RESEARCH COMMUNICATION

# Meat Consumption, Meat Cooking and Risk of Lung Cancer Among Uruguayan Men

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## Abstract

**A case-control study was conducted in Uruguay, including 876 male cases of lung cancer and 876 male hospitalized controls, frequency matched for age (ten-year intervals), residence and hospital. The following explanatory variables were included in the study: fried red meat, barbecued red meat, boiled red meat, and salted red meat. These items were log transformed and energy-adjusted by the residuals method. The following potential confounders were included into the models: age, residence, hospital, education, family history of lung cancer, body mass index, smoking index, alcohol drinking, mate consumption, total energy intake, non-meat fatty foods and total fruits. The main objective was to estimate the odds ratios associated with lung cancer risk. Whereas fried meat, barbecued meat, and salted meat were positively associated with risk (OR of the highest quartile of salted meat versus the lowest, 2.90, 95 % CI 1.99-4.25, p-value for trend <0.0001), boiled red meat was mainly protective. We conclude that salted meat was the main risk factor. The mechanisms could be related to the content of N-nitroso compounds in salted meat.**

**Keywords:** Lung cancer - case-control study - meat consumption - Uruguayan males

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## Introduction

Lung cancer is the most frequent malignancy in Uruguayan males (Parkin et al., 2002). The male Uruguayan incidence rate is the highest among countries of South America and the Caribbean (Parkin et al., 2002). As elsewhere smoking is by far the major risk factor of lung cancer, followed by occupational risk and nutritional factors (World Cancer Research Fund/American Institute for Cancer Research, 2007).

Red meat (and processed meat) has been considered as implicated in lung carcinogenesis (World Cancer Research Fund/American Institute for Cancer Research, 2007). In fact red meat is a major source of saturated fat, cholesterol, heme iron, heterocyclic amines, and nitrosamines. Previous studies suggested that fat and cholesterol could be responsible of the carcinogenicity of red meat (Hinds, 1983; Goodman et al., 1988; Goodman et al., 1992; Alavanja et al., 1993; De Stefani et al., 1997; Linseisen et al., 2002). More recent publications have suggested that well-done red meat is a source of heterocyclic amines, powerful carcinogens in animal and human studies (Deneo-Pellegrini et al., 1996; Sinha et al., 1998; Sinha and Rothman, 1999; Sinha et al., 2000; Alavanja et al., 2001; De Stefani et al., 2002; Balder et al., 2005). Therefore, recent studies have focused the attention in cooking methods of red meat (Sinha et al., 2000; Cross et al., 2007; De Stefani et al., 2009; Lam et al., 2009). Furthermore, Uruguay is the leading producer of beef in the World (Matos and Brandani, 2002).

For this reason we considered timely to conduct a study in Uruguay, a high-risk country, analyzing the cooked method of red meat in relation with the risk of lung cancer. Thus, we hypothesized that well-done red meat is a strong risk factor for lung cancer in Uruguayan males.

## Materials and Methods

*Selection of cases and controls*

In the time period 1996-2004, all newly diagnosed and microscopically confirmed cases of lung cancer in males were considered eligible for this study. These cases were drawn from the four major public hospitals of Montevideo, Uruguay. In this period 896 cases of lung cancer were identified. From these cases, 20 patients refused the review, leaving 876 cases for inclusion in the study (response rate 97.8 %). These patients were distributed by cell type as follows: squamous cell carcinoma (301 patients, 34.4 %), small cell carcinoma (144, 16.4 %), adenocarcinoma (201, 22.9 %), and other types (large cell carcinoma, carcinoma not otherwise specified) (230, 26.3 %).

In the same time period and the same hospitals, all male patients hospitalized for conditions not related with

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smoking, alcohol drinking, and without recent changes in their diets were considered eligible for the study. One thousand and three hundred twenty two (1,322) patients were considered eligible. Three eighty (38) patients refused the interview leaving 1,284 patients as potential controls (response rate 97.2 %). From these potential controls, 876 patients were included into the study. They were frequency matched to cases on age, residence, and hospital. Controls were classified as follows: abdominal hernia (172 patients, 19.6 %), bone diseases (166, 18.9 %), eye disorders (152, 17.4 %), injuries (77, 8.8 %), diseases of the skin (75, 8.6 %), acute appendicitis (62, 8.1 %), varicose veins (45, 5.1 %), urinary stones (40, 4.6 %), hydatid cyst (35, 4.0 %), prostate hypertrophy (27, 3.1 %), and blood disorders (16, 1.8 %).

