Processed meat consumption and risk of cancer: a multisite case–control study in Uruguay

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BACKGROUND: The role of processed meat in the aetiology of several cancers was explored in detail.

METHODS: In the time period 1996–2004, a multisite case–control study was conducted in Montevideo, Uruguay. The study included 6 060 participants (3 528 cases and 2 532 controls) corresponding to cancers of the oral cavity, pharynx, oesophagus, stomach, colon, rectum, larynx, lung, female breast, prostate, urinary bladder, and kidney (renal cell carcinoma only).

RESULTS: The highest odds ratios (ORs) were positively associated with cancers of the colon, rectum, stomach, oesophagus, and lung. With the exception of renal cell carcinoma, the remaining cancer sites were significantly associated with elevated risks for processed meat consumption. Furthermore, mortadella, salami, hot dog, ham, and salted meat were strongly associated with risk of several cancer sites.

CONCLUSION: It could be concluded that processed meat intake could be a powerful multiorgan carcinogen.

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Uruguay is a developing country characterised by high incidence rates of cancer (ASR 386.0 cases per 100 000 males and 303.2 cases per 100 000 females; Parkin et al, 2002). The leading cancer site among men is the lung, whereas the main cancer site among women is the breast, following the pattern of the developed countries. The main reasons for these elevated rates are related to the prevalence of tobacco smoking, alcohol drinking, the high consumption of red meat, and the low consumption of vegetables and fruits.

In fact, the Uruguayan population is characterised by a very high consumption of red meat (the highest in the world (Matos and Brandani, 2002)), a high consumption of processed meat, and a low intake of white meat. Several reports have suggested that processed meat is linked to the aetiology of frequent malignancies like gastric cancer and colon cancer (Larsson et al, 2006; Cross et al, 2007). In fact, the consumption of processed meat is much higher in Uruguay compared with consumption in the United States (Cross et al, 2007).

For this reason, we decided to conduct a multisite case–control study in order to explore the role of processed meat in 11 cancer sites in Uruguay.

MATERIALS AND METHODS

Selection of cases

In the time period 1996–2004, all newly diagnosed and microscopically confirmed cases of cancers of the oral cavity, pharynx, oesophagus, stomach, colon, rectum, larynx, lung, female breast, prostate, bladder, and kidney were considered eligible for this study (3 641 cases). One hundred and thirteen patients refused the interview, leading to a final total of 3 528 cases (2 648 men and 880 women) (response rate: 96.9%). All the cases were drawn from the four major public health hospitals of Montevideo. These hospitals admit only patients of low socioeconomic status, with a monthly income <200 US dollars.

Selection of controls

In the same time period and in the same hospitals, all patients with conditions not related to smoking and drinking were considered eligible for the study. In this period, 2 608 potential controls were approached for a possible participation and 76 patients refused the interview, leaving a final number of 2 532 controls (response rate: 99.1%). These controls presented the following diseases: eye disorders (622 patients, 24.6%), abdominal hernia (513 patients, 20.3%), fractures (258 patients, 10.2%), injuries (200 patients, 7.9%), varicose veins (178 patients, 7.0%), acute appendicitis (176 patients, 6.9%), diseases of the skin (160 patients, 6.3%), hydatid cyst (127 patients, 5.0%), urinary stones (119 patients, 4.7%), blood disorders (89 patients, 3.5%), bone disorders (50 patients, 2.0%), and prostate hypertrophy (40 patients, 1.6%).

Interviews and questionnaire

All the participants (6 060 cases and controls) were interviewed shortly after admission to the hospital by two trained social workers, unaware of the purposes of the present study. In all the instances, the interview was conducted face to face and proxy interviews were not allowed. The participants were administered a
structured questionnaire, which included the following sections: (1) a sociodemographic section (age, sex, residence, education, monthly income), (2) an occupational history based on the basis of the last four jobs and their duration, (3) self-reported height and weight, 5 years before the date of the interview, (4) a complete smoking history (age at start, age at quit, number of cigarettes smoked per day, type of tobacco, type of cigarette, inhalation practices), (5) a complete alcohol-drinking history (age at start, age at quit, number of glasses drunk per day, type of alcoholic beverage), (6) a complete history of non-alcoholic beverages (age at start, age at quit, number of cups per day, type of beverage: mate, coffee, soft drinks), (7) menstrual and reproductive events, (8) a food frequency questionnaire (FFQ) on 64 food items. This FFQ was recorded in servings per week and was previously tested for reproducibility with good results (Ronco et al, 2006).

Components of processed meat
The following meats were analysed in the study: bacon, sausage, mortadella, salami, saucisson, hot dog, ham, and air-dried and salted lamb. These components were energy-adjusted by the residual method (Willett, 1998).

Statistical analysis
Relative risks, approximated by the OR, were estimated by unconditional logistic multiple regression (Rothman et al, 2008).

Table 1 Number and percentages by cancer sites and controls

| Cancer site          | Males Number (%) | Females Number (%) | Both sexes Number (%) |
|----------------------|------------------|--------------------|-----------------------|
| Oral/pharynx         | 27.4 (10.3)      | 9 (1.0)            | 283 (8.0)             |
| Oesophagus           | 184 (6.9)        | 50 (5.7)           | 234 (6.6)             |
| Stomach              | 190 (7.2)        | 84 (9.5)           | 274 (7.8)             |
| Colon                | 87 (3.3)         | 89 (10.5)          | 176 (5.0)             |
| Rectum               | 127 (4.8)        | 58 (6.6)           | 185 (5.2)             |
| Larynx               | 274 (10.3)       | 7 (0.8)            | 281 (8.0)             |
| Lung                 | 865 (32.7)       | 55 (6.3)           | 920 (26.1)            |
| Breast               | —                | 461 (52.4)         | 461 (13.1)            |
| Prostate             | 345 (13.0)       | —                  | 345 (9.8)             |
| Bladder              | 225 (8.5)        | 30 (3.4)           | 255 (7.2)             |
| Kidney               | 77 (2.9)         | 37 (4.2)           | 144 (4.3)             |
| All cases            | 2648 (100.0)     | 880 (100.0)        | 3528 (100.0)          |
| All controls         | 1640 (100.0)     | 892 (100.0)        | 2532 (100.0)          |

Table 2 Means of cancer sites and controls for age, education, smoking intensity, alcohol drinking, and processed meat

| Cancer site          | Age (years) | Education (years) | Smoking (cigarettes per day) | Alcohol (ml/ethanol per day) | Processed meat (grams per day) |
|----------------------|-------------|-------------------|-----------------------------|------------------------------|--------------------------------|
|                      | Men         | Women             | Men                         | Women                        | Men                           | Women                        |
| Oral/pharynx         | 60.0        | 54.9              | 4.3                         | 4.4                          | 27.6                          | 14.0                          |
| Oesophagus           | 65.5        | 68.9              | 3.5                         | 3.8                          | 22.2                          | 7.0                           |
| Stomach              | 66.1        | 64.3              | 3.6                         | 4.7                          | 20.3                          | 5.9                           |
| Colon                | 63.9        | 64.6              | 4.7                         | 4.3                          | 22.0                          | 5.5                           |
| Rectum               | 66.1        | 66.5              | 4.2                         | 6.1                          | 20.1                          | 3.0                           |
| Larynx               | 62.3        | 53.7              | 4.1                         | 5.7                          | 32.9                          | 18.3                          |
| Lung                 | 62.1        | 59.4              | 4.2                         | 5.2                          | 32.3                          | 20.5                          |
| Breast               | 59.7        | —                 | —                           | 5.3                          | 32.3                          | 20.5                          |
| Prostate             | 70.6        | —                 | 3.7                         | —                            | 18.0                          | —                             |
| Bladder              | 67.2        | 65.7              | 4.4                         | 4.5                          | 21.1                          | 7.2                           |
| Kidney               | 61.6        | 58.5              | 4.5                         | 5.2                          | 20.1                          | 6.2                           |
| All cases            | 64.2        | 61.6              | 4.1                         | 5.1                          | 26.6                          | 5.9                           |
| All controls         | 64.2        | 60.5              | 4.2                         | 4.8                          | 18.0                          | 4.1                           |

As the number of controls was smaller than the number of cases, we were unable to use multiple polynomial regression, and the ORs for each cancer site for processed meat intake were estimated by unconditional multiple logistic regression. We fitted the following model for each site including age (continuous), sex (when necessary), residence (urban, rural), education (categorical, 3 strata), body mass index (continuous), smoking index (smoking status, smoking cessation, number of cigarettes smoked per day among current smokers, categorical, 8 strata), alcohol drinking (categorical, 5 strata), maternal consumption (categorical, 4 strata), total energy (continuous), total vegetables and fruits (continuous), total white meat (continuous), and red meat (continuous). We then included 3 terms for meat intake (red, processed and white meat) to capture the effect of total meat in each estimation. All the calculations were performed using the STATA software (Stata Corp., College Station, TX, USA), release 11 (StataCorp., 2008).

RESULTS
The distribution of cases and controls by cancer site, stratified by sex, is shown in Table 1. For both sexes, lung cancer occupied the first place (26.1%), followed by breast cancer (13.1%), colorectal cancer (10.2%), and prostate cancer (9.8%).

Cases and controls showed similar age and education, the cases being heavy smokers, and consuming more alcohol and mate than controls (Table 2).

Odds ratios of cancer sites for processed meat intake are shown in Table 3. Cancers of the colon (OR for the highest tertile vs the first tertile 2.75, 95% CI 1.80–4.22), rectum (OR 2.14, 95% CI 1.42–3.22), colorectum (OR 2.39, 95% CI 1.76–3.24), stomach (OR 2.60, 95% 1.83–3.70), and larynx (OR 2.37, 95% CI 1.59–3.53) showed the highest risks. With the exception of oropharyngeal cancer and renal cell carcinoma, the remaining sites displayed a significantly positive association with processed-meat consumption, including cancers of the oesophagus, lung, upper aerodigestive tract, female breast, prostate, and urinary bladder. The model fitted included white meat and red meat intakes, thus it captured total meat in the estimations.

Odds ratios of cancer sites for different types of processed meat are shown in Table 4. Curiously, bacon was inversely associated with most cancer sites and sausage was not associated with the risk of cancer. On the other hand, mortadella intake was positively associated with cancers of the stomach (OR 1.13, 95% CI 1.02–1.26), colon (OR 1.18, 95% CI 1.04–1.34), larynx (OR 1.28, 95% CI 1.14–1.42), lung (OR 1.15, 95% CI 1.07–1.23), breast (OR 1.29, 95% CI 1.16–1.43), and prostate (OR 1.29, 95% CI 1.16–1.42). Similarly,
Table 3 Odds ratios of cