Salted Meat Consumption as a Risk Factor for Cancer of the Oral Cavity and Pharynx: A Case-Control Study from Uruguay

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Abstract

A hospital-based, case-control study of oropharyngeal cancer was conducted in the Oncology Institute, Montevideo, Uruguay, during 1988–1992, in which 246 new cases and 253 controls were interviewed. The study was restricted to males. As in most previous studies, tobacco smoking and alcohol drinking were the major risk factors. Past and current salted meat consumption was associated with increased risks of oropharyngeal cancer after controlling for the effects of tobacco and alcohol; current consumption was associated with a significant increase in risk (odds ratio, 2.3; 95% confidence interval, 1.1–5.2). Current heavy consumption of salted meat was associated with a significant 4.7% increased risk of oropharyngeal cancer after adjusting for tobacco smoking and alcohol drinking. These findings suggest that current consumption of salted meat is more relevant to the etiology of this set of neoplasms than past consumption. Furthermore, the joint effect of pack-years of cigarette smoking, alcohol drinking, and ever consumption of salted meat was associated with a high risk of oral and pharyngeal cancer (odds ratio, 10.0; 95% confidence interval, 4.7–21.3) using the referent category of moderate smokers, moderate drinkers, and never users of salted meat.

Introduction

Cancer of the mouth and pharynx is a frequent malignancy in Uruguay, representing 6.4% of all cancers with incidence rates of 15.7 and 3.3/100,000 persons/year for men and women, respectively (1–2). In previous studies, the main risk factors for cancer of the mouth and pharynx among Uruguayan men were black tobacco smoking and alcohol consumption (3–5). Also, the risk decreased with frequent consumption of vegetables and fruits.

Recently, Zheng *et al.* (6) provided further evidence that dietary factors play an important role in the carcinogenesis of this group of sites. In particular, they reported an important new finding, namely an excess risk for oral and pharyngeal cancer associated with high consumption of salt-preserved meat and fish in Shanghai, China (6). Since salted meat is a traditional dietary item in Uruguay, it was decided that a case-control study would be conducted in order to assess the relationship between salted meat intake and oropharyngeal cancer risk in this country.

Materials and Methods

All patients ages 40–89 years who were admitted to the Instituto Nacional de Oncologia with an incident and histologically proven squamous cell carcinoma of the oral cavity and pharynx during the period of January 1988 to December 1992 were considered eligible for the study. Cancer of the lip, salivary glands, and nasopharynx were considered not suitable for this study since they are partially determined by different sets of risk factors (solar radiation, ionizing radiation, and Epstein-Barr virus infection among others) (6). Thus, 316 cases of oral and pharyngeal cancer were identified. Since there were only 27 cases occurring in women, it was decided to restrict the study to men. The low proportion of female cases is believed to be the result of the low prevalence of tobacco smoking and alcohol drinking among women in Uruguay. Among male cases, 43 cases were excluded due to advanced illness, leading to a final total of 246. Sixty-eight (27.6%) patients showed tumors located in the hypopharynx, 66 (26.8%) had oropharyngeal cancers, and 56 (22.8%) had cancer of the tongue. Fifty patients were diagnosed with tumors located in other parts of the mouth, whereas only six (2.4%) presented extensive lesions classified as pharynx not otherwise specified. In all cases, the topography of the lesion was validated by a careful clinical examination performed by two otolaryngologists (F. O. and S. R.). The sociodemographic characteristics of the 43 cases excluded due to terminal illness were similar to the selected cases. Controls were selected from all admissions registered in the Institute in the same period and they were frequency matched by age to cases. All patients diagnosed with diseases related with tobacco and alcohol consumption (including cardiovascular diseases), oral benign tumors, nonneoplastic conditions of the mouth and pharynx, or digestive diseases were considered noneligible. Among control series, nonmelanoma skin cancer was the main category (77 patients, 30.4%), followed by non-Hodgkin's lymphoma (30, 11.9%), soft-tissue sarcomas (22, 8.7%), nonneoplastic skin diseases (19, 7.5%), malignant melanoma (16, 6.3%), eye and ear disorders (14, 5.6%), varicose veins (13, 5.1%), diseases of bones and joints (11, 4.4%), endocrine tumors (10, 4.0%), and less frequent categories (41, 16.0%).

All patients (cases and controls) were personally interviewed shortly after admission by 2 trained social workers. No refusals were recorded among cases and controls, and the base population was extremely cooperative. Each inter-

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viewer questioned a similar proportion of cases and controls. The patients were given a structured questionnaire, which covered the following sections: (*a*) sociodemographic variables; (*b*) tobacco use (age at start, age at quit, smoking amount, type (color) of tobacco, and filter use); (*c*) alcohol consumption (age at start, age at quit, and amount in ml/day of ethanol); and (*d*) a short food frequency form. The form included information on: fresh, salted (past and current consumption), and barbecued meat; sausage; milk; raw vegetables; and fresh fruits. Although the limited information on food (or groups of foods) items is acknowledged, the questionnaire contains precise data on meat consumption, which is the main subject of the present study. Past consumption of salted meat was defined as consumption in adolescence but not currently, whereas present consumption refers to lifelong consumption up to the onset of symptoms of the disease. Only current exposure (before the onset of the disease) was recorded for remaining dietary items. Consumption of beer, wine, and hard liquor was converted into ethanol intake using the following average ethanol concentration: beer, 6%; wine, 12%; and hard liquor, 46%. Frequencies of dietary items was expressed in times/year and categorical variables were created using the percentile distribution for cases and controls. Stratified analysis and unconditional logistic regression were used to derive crude and adjusted odds ratios (7). In particular, ORs[2] for consumption of different types of meat were adjusted for the following potential confounders: age, residence, education, pack-years of cigarette smoking, and total alcohol consumption. All the calculations were carried out using the GLIM package (Numerical Algorithm Group, Oxford, UK).

Results

Table 1 presents the distributions for sociodemographic characteristics. Cases and controls were very close regarding age distribution, and rather similar regarding birthplace, residence, education, and income. Odds ratios of oropharyngeal cancer for tobacco and alcohol consumption after adjusting for age and education are shown in Table 2. Tobacco smoking, measured by pack-years, was associated with high risk (OR, 8.9 for smokers of more than 71 units) of oral and pharyngeal cancer and also displayed a well defined dose-response. Total alcohol consumption, measured in ml/day of ethanol, showed similar ORs for heavy drinkers (OR, 7.9), and the dose-response displayed a linear increase in risk. Additional adjustment for each other resulted in a modest decrease in the relative risks of pack-years and total alcohol consumption. Patients who had quit smoking for 10 years or more showed a reduction in risk of 80%. Black tobacco smoking was associated with an increased risk of 2.1 compared with blond cigarette smoking (results not shown). Odds ratios of oral and pharyngeal cancer associated with selected food items are shown in Table 3. No association with fresh barbecued meat, sausage, or milk was detected. Current salted meat consumption showed significant increases in the risk of oropharyngeal cancer after controlling for age, residence, education, cigarette smoking, and alcohol drinking. Former consumption of salted meat was associated with a moderate increase in risk of 40% (not formally significant), whereas current consumption of this item was associated with a significant 2-fold increase in the risk of oropharyngeal cancer. Moreover, in the category of current consumers, heavy ingestion of salted meat showed a significantly increased OR of 4.7. A nonsignificant decrease in risk was associated with heavy consumption of fresh fruits (OR, 0.6), whereas vegetable consumption was associated with a 60% reduction in risk. The possible interactive effects of tobacco variables and alcohol consumption with salted meat consumption were investigated; the results are shown in Table 4. Heavy smokers and current consumers of salted meat showed an OR of 5.2 (95% confidence interval, 1.7–15.9), whereas current smokers and current consumers of salted meat were associated with an OR of 12.3. A supramultiplicative effect between alcohol consumption and salted meat was de-

Table 1 Distribution of cases and controls by sociodemographic variables

Variable	Cases (%)	Controls (%)
Age (yr)		
40–49	16 (6.5)	19 (7.5)
50–59	80 (32.5)	82 (32.4)
60–69	104 (42.3)	105 (41.5)
70–79	35 (14.2)	36 (14.2)
80–89	11 (4.5)	11 (4.3)
Birthplace		
Montevideo	52 (21.1)	63 (24.9)
Other county	194 (78.9)	190 (75.1)
Residence		
Montevideo	100 (40.7)	119 (47.0)
Other county	146 (59.3)	134 (53.0)
Urban	201 (81.7)	185 (73.1)
Rural	45 (18.3)	68 (26.9)
Education (yr)		
0–4	149 (60.6)	151 (59.7)
5+	97 (39.4)	102 (40.3)
Monthly income (United States dollars)		
0–58	133 (54.1)	144 (56.9)
59+	113 (45.9)	109 (43.1)
No. of patients	246 (100)	253 (100)

Table 2 Relative risk of cancer of mouth and pharynx for tobacco and alcohol consumption

Variable	Cases/controls	OR[a]	OR[b]	95% CI[c]
Pack-years				
Nonsmokers	7/34	1.0	1.0	
1–26	36/82	2.0	1.5	0.6–3.9
27–45	62/55	5.2	3.3	1.3–8.3
46–70	70/44	7.4	4.2	1.6–10.9
71+	71/38	8.9	4.5	1.7–11.6
Total alcohol (ml/day)				
Nondrinkers	28/88	1.0	1.0	
1–60	46/69	2.1	1.7	0.9–3.0
61–120	48/29	4.9	3.5	1.8–6.8
120–235	55/35	5.1	3.5	1.8–6.6
236+	69/32	7.9	5.0	2.6–9.6

[a] Adjusted for age, residence, and education.
[b] Adjusted for age, residence, education, and each other.
[c] CI, confidence interval.