*Interviews and questionnaire*

All the participants (cases and controls) were interviewed in the hospital shortly after admittance by two trained social workers. They administered a structured questionnaire which included the following sections: sociodemographic variables (age, residence, education, 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, family history of cancer (including lung cancer) in first degree relatives, a complete history of smoking (age of start, age of quit, number of cigarettes smoked per day, type of tobacco, type of cigarette, inhalation practices), a complete history of alcohol drinking (age of start, age of quit, number of glasses drunk per day, type of beverage), a complete history of non alcoholic beverages (mate drinking, coffee, tea, soft drinks), and a food frequency questionnaire (FFQ) on 64 food items. This FFQ was considered as representative of the Uruguayan diet and allowed the estimation of total energy intake. It could also be tested for reproducibility with very good results (Ronco et al., 2006).

*Definition of meat variables*

In our FFQ, red meat was divided in beef and lamb. Both food items were classified according to the cooking method into fried, barbecued, boiled, and salted. Therefore red meat was classified into fried meat, barbecued meat, boiled meat, and salted meat. These variables were log transformed and energy-adjusted using the residuals method.

*Statistical analysis*

Relative risks, approximated by the odds ratios, was estimated by unconditional multiple logistic regression (Breslow and Day, 1980) for types of red meat. We fitted a multivariate equation with included the following terms: age (continuous), residence (categorical, 3 strata), hospital (categorical, 4 strata), education (categorical, 3 strata), family history of lung cancer among first-degree relatives (ordinal), body mass index (continuous), smoking index (categorical, 8 strata), alcohol drinking (categorical, 5 strata), mate consumption (4 strata), total energy intake (continuous), non-meat fatty foods (continuous), and total fruit consumption (continuous). The terms of cooked red meat were estimated for each one and then all adjusted for the others. Odds ratios for histologic type were estimated using polytomous regression, taking as base outcome the controls (Rothman and Greenland, 1998). Goodness-of-fit was estimated by the method of Hosmer-Lemeshow (Hosmer et al., 1988). The level of statistical significance was alpha=0.05 %. Standard deviation was estimated by the robust method. All calculations were done with STATA version 9.1 (STATA, 2005).

## Results

The distribution of cases and controls by sociodemographics and selected risk factors is shown in Table 1. As a result of the matched design, age, residence and hospital were similar among cases and controls. Education and income were also similar between both groups of participants. Family history of lung cancer was higher among cases compared with controls (OR 2.3, 95 % CI 1.6-3.5). Also cases were leaner compared with controls

