex, residence, education, monthly income, body mass index, smoking index, alcohol drinking, and total energy intake. It is noteworthy that when a variable called "fresh vegetables and fruits" was introduced into the model, raw vegetables and citrus fruits were deleted and, similarly, when the "hot" variable (a combination of mate, boiled meat, and whole milk) was entered in the model, mate, and boiled meat were deleted. This suggests that these combined variables have a synergistic

Table 2. Odds Ratios of Squamous Cell Oesophageal Cancer for Types of Meat[a, b]

Type of meat	Tertiles II OR	Tertiles II 95%CI	Tertiles III OR	Tertiles III 95%CI	p value for trend
Total meat	1.12	0.73-1.72	1.81	1.22-2.68	0.002
Red meat	1.04	0.68-1.60	1.44	0.96-2.14	0.07
Beef	0.89	0.58-1.36	1.16	0.79-1.71	0.41
Lamb	0.74	0.48-1.14	1.64	1.07-2.51	0.09
Fried red meat	0.68	0.46-1.00	0.50	0.34-0.76	0.001
Barbecued red meat	0.98	0.65-1.46	0.91	0.61-1.36	0.64
Boiled red meat	1.36	0.85-2.16	2.59	1.69-3.97	<0.0001
White meat	0.69	0.46-1.02	0.80	0.52-1.24	0.27
Poultry	1.00	0.68-1.47	1.13	0.74-1.73	0.57
Fresh fish	0.61	0.41-0.89	0.57	0.37-0.86	0.005
Processed meat	1.00	0.66-1.53	1.49	1.01-2.21	0.04
Liver	0.53	0.33-0.87	0.65	0.42-1.00	0.09
Salted meat	0.62	0.32-1.17	1.91	1.06-3.43	0.18
Frankfurter	1.07	0.65-1.76	1.78	1.22-2.59	0.004

[a]Multivariate adjusted for age, sex, residence, education, monthly income, smoking status, smoking cessation, number of cigarettes smoked per day among current smokers, alcohol drinking, mate consumption, total energy, and fresh vegetables and fruits; [b]reference category: tertile I

Table 3. Odds ratios of Oesophageal Squamous cell Cancer for Dairy Foods, Eggs, Desserts and Grains[a]

Foods	Tertiles II OR	Tertiles II 95%CI	Tertiles III OR	Tertiles III 95%CI	p value for trend
Dairy foods	1.85	1.22-2.82	1.78	1.18-2.67	0.005
Cheese	0.88	0.59-1.32	0.99	0.67-1.46	0.99
Butter	0.69	0.45-1.05	1.18	0.80-1.73	0.42
Whole milk	1.86	1.21-2.84	1.78	1.19-2.68	0.004
Boiled eggs	0.89	0.60-1.32	0.85	0.57-1.27	0.44
Fried eggs	0.91	0.60-1.37	1.13	0.76-1.69	0.51
Total grains	0.79	0.51-1.21	1.44	0.97-2.13	0.054
Total desserts	1.12	0.76-1.66	1.14	0.76-1.71	0.51

[a]Multivariate adjusted for age, sex, residence, education, monthly income, smoking status, smoking cessation, number of cigarettes smoked per day among current smokers, alcohol drinking, mate consumption, total energy, and fresh vegetables and fruits; [b]reference category: lowest tertile

Table 4. Odds Ratios of Squamous Cell Oesophageal Cancer for Plant Foods[a]

Foods	Tertiles II OR	Tertiles II 95%CI	Tertiles III OR	Tertiles III 95%CI	p value for trend
Total vegetables & fruits	0.71	0.48-1.05	0.96	0.65-1.42	0.76
Fresh vegetables & fruits	0.53	0.37-0.78	0.42	0.27-0.63	<0.0001
Total vegetables	0.83	0.55-1.24	1.28	0.87-1.89	0.21
Total fruits	0.59	0.40-0.88	0.71	0.48-1.04	0.07
Raw vegetables	0.56	0.38-0.83	0.48	0.32-0.70	0.0001
Cooked vegetables	0.83	0.54-1.27	1.27	0.85-1.88	0.19
Potato	0.66	0.43-1.02	1.60	1.09-2.35	0.01
Citrus fruits	0.77	0.53-1.12	0.48	0.31-0.73	0.0004
Other fruits	0.67	0.45-1.00	0.79	0.53-1.18	0.2
Legumes	0.95	0.65-1.39	0.73	0.50-1.10	0.14
Low vegetables & fruits	1.28	0.81-2.02	2.40	1.58-3.64	<0.0001

[a]Multivariate adjusted for age, sex, residence, education, monthly income, smoking status, smoking cessation, number of cigarettes smoked per day among current smokers, alcohol drinking, mate consumption, and total energy intake

Table 5. Odds Ratios of Oesophageal Squamous Cell Cancer for Non-Alcoholic Beverages[a]

Beverages	Tertiles II OR	Tertiles II 95%CI	Tertiles III OR	Tertiles III 95%CI	p value for trend
Coffee	0.95	0.65-1.39	0.61	0.38-0.98	0.07
Black tea	0.62	0.40-1.00	0.10	0.04-0.28	<0.0001
Mate years	1.88	1.23-2.87	2.04	1.32-3.16	0.002

[a]Multivariate adjusted for age, sex, residence, education, monthly income, smoking status, smoking cessation, number of cigarettes smoked per day among current smokers, alcohol drinking, total energy intake and for each other

Table 6. Final Model Fitted by Stepwise Forward Method[a]

