

## RESEARCH ARTICLE

# Processed Meat Consumption and Squamous Cell Carcinoma of the Oesophagus in a Large Case-Control Study in Uruguay

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### Abstract

**Background:** The role of processed meat in the aetiology of squamous cell oesophageal cancer has been explored in detail. **Methods:** In the time period 1990-2005, a case-control study was conducted in Montevideo, Uruguay including 2,368 participants (876 cases of oesophageal cancer and 1,492 controls). Relative risks, approximated by the odds ratios, were estimated by multiple unconditional logistic regression. **Results:** Processed meat was positively associated with oesophageal cancer (upper quartile vs lower quartile OR 2.30, 95% CI 1.72-3.07), whereas salted meat intake was positively associated with squamous cell oesophageal cancer (OR 3.82, 95% CI 2.74-5.33). Finally other cured meats were positively associated with oesophageal cancer (OR 1.65, 95% CI 1.22-2.22). **Conclusions:** It could be concluded that processed meat consumption could be an important risk factor for the aetiology of squamous cell oesophageal cancer in Uruguay.

**Keywords:** Squamous cell oesophageal cancer - processed meat - salted meat - other cured meats

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### Introduction

Oesophageal cancer is a frequent malignancy in Uruguay, mainly in the northeastern counties, in the border with Brazil (Barrios et al., 2010). Age-standardised incidence rates were of 25.3 per 100,000 men and 6.5 per 100,000 women (Barrios et al., 2010). This belt is rather similar with that one observed in Northern Iran and Northern China (Parkin et al., 2002; He et al., 2005; Mao et al., 2011). The main reasons of this high incidence are unknown, although the incidence is declining, reflecting the declination of squamous cell oesophageal cancer, which is the main histologic type in Uruguay (Devesa et al., 1998).

This declination of squamous cell oesophageal cancer could be correlated with the decrease of the use of hand-rolled cigarettes filled with black tobacco (De Stefani et al., 1994). This type of cigarette is a rich source of tobacco-specific nitrosamines (IARC, 2004), particularly nitrosonornicotine, known as an important carcinogen for oesophageal mucosa. Also the decrease in the consumption of salted meat is highly correlated with the decrease of the incidence of oesophageal carcinoma in Uruguay. Salted meat intake is the source of nitrosamines, important chemicals in oesophageal carcinogenesis (Craddock, 1991).

In the rather recent monograph of World Cancer

Research Fund/American Institute for Cancer Research (2007) alcohol is cited as a convincing factor for oesophageal cancer, whereas there is probable evidence that hot *mate* consumption is a risk factor for oesophageal carcinoma and there is limited/suggestive evidence that processed meat consumption could be a risk factor for this malignancy. The role of *mate* consumption in oesophageal cancer has been replicated in a recent pooled study (Lubin et al., 2013).

For all these reasons, we decided to conduct a large case-control study with the objective of studying in detail the role of processed meat consumption in the aetiology of squamous cell oesophageal carcinoma.

### Materials and Methods

#### *Selection of cases*

In the time period 1990-2005 all newly diagnosed and microscopically validated cases of squamous cell carcinoma of the oesophagus, drawn from the four major public health hospitals. In total 897 cases were eligible for this study. Twenty-one (21) refused the interview leaving a final total of 876 cases, which were discriminated by gender in 666 males and 210 women. The cases were classified by anatomic site as follows: upper third 66 patients (7.5%), middle third 226 (25.8%), lower third 118 (13.5%), and site not otherwise specified 466 (53.2%).

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### Selection of controls

In the same time period and in the same hospitals, all patients afflicted by non-neoplastic conditions, not related with tobacco smoking or alcohol drinking were eligible for the study. In total 1,532 patients were eligible and 40 of them refused the interview, leaving a final total of 1,492 controls (97.4%). The patients presented the following diseases: diseases of the skin (841 patients, 56.4%), abdominal hernia (222, 14.9%), eye disorders (145, 9.7%), urinary stones (79, 5.3%), varicose veins (51, 3.4%), blood disorders (40, 2.7%), injuries (36, 2.4%), hydatid cyst (36, 2.4%), fractures (29, 1.9%), and genital tract diseases (13, 0.9%).

### Interviews and questionnaire

All participants (cases and controls) were hospitalised and shortly after this were administered with a structured questionnaire by four trained social workers. The interviewers were not aware of the objectives of the study. No proxy interviews were accepted. The questionnaire presented the following sections: sociodemographics (last name, first name, age, sex, education, monthly income, identification number), self-reported height and weight 5 years before the date of the of the interview, family history of cancer among first-degree relatives, a complete occupational history based in the jobs and its duration, a complete history of tobacco smoking (age at start, age at quit, number of cigarettes smoked per day, type of tobacco, type of cigarette), a complete history of alcohol drinking (age at start, age of quit, number of glasses drunked by day or week, type of alcoholic beverage), a complete history of *mate* consumption (age at start, age at quit, number of liters drunked per day, temperature of the beverage), menstrual and reproductive events, and a food frequency questionnaire (FFQ) focused on meat consumption, dairy foods, vegetables, and fruits. This FFQ allowed the estimation of total energy intake and was considered as representative of the Uruguayan diet.

### Statistical analysis

Relative risks, approximated by the odds ratios, were calculated by multiple unconditional logistic regression (Rothman et al., 2008). We fitted a basic model which included the following terms: age (continuous), sex (categorical), residence (categorical), education (categorical), smoking in pack years (categorical), alcohol drinking (categorical), *mate* consumption (categorical), total energy intake (continuous), total vegetable and fruit intake (continuous), and red meat (continuous). This basic model included total processed meat as a categorical variable. Processed meat was replaced by salted meat and other cured meats (bacon, sausage, *mortadella*, salami, *saucisson*, frankfurter, and ham) and these variables were included into the basic model. The estimates were two-sided and P value for trend was considered as significant when alpha was 95%. Interactions were calculated using the likelihood-ratio test. All the estimates were calculated using the statistical software Stata, release 13.1 (StataCorp, 2013).

## Results

Distribution of cases and controls by sociodemographics and selected risk factors are shown in Table 1. Categorical age was rather similar among both groups of participants. Female controls showed a higher percentage compared with cases. Similarly, controls displayed a higher proportion of urban patients, compared with urban cases. Finally, cases were significantly less educated compared with controls. Smoking, alcohol drinking, and *mate* consumption were significantly higher than controls.

The homogeneity of variables of processed meat intake is shown in Table 2. Total processed meat, salted meat, and other foods of the group of processed meat were homogeneous. For this reason we decided to fit a model for both sexes, including a term for gender in further analyses.

Odds ratios of squamous cell oesophageal cancer for processed meats are shown in Table 3. Odds ratios of squamous cell oesophageal cancer (higher quartile vs the lower quartile 2.30, 95%CI 1.72-3.07) for total processed

**Table 1. Distribution of Cases and Controls by Sociodemographics and Selected Risk Factors**

Variable	Category	Cases		Controls	
		No	%	No	%
Age (years)	30-39	4	0.5	8	0.5
	40-49	53	6.0	106	7.1
	50-59	160	18.3	250	16.8
	60-69	286	32.6	468	31.4
	70-79	291	33.2	496	33.2
	80-89	82	9.4	164	11.0
Sex	Males	666	76.0	1072	71.9
	Females	210	24.0	420	28.1
Residence	Urban	591	67.5	1185	79.4
	Rural	285	32.5	307	20.6
Education (years)	0-2	314	35.8	367	24.6
	3-5	370	42.2	556	37.3
	6+	192	22.0	569	38.1
Smoking (pack yrs)	Never	182	20.8	556	37.3
	1-29	93	10.6	193	12.9
	30-39	133	15.2	195	13.1
	40-49	204	23.3	257	17.2
	50+	264	30.1	291	19.5
	Alcohol drinking (ml/ethanol/day)	Never	270	30.8	776
1-60	171	19.5	315	21.1	
	v61-120	143	16.3	184	12.3
	121-240	153	17.5	129	8.6
	241+	139	15.9	88	5.9
<i>Mate</i> consumption (liters/day)	Never	32	3.6	209	14.0
	0.1-0.9	209	23.9	415	27.8
	1.0-1.9	415	47.4	649	43.5
	2.0+	220	25.1	219	14.7
No participants		876	100.0	1492	100.0

**Table 2. Homogeneity of Processed Meat by Sex**

Variable	Gender				P homogeneity
	Males		Females		
	OR	95%CI	OR	95%CI	
Total processed meat	1.15	1.11-1.19	1.12	1.07-1.17	0.32
Salted meat	1.18	1.14-1.21	1.18	1.12-1.24	0.93
Other cured meats	1.09	1.06-1.13	1.09	1.04-1.15	0.99

**Table 3. Odds Ratios of Squamous Cell Oesophageal Cancer for Processed Meat**

Variable	Cases/Controls	OR	95%CI
<b>Total processed meat<sup>a</sup></b>			
≤4.1	103/373	1.0	reference
4.2-17.9	173/373	1.47	1.07-2.02
18.0-53.8	265/373	2.18	1.62-2.93
53.9+	335/373	2.30	1.72-3.07
P value trend	<0.0001		
Continuous		1.11	1.08-1.15
<b>Salted meat<sup>b</sup></b>			
0	537/1252	1.0	reference
0.1-8.9	104/123	1.53	1.12-2.07
9.0-25.7	91/58	2.84	1.95-4.14
25.8+	144/59	3.82	2.74-5.33
P value trend	<0.0001		
Continuous		1.13	1.10-1.16
<b>Other cured meats<sup>c,d</sup></b>			
≤4.1	112/373	1.0	reference
4.2-8.5	238/373	1.57	1.16-2.12
8.6-24.8	288/373	1.94	1.45d-2.60
24.9+	238/373	1.65	1.22-2.22
P value for trend	0.001		
Continuous		1.07	1.04-1.11

<sup>a</sup>Multivariate adjusted for age, sex, residence, education, tobacco smoking (in pack years), alcohol drinking, mate consumption, total energy, total vegetable and fruit intake, and red meat consumption; <sup>b</sup>Multivariate adjusted for age, sex, residence, education, tobacco smoking (in pack years), alcohol drinking, mate consumption, total energy, total vegetable and fruit intake, red meat consumption, and other cured meats; <sup>c</sup>Multivariate adjusted for age, sex, residence, education, tobacco smoking (in pack years), alcohol drinking, mate consumption, total energy, total vegetable and fruit intake, red meat consumption, and salted meat intake; <sup>d</sup>Bacon, sausage, mortadella, salami, saucisson, frankfurter, and ham

**Table 4. Odds Ratios Squamous Cell Oesophageal Cancer by Location of the Malignancies**

Variable	Cancer site					
	Upper third (No. 66)		Middle third (No. 226)		Lower third (No. 118)	
	OR	95 % CI	OR	95 % CI	OR	95 % CI
<b>Processed meat<sup>a</sup></b>						
	1.0	reference	1.0	reference	1.0	reference
	1.91	0.80-4.55	1.25	0.76-2.03	1.01	0.52-1.98
	1.97	0.84-4.64	1.60	1.00-2.54	1.45	0.78-2.70
	2.18	0.94-5.07	1.61	1.03-2.52	1.51	0.83-2.76
	0.09 <sup>d</sup>		0.02		0.07	
<b>Salted meat<sup>b</sup></b>						
	1.0	reference	1.0	reference	1.0	reference
	0.29	0.07-1.30	2.49	1.61-3.84	1.50	0.84-2.68
	1.70	0.65-4.45	3.49	2.08-5.84	2.03	0.99-4.12
	2.03	0.86-4.83	2.96	1.80-4.85	1.81	0.92-3.55
	0.17 <sup>d</sup>		<0.0001		0.01	
<b>Other cured meats<sup>c</sup></b>						
	1.0	reference	1.0	reference	1.0	reference
	1.62	0.72-3.64	1.38	0.88-2.17	1.42	0.75-2.72
	1.43	0.62-3.30	1.46	0.94-2.28	1.49	0.78-2.84
	1.70	0.77-3.75	1.09	0.68-1.74	2.12	1.12-4.00
	0.27 <sup>d</sup>		0.74		0.02	

<sup>a</sup>Multivariate adjusted for age, sex, residence, education, tobacco smoking (in pack years), alcohol drinking, mate consumption, total energy, total vegetable and fruit intake, and red meat consumption; <sup>b</sup>Multivariate adjusted for age, sex, residence, education, tobacco smoking (in pack years), alcohol drinking, mate consumption, total energy, total vegetable and fruit intake, red meat consumption, and other cured meats; <sup>c</sup>Multivariate adjusted for age, sex, residence, education, tobacco smoking (in pack years), alcohol drinking, mate consumption, total energy, total vegetable and fruit intake, red meat consumption, and salted meat intake; <sup>d</sup>P value for linear trend

meat which was positively associated with oesophageal cancer. Salted meat consumption was positively associated with oesophageal carcinoma (OR 3.82, 95%CI 2.74-5.33). Finally the remaining cured meats (bacon, sausage, *mortadella*, salami, *saucisson*, frankfurter, and ham) were also positively associated with oesophageal squamous cell cancer (OR 1.65, 95%CI 1.22-2.22).

**Table 5. Odds Ratios of Oesophageal Carcinoma Stratified by Residence<sup>a</sup>**

Variable	Residence				P heterogeneity
	Urban		Rural		
	OR	95 % CI	OR	95%CI	
Processed meat	1.0	reference	1.0	reference	
	1.59	1.12-2.26	1.36	0.70-2.64	
	1.97	1.42-2.75	2.96	1.54-5.68	
	1.95	1.41-2.71	3.83	2.02-7.23	0.01 <sup>b</sup>

<sup>a</sup>Multivariate adjusted for age, sex, education, tobacco smoking (in pack years), alcohol drinking, mate consumption, total energy, total vegetable and fruit intake, and red meat consumption, <sup>b</sup>Estimated by the likelihood-ratio test

Odds ratios of squamous cell oesophageal cancer stratified by topography are shown in Table 4. Only 66 cases were located in the upper third of the oesophagus, and the estimates showed wide confidence intervals. Total processed meat was positively associated with oesophageal carcinoma (OR 2.18, 95% 0.94-5.07), whereas salted meat consumption displayed an increased risk of 2.03 (95% 0.86-4.83) and other cured meats (OR 1.70, 95% 0.77-3.75) were positively non-significant associated with oesophageal cancer. The number of cases in the middle third of the oesophagus was 226. Processed meat was positively associated with cancer of the oesophagus located in this third (OR 1.61, 95%CI 1.03-2.52, P value trend=0.02). Salted meat intake displayed a significantly associated with oesophageal cancer located in the middle third of the organ (OR 2.96, 95%CI 1.80-4.85, P value for trend <0.0001). Other cured meats were not associated with squamous cell oesophageal cancer in the quoted location. Finally, 118 cases were present in the lower third of the oesophagus. Preserved meat intake was non-significantly positively associated with abdominal oesophageal carcinoma (OR 1.51, 95%CI 0.83-2.76). Similarly, salted meat intake was non-significantly positively associated with oesophageal cancer located in the lower third (OR 1.81, 95%CI 0.92-3.55), whereas other cured meats showed a significant positive association in this location (OR 2.12, 95%CI 1.12-4.00, P value for trend=0.02).

The heterogeneity of squamous cell oesophageal cancer by residence is shown in Table 5. Whereas processed meat among urban residents displayed a risk of 1.95 (95%CI 1.41-2.71), the same variable showed a higher increased risk of 3.83 (95%CI 2.02-7.23) among rural residents. The P value for heterogeneity (estimated by likelihood-ratio test) was of 0.01.

## Discussion

According to the results of the present study, total processed meat, salted meat, and other cured meats were positively associated with increased risk of squamous cell oesophageal carcinoma. We performed an extensive search of the literature on processed meat consumption and squamous cell oesophageal cancer risk, showing some similarities and differences with our results.