**Table 1. Distribution of Cases and Controls by Socio-Demographic Variables and Selected Risk Factors**

| | | Cases | | Controls | | Global |
|---|---|---|---|---|---|---|
| Variable | Category | N° | % | N° | % | p-value |
| Age (years) | 30-39 | 14 | 1.6 | 14 | 1.6 | |
| | 40-49 | 95 | 10.8 | 95 | 10.8 | |
| | 50-59 | 205 | 23.4 | 205 | 23.4 | |
| | 60-69 | 341 | 38.9 | 341 | 38.9 | |
| | 70-79 | 203 | 23.2 | 203 | 23.2 | |
| | 80-89 | 18 | 2.1 | 18 | 2.1 | 1.00 |
| Residence | Capital | 444 | 50.7 | 444 | 50.7 | |
| | Urban counties | 256 | 29.2 | 256 | 29.2 | |
| | Rural counties | 176 | 20.1 | 176 | 20.1 | 1.00 |
| Hospital | Cancer | 173 | 19.7 | 176 | 19.7 | |
| | Pasteur | 231 | 26.4 | 231 | 26.4 | |
| | Clínicas | 254 | 29.0 | 254 | 29.0 | |
| | Maciel | 218 | 24.9 | 218 | 24.9 | 1.00 |
| Education (yrs) | 0-2 | 232 | 26.5 | 232 | 26.5 | |
| | 3-5 | 343 | 39.2 | 330 | 37.7 | |
| | 6+ | 301 | 34.3 | 314 | 35.8 | 0.77 |
| Income | <142 | 357 | 40.7 | 388 | 42.3 | |
| (dollars/month) | 143+ | 339 | 38.7 | 338 | 38.6 | |
| | Unknown | 180 | 20.6 | 150 | 17.1 | 0.42 |
| Family history | No | 796 | 90.9 | 840 | 95.9 | |
| of lung cancer | Yes | 80 | 9.1 | 36 | 4.1 | <0.001 |
| Body mass index | <22.7 | 283 | 32.3 | 219 | 25.0 | |
| | 22.8-24.7 | 225 | 25.7 | 219 | 25.0 | |
| | 24.8-27.0 | 179 | 20.4 | 219 | 25.0 | |
| | 27.1+ | 189 | 21.6 | 219 | 25.0 | 0.002 |
| Smoking index | Never smokers | 19 | 2.2 | 170 | 19.4 | |
| Cessation (yrs) | 20+ | 36 | 4.1 | 77 | 8.8 | |
| | 10-19 | 51 | 5.8 | 76 | 8.7 | |
| | 1-9 | 132 | 15.1 | 100 | 11.4 | |
| Cigarettes/day current smokers | 1-9 | 21 | 2.4 | 81 | 9.2 | |
| | 10-19 | 88 | 10.0 | 156 | 17.8 | |
| | 20-29 | 200 | 22.8 | 128 | 14.6 | |
| | 30+ | 329 | 37.6 | 88 | 10.0 | <0.0001 |
| N° patients | | 876 | 100.0 | 876 | 100.0 | |

(OR 0.7, 95 % CI 0.5-0.9). Finally current heavy smokers displayed a high OR compared with never smokers (OR 33.4, 95 % 16.7-66.9).

Odds ratios of lung cancer for red meat consumption is shown in Table 2. Fried meat and barbecued red meat were directly associated with increased risk of lung cancer (OR for the highest quartile of fried meat versus the lowest one 1.65, 95 % CI 1.19-2.30, p-value for trend=0.003). On the other hand boiled red meat was inversely associated with risk of lung cancer (OR 0.81, 95 % CI 0.58-1.13, p-value for trend=0.04). Finally salted meat intake displayed a high risk of lung cancer (OR 2.90, 95 % CI 1.99-4.25, p-value for trend <0.0001). This model presented a high goodness-of-fit of 0.89.

Odds ratios of lung cancer for red meat intake stratified by histology are shown in Table 3. Squamous cell carcinoma (SCC) was positively associated with fried meat, barbecued meat, and salted meat intakes (OR for barbecued meat 2.28, 95 % CI 1.44-3.60) and inversely associated with boiled red meat consumption (OR 0.66, 95 % CI 0.42-1.02). Small cell carcinoma (SCLC) was directly associated with barbecued meat and salted meat

**Table 2. Odds Ratios of Lung Cancer for Red Meat Consumption**

| Meat preparation | Servings/week | Cases/Controls | OR [1] 95 % CI | OR [2] 95 % CI |
|---|---|---|---|---|
| Fried red meat | <1.0 | 189/219 | 1.0 reference | 1.0 reference |
| | 1.1-2.4 | 200/219 | 1.13 0.82-1.57 | 1.18 0.84-1.65 |
| | 2.5-3.7 | 211/219 | 1.31 0.95-1.81 | 1.38 0.98-1.92 |
| | 3.8+ | 276/219 | 1.67 1.22-2.28 | 1.65 1.19-2.30 |
| | | p-value trend | 0.001 | 0.003 |
| Barbecued meat | <0.5 | 177/219 | 1.0 reference | 1.0 reference |
| | 0.6-1.0 | 217/219 | 1.40 1.01-1.94 | 1.26 0.91-1.75 |
| | 1.1-2.2 | 222/219 | 1.30 0.94-1.79 | 1.24 0.89-1.72 |
| | 2.3+ | 260/219 | 1.64 1.19-2.26 | 1.57 1.13-2.18 |
| | | p-value trend | 0.007 | 0.02 |
| Boiled meat | <1.2 | 243/219 | 1.0 reference | 1.0 reference |
| | 1.3-2.5 | 242/219 | 0.90 0.67-1.22 | 0.88 0.65-1.20 |
| | 2.6-4.5 | 164/219 | 0.58 0.42-0.80 | 0.59 0.42-0.81 |
| | 4.6+ | 227/219 | 0.73 0.53-1.01 | 0.81 0.58-1.13 |
| | | p-value trend | 0.01 | 0.04 |
| Salted red meat | 0 | 175/219 | 1.0 reference | 1.0 reference |
| | 0.1-0.5 | 194/219 | 1.46 1.03-2.05 | 1.50 1.06-2.11 |
| | 0.6-1.7 | 187/219 | 1.55 1.03-2.32 | 1.62 1.07-2.45 |
| | 1.8+ | 320/219 | 2.80 1.92-4.09 | 2.90 1.99-4.25 |
| | | p-value trend | <0.0001 | <0.0001 |