Variable	OR	95%CI	z	p value
Black tea	0.86	0.79-0.94	-3.37	0.001
Boiled red meat	1.39	1.14-1.69	3.28	0.001
Raw vegetables	0.76	0.65-0.90	-3.26	0.001
Frankfurter(hot dog)	1.31	1.13-1.52	3.62	0.001
Fried red meat	0.81	0.71-0.92	-3.21	0.001
Lamb	1.15	1.04-1.27	2.71	0.007
Fresh fish	0.83	0.71-0.97	-2.41	0.020
Mate years	1.19	1.03-1.39	2.31	0.020
Citrus fruits	0.89	0.81-0.98	-2.31	0.020

[a]Multivariate adjusted for age, sex, residence, education, income, body mass index, smoking index, alcohol drinking, and total energy intake

Discussion

According to the present study, boiled red meat was strongly associated with an increased risk of squamous

cell oesophageal cancer. Thus, this result replicates the suggestion made by Islami et al. (2009), that the effect of boiled meat could be related to thermal injury of the oesophageal mucosa (Kinner et al., 2007). In fact, in rural areas of Uruguay red meat is frequently cooked with vegetables and rice leaving to stew ("guiso"), a staple food among the Uruguayan population. This prepared meat is ingested very hot, and, although its temperature has not been measured, it is plausible to suppose that "guiso" may reach the oesophageal mucosa at a high temperature, resulting in chronic oesophagitis. This lesion could allow the penetration of carcinogens from tobacco and alcohol, source of potent carcinogens and initiators of squamous cell oesophageal carcinoma (18). In fact, the same mechanism applies to mate (Vassallo et al., 1985; Victora et al., 1987; De Stefani et al., 1990; Castelletto et al., 1994; Rolon et al., 1995; Castellsague et al., 2000; Sewram et al., 2003; De Stefani et al., 2003). It should be taken into account that mate contains benzo(a)pyrene, a ubiquitous carcinogen (Fagundes et al., 2006; Kamangar et al., 2008). In fact the role of benzo(a)pyrene in the aetiology of squamous cell oesophageal cancer has not been extensively studied to date. Contamination of cereals with fumonisin B1, another carcinogen, is know to be associated risk of esophageal cancer in a high risk area in Northeastern Iran (Alizadeh et al., 2012).

Previous studies suggest that the consumption of processed meat may increase the risk of squamous cell oesophageal carcinoma (Bosetti et al., 2000; Levi et al., 2000; Tran et al., 2005; Jaskyn et al., 2006; Cross et al., 2011; De Stefani et al., 2012b; Choi et al., 2013). At difference with boiled meat, the intake of processed meat is not associated with the temperature as it is frequently ingested cold or warm. It is thus that processed meat mechanisms appear to be related to the presence of nitrosamines, nitrites, and nitrates (Jaksyn et al., 2006). Nitrosamines are potent carcinogens and have been related to the aetiology of oesophageal cancer (Craddock et al., 1991). In our study, the types of processed meat which were more strongly associated with the aetiology of oesophageal cancer were salted meat and hot dog.

In the present study milk consumption was positively associated with the risk of oesophageal carcinoma. It has been suggested that milk is consumed as a hot beverage, either added to coffee or alone. It is less plausible to suggest that milk consumption increases the risk of oesophageal cancer due to its content of saturated fatty acids, since cheese and butter were not risk factors for oesophageal cancer and they are a rich source of saturated fat as well. When the consumption of milk was combined with mate and boiled red meat, the risk of squamous cell oesophageal cancer had a nearly three-fold increase, supporting the hypothesis that milk as a hot beverage, consumed like mate can favour dysplasia of the squamous epithelium in the oesophageal mucosa through thermal injury.

In our study, raw vegetables and citrus fruits were inversely associated with risk and, conversely, low intake of these items was positively associated with the risk of squamous cell oesophageal cancer. In fact, the Uruguayan population usually consume raw carrots, in the same manner as tomato, lettuce, orange, and tangerine. According to Block et al. (2001), citrus fruits are rich in vitamin C and beta-cryptoxanthin. In a randomised trial conducted by one of the authors, beta-carotene and ascorbic acid were strongly protective of gastric dysplasia produced by Helicobacter pylori (Correa et al., 2000). On the other hand, cooked vegetables slightly increased the risk of oesophageal cancer, and, in the case of potato, the increase was significant for this malignancy. It could be hypothesized that the temperature of cooked vegetables contributes to the risk of hot foods and the loss of the antioxidant effect due to the temperature, inhibiting vitamins and other bioactive antioxidants.

Tea consumption has been extensively studied in several locations (IARC, 1991). Also several studies on oesophageal cancer have been conducted in different countries (IARC, 1991). In the study by Cook-Mozzafari et al (1979) hot tea consumption was positively associated with the risk of squamous cell oesophageal cancer. Similar findigns were published from China (Tang et al., 2013). Castellsague et al (2000) replicated these findings in the pool analysis of oesophageal carcinoma in South America. The present study displayed a huge reduction in risk of 90%, but the temperature at which tea is drunk was not present in our FFQ. The reduction in risk could be due to high content of flavanols and flavonoids, known as antioxidants (IARC, 1991; Heck et al., 2007).

As other case-control studies, the present one has strengths and limitations. The major strength is related to the high response rate, both for cases and controls. Also the matched design on age, sex, and residence can be regarded as a strength of the study. On the other hand, our study could be affected by the possibility of selection and recall biases. Although the matched design and the reasonable number of controls possibly counterbalance severe selection bias, it is impossible to eliminate potential recall bias. This could result in a misclassification and the possibility of differential misclassification is a major limitation.

In conclusion, the present study showed an important role played by certain hot food items, mainly boiled red meat and mate consumption. Also, raw vegetables and citrus fruits were found to be strongly protective. Finally, tea intake was also strongly and inversely associated with risk of squamous cell oesophageal cancer.

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