Among prospective studies, the association between processed meat and oesophageal cancer has not been studied as extensively as red meat. To date, only a few cohort studies (Chyou et al., 1995; Kjaerheim et al.,

1998; Gonzalez et al., 2006) have been conducted on this topic. Chyou et al. (1995) combined oropharyngeal, laryngeal and oesophageal cancer into one endpoint and found a non-significant positive association with intake of ham, bacon and sausage (RR=1.24, 95% CI: 0.73-2.1). A strong association between unspecific processed meat consumption and oesophageal adenocarcinoma among people in the highest exposure category (RR=3.54, 95% CI: 1.57-7.99) was reported in the EPIC cohort (Gonzalez et al. 2006). In a sample of more than 10,900 Norwegian men, Kjaerheim et al. (1998) reported positive associations among consumers of processed meat and bacon; however the association was only significant (marginally) among people who consumed bacon six or more times per month (RR=2.2, 95% CI: 1.0-5.0).

More recently, Steffen et al. (2012) conducted a prospective study in the framework of EPIC on meat and heme iron and oesophageal cancer. This study replicated previous findings. Interestingly, processed meat was positive, though non-significantly, associated with squamous cell oesophageal cancer in the large NIH-AARP Diet and Health study (Cross et al., 2011). Thus, most of the prospective studies reported an increased risk of squamous cell oesophageal cancer associated with intake of processed meat (Choi et al., 2013).

More than 10 case-control studies have evaluated the association between processed meat and oesophageal cancer. Of these, the study in Switzerland found a statistically significant increase in risk in the highest intake category of processed meat (OR=4.68, 95% CI: 2.54-8.62), although the association was imprecise (Levi et al. 2004). The study of Rolon et al. (1995) displayed a huge risk of 4.7 for red meat, but processed meat consumption was not investigated. Brown et al. (1998) showed a significant positive association between processed meat and squamous cell esophageal cancer among black men with an OR of 1.6 (P value trend=0.04). The estimates for white men in this study were rather similar (OR 1.7) but did not reach statistical significance. The higher risks associated with processed meat among black men suggest an effect of N-nitroso compounds with the nitrosation process accelerated by low levels of micronutrients (Brown et al., 1998). A recent study in Uruguay reported an increased risk of oesophageal cancer for high intake of processed meat (De Stefani et al., 2014). Recently, Lagiou et al. (2008) reported higher consumption of all examined types of red meat associated with increased UADT cancer risk, but the association was stronger for cancer of the esophagus. In particular, cold cuts displayed a 26% increased in risk for oesophageal cancer in the ARCAGE study (Lagiou et al., 2008). Not all case-control studies showed association between processed meat consumption and oesophageal cancer (De Stefani et al., 1999).

Processed meat intake is not only positively associated with cancers like lung (Lam et al., 2009), oesophagus (Steffen et al., 2012), stomach (Larsson et al., 2006) and colorectal (Larsson et al., 2005; De Stefani et al., 2012a) but also with coronary heart disease, stroke, and diabetes mellitus (Micha et al., 2010). Thus, processed meat consumption is a major public health problem.

According to Santarelli et al. (2008) the mechanisms

of processed meat intake in the aetiology of colorectal cancer could be related with the fat consumption, salt, nitrites, nitrates and N-nitroso compounds. We have examined the role of nitrites, nitrates, and sodium in colorectal cancer in a factor analysis (De Stefani et al., 2012b). Aside of human evidence, experimental evidence supports the effect of these chemicals in the aetiology of cancer (Santarelli et al., 2008).

As other case-control studies, the present one has strengths and limitations. Perhaps, the major strength of the present study is the high response rate, both for cases and controls. Another major strength is the statistical power of our study. Also the study has limitations. The major limitations are related with selection and recall biases. Although selection bias is liable to manage by statistical procedures, recall bias could lead to differential and non-differential misclassification which, in turn, could derive into faulty results.

In conclusion, our study showed that squamous cell oesophageal carcinoma is strongly and positively associated with total processed meat, salted meat, and other cured meats. As pointed out, intake of processed meat is a major public health problem and it is recommended to limit the consumption of this dangerous foods.

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