[1]Multivariate odds ratios adjusted for age, residence, hospital, education, family history of lung cancer among first-degree relatives, body mass index, smoking index, alcohol drinking, mate amount, total fruits, total energy intake, non-meat fatty foods, and each meat type preparation; [2]Multivariate odds ratios with the same terms and all types of red meat adjusted for each other

**Table 3. Odds Ratios of Lung Cancer for Red Meat Intake by Histology[1]**

| | Squamous cell | | Small cell | | Adenocarcinoma | |
|---|---|---|---|---|---|---|
| Type of red meat | OR | 95 % CI | OR | 95 % CI | OR | 95 % CI |
| Fried red meat | 1.0 | reference | 1.0 | reference | 1.0 | reference |
| | 1.18 | 0.74-1.88 | 1.20 | 0.70-2.08 | 1.97 | 1.15-3.38 |
| | 1.47 | 0.94-2.32 | 1.48 | 0.87-2.52 | 2.12 | 1.23-3.67 |
| | 1.69 | 1.09-2.62 | 1.56 | 0.89-2.74 | 2.25 | 1.31-3.86 |
| | 0.01 [2] | | 0.13 | | 0.004 | |
| Barbecued red meat | 1.0 | reference | 1.0 | reference | 1.0 | reference |
| | 1.54 | 0.96-2.45 | 1.06 | 0.61-1.83 | 1.74 | 1.01-2.98 |
| | 1.75 | 1.11-2.77 | 1.20 | 0.71-2.05 | 1.84 | 1.09-3.10 |
| | 2.28 | 1.44-3.60 | 1.61 | 0.95-2.72 | 2.60 | 1.56-4.34 |
| | 0.001 | | 0.10 | | <0.0001 | |
| Boiled red meat | 1.0 | reference | 1.0 | reference | 1.0 | reference |
| | 0.90 | 0.61-1.34 | 0.81 | 0.49-1.33 | 0.91 | 0.57-1.44 |
| | 0.54 | 0.35-0.85 | 0.47 | 0.27-0.80 | 0.63 | 0.39-1.05 |
| | 0.66 | 0.42-1.02 | 0.67 | 0.39-1.14 | 0.90 | 0.55-1.48 |
| | 0.01 | | 0.04 | | 0.41 | |
| Salted red meat | 1.0 | reference | 1.0 | reference | 1.0 | reference |
| | 1.35 | 0.84-2.17 | 1.62 | 0.91-2.88 | 1.36 | 0.80-2.33 |
| | 1.47 | 0.85-2.54 | 1.47 | 0.75-2.87 | 1.69 | 0.92-3.09 |
| | 2.73 | 1.68-4.43 | 2.66 | 1.42-4.99 | 2.78 | 1.63-4.75 |
| | <0.0001 | | 0.002 | | <0.0001 | |

[1]Multivariate odds ratios adjusted by age, residence, hospital, education, family history of lung cancer among first-degree relatives, body mass index, smoking status, smoking cessation, smoking intensity, alcohol drinking, mate consumption, total energy intake, non-meat fatty foods, total fruit consumption and all types of meat consumed; [2]*p*-value for linear trend

consumption (OR for salted meat 2.66, 95 % CI 1.42-4.99) and inversely associated with boiled red meat (OR 0.67, 95 % CI 0.39-1.14, p-value for trend=0.04).

Finally adenocarcinoma of the lung was positively associated with fried, barbecued, and salted meat intakes, with similar increases in risk for each case, but boiled meat was not associated with risk of lung cancer.

## Discussion

According to this study fried meat, barbecued meat, and salted meat were positively associated with risk of lung cancer, whereas boiled meat was mainly protective. This emphasizes the importance of the cooking method of red meat in lung carcinogenesis.

Previous studies on fat, cholesterol, and risk of lung cancer (Hinds, 1983; Goodman et al., 1988; Goodman et al., 1992; Alavanja et al., 1993; Deneo-Pellegrini et al., 1996; De Stefani et al., 1997; De Stefani et al., 2002; Linseisen et al., 2002) suggested that both nutrients were directly associated with risk of lung cancer. Nevertheless, a large pool analysis failed to replicate these previous findings (Smith-Warner et al., 2002). More recently, meat consumption have been extensively studied in relation with lung cancer (Sinha et al., 1998; Sinha and Rothman, 1999; Sinha et al., 2000; Alavanja et al., 2001; Matos and Brandani, 2002 Balder et al., 2005; Cross et al., 2007; De Stefani et al., 2009; Lam et al., 2009). Also the role of meat mutagens was directly associated with the risk of lung cancer (De Stefani et al., 2009; Lam et al., 2009). Thus, the evidence links saturated fat, cholesterol, red meat, and meat mutagens with lung cancer.

The mechanisms through which these nutrients, mutagens, and doneness of red meat is largely unknown. Nevertheless both meat mutagens and well done red meat have been hypothesized as an important source of heterocyclic amines, powerful carcinogens in animal and human studies (Sinha et al., 1998; Sinha and Rothman, 1999; Sinha et al., 2000; Alavanja et al., 2001; Cross et al., 2007; De Stefani et al., 2009; Lam et al., 2009). These amines has been extensively studied (Sinha, 2002). Furthermore, as suggested by Weisburger (Weisburger, 2002), heterocyclic amines appear to be initiators in lung carcinogenesis and saturated fat could act as a promoter.

To our knowledge there is one study which reported a positive association between salted meat intake and lung cancer; this study was unpublished yet. Salted meat is prepared by salting and air-drying red meat (usually lamb) and is generally ingested in stews. Moreover, salted meat was a common item in Uruguayan diet before the advent of refrigeration in the late years of the twenties. Nowadays, its consumption is not very frequent. Salted meat is a rich source of salt and nitrites. Moreover it has been suggested that salted meat is rich in nitrosamines (Lijinsky, 1999). These chemicals are considered as potent carcinogens. Furthermore, salted meat promoted lipid oxidation (Basu and Marrett, 1983; Torres et al., 1989; Ferrari and Torres, 2002), and is a source of malondialdehyde, considered as a mutagen (Basu and Marrett, 1983) Our results suggest that salted meat is a more potent carcinogen compared with fried and barbecued well done red meat.

As other case-control studies, our study has several limitations. Although selection bias is a difficult to eliminates. The results after stratification by potential determinants of selection bias (residence, education, income) have minimized this major problem. Recall bias may bean important source of error. In fact, at difference with prospective studies, case-control studies are specially prone to recall bias. Since cases, controls, interviewers and, also the general population, is unaware of the importance of diet in the etiology of lung cancer, differential misclassification is unlikely. In fact, non-differential misclassification is more probable. This type of bias could result in estimates closer to the null. Another limitation is the lack of validation of our FFQ. Nevertheless this questionnaire was tested for reproducibility with good results. Our study has also strengths. Perhaps, the major strength was the high response rate, both for cases and controls. Another strength is related with the same catchments areas in both series of participants, regarding hospital and residence. The microscopic validation of histology by expert pathologists is another strength. Since smoking is a potent confounder in studies on diet and lung cancer, we adjusted red meat intake for a smoking index which included smoking status, smoking cessation and smoking intensity (Boshuizen et al., 2002).

In summary, the major finding of this study is the strong positive association between salted meat intake and risk of lung cancer. Also other cooking methods were directly associated with this malignancy and doneness of red meat is a strong risk factor for lung cancer. Although these food determinants of lung carcinogenesis are strong risk factors, smoking remains the major problem and cessation of this habit should be the major objective for public health planning.

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