[2] The abbreviation used is: OR, odds ratio.

Table 3 Relative risk of cancer of the mouth and pharynx for consumption of selected foods[a]

Variable	Cases/ controls	OR	95% CI[b]
Fresh meat (times/yr)			
0–363	67/95	1.0	
364–482	110/97	1.1	0.7–1.8
483+	69/61	1.1	0.7–1.9
Barbecue (times/yr)			
0–12	62/69	1.0	
13–52	98/98	1.0	0.6–1.7
53+	86/86	0.8	0.5–1.4
Salted meat[c]			
Never	134/157	1.0	
Past	89/82	1.4	0.9–2.1
Current	23/14	2.3	1.1–5.2
Salted meat[d] (times/yr)			
Never	134/157	1.0	
Past 1–52	59/55	1.3	0.8–2.2
Past 53+	30/27	1.4	0.7–2.7
Current 1–24	8/9	1.3	0.4–3.8
Current 25+	15/5	4.7	1.3–16.9
Sausage (times/yr)			
0–12	59/64	1.0	
13–52	82/59	0.8	0.5–1.4
53+	77/68	0.8	0.5–1.4
Missing	28/32	0.7	0.4–1.5
Milk (times/yr)			
0–363	103/86	1.0	
364–727	84/95	1.0	0.7–1.7
728+	59/72	1.1	0.6–1.8
Vegetables (times/yr)			
Never	35/21	1.0	
1–104	130/136	0.4	0.2–0.9
105+	81/96	0.4	0.2–0.9
Fresh fruits (times/yr)			
Never	26/17	1.0	
1–156	128/127	0.7	0.3–1.4
157+	92/109	0.6	0.3–1.4

[a] Adjusted for age, residence, education, pack-yrs and total alcohol consumption.
[b] CI, confidence interval.
[c] Exclusively before 20 years of age.
[d] Lifetime consumption including current consumption.

Table 4 Relative risks of cancer of the mouth and pharynx for consumption of salted meat, stratified by other risk factors

Risk factor	Consumption of salted meat		
	Never (95% CI)[a]	Ex-consumers (95% CI)	Current consumers (95% CI)
Pack-years[b]			
0–41	1.0	1.1 (0.7–1.9)	2.4 (0.9–6.4)
43+	2.5 (1.5–3.9)	4.4 (2.4–7.9)	5.2 (1.7–15.9)
Smoking status[b]			
Nonsmokers	1.0	0.6 (0.1–5.9)	
Ex-smokers	2.0 (0.7–5.6)	1.8 (0.6–5.3)	2.9 (0.4–20.3)
Current smokers	5.8 (2.2–15.1)	8.8 (3.2–23.7)	12.3 (3.5–42.7)
Type of tobacco[c]			
Blond	1.0	1.1 (0.6–2.2)	1.7 (0.5–5.7)
Black	2.2 (1.3–3.6)	2.6 (1.5–4.6)	4.7 (1.7–13.2)
Total alcohol consumption[b]			
0–83	1.0	1.2 (0.7–2.2)	1.6 (0.6–4.8)
84+	3.6 (2.2–5.9)	5.4 (3.0–9.8)	10.5 (3.2–34.4)

[a] CI, confidence interval.
[b] Adjusted for age, residence, education, and alcohol consumption.
[c] Adjusted for age, residence, education, and pack-years of tobacco smoking.

Table 5 Relative risks of cancer of the mouth and pharynx for joint effects of tobacco smoking (pack-years), total alcohol consumption, and ever salted meat consumption, after adjusting for age, residence, and education

Pack-years	Alcohol	Salted meat	Cases/ controls	OR	95% CI[a]
<41	<83	Never	24/69	1.0	
<41	<83	Ever	18/49	1.0	0.5–2.1
<41	<83	Ever	18/49	1.0	0.5–2.1
<41	84+	Never	24/26	3.2	1.5–6.7
<41	84+	Ever	25/15	5.5	2.4–12.4
42+	<83	Never	22/32	1.9	0.9–3.9
42+	<83	Ever	19/16	3.9	1.7–8.9
42+	84+	Never	62/32	5.8	3.1–11.0
42+	84+	Ever	50/16	10.0	4.7–21.3

[a] CI, confidence interval.

tected with an OR of 10.5 for heavy drinkers and current salted meat consumers. The interactive term in the multiplicative model which included salted meat and alcohol drinking was statistically significant. The joint effect of tobacco smoking, alcohol ingestion, and ever consumption of salted meat is shown in Table 5. The joint effect for heavy smokers, heavy drinkers, and ever consumers of salted meat displayed a 10-fold increase in risk.

Discussion

As expected, tobacco smoking and alcohol drinking were the main determinants of oropharyngeal cancer in this study, replicating previous findings (3–6, 9–14). Also, black tobacco smoking was associated with a 2-fold increase in the risk of oropharyngeal cancer, as shown in previous studies (3–5). Concerning food items, vegetable and fruit consumption were associated with reduced risk of oral cancer as shown in previous reports (3–4, 8–13).

Recently, Zheng *et al.* (6) reported an increase in the risk of oropharyngeal cancer associated with the consumption of salted fish/meat. This new finding could be of great importance in the understanding of oral and pharyngeal cancer etiology. Our study replicates this finding, mainly for current exposure. Salted fish/meat has been implicated in the causation of cancer in a number of sites, such as the nasopharynx (14), nasal cavity (15, 16), stomach (17), larynx (18), and lung (19). In the Uruguayan setting, ever use of salted meat has been associated with a 2-fold increase in the risk of stomach cancer (17). This study suffered from a restricted food frequency questionnaire. Of particular interest was the study of Zheng *et al.* (18), according to which salted meat was associated with a 5-fold increase in the risk of laryngeal cancer. Although the food-frequency question-

naire was still limited, it covered more than 30 items. On the other hand, the similarities in etiological determinants between oropharyngeal and laryngeal cancer supports a role of salted meat in these closely linked neoplasms.

Uruguayan population is characterized by a heavy consumption of meat, whereas fish meat is a rather uncommon diet item. Dried and salt-preserved meat was a frequent dietary item, mainly in rural areas. Beef or lamb meat is embedded in rock salt and subsequently air dried. With the advent of refrigeration, a trend to lower consumption has been detected. Concerning the possible mechanism(s) of action of salted meat consumption, a role of *N*-nitroso compounds in the carcinogenesis of oropharyngeal cancer has been suggested by Zheng *et al.* (6). Gao *et al.* (20) reported the presence of *N*-nitrosodimethylamine and *N*-nitrosoethylamine in preserved meat. On experimental grounds, *N*-nitrosoethylamine was considered a carcinogen for esophageal, oral, and tracheal mucosa in different species (21–23). Swann (24) has shown that small amounts of ethanol alter the distribution and metabolism of small oral doses of *N*-nitrosodimethylamine and *N*-nitrosoethylamine in rats, to increase by severalfold the alkylation of DNA in organs, like the mouth and pharynx, that are particularly susceptible to their carcinogenic effect. The results have led to the hypothesis that the influence of alcohol ingestion on human cancer may be mediated through the effect of ethanol on the pharmacokinetics of nitrosamines derived from diet and tobacco smoking. This unified hypothesis has some support from the findings of this study, in which the joint effect of tobacco smoking, alcohol drinking, and salted meat consumption resulted in very high OR of 10.0 (95% confidence interval, 4.7–21.3).

Concerning methodological issues, selection bias appears to be of minor importance, taking into account the similar distribution of cases and controls by residence and education. We were concerned by the problem of the excluded cases due to advanced disease. We were unable to obtain proxy interviews for these subjects. Since they were very similar in age distribution and other sociodemographic characteristics, it is reasonable to suppose a similar set of exposures. The possibility of recall bias could be considered mainly for past consumption of salted meat; notwithstanding, there are no reasons to suspect that recalled salted meat consumption could have been different between cases and controls, since a large proportion of controls were afflicted with cancer (25, 26). Finally, residual confounding by tobacco smoking and alcohol drinking remains a matter of concern in a disease like oropharyngeal cancer, in which both factors are major determinants. However, we adjusted for tobacco smoking and alcohol drinking using Mantel-Haenszel analysis with increasing finer stratification, and the regression models included pack-years as continuous and categorical terms without significant changes in the ORs for salted meat. In conclusion, salted meat intake could have an important role in oropharyngeal carcinogenesis. It remains for future studies to replicate this finding and to elucidate in which step of the process salted meat consumption acts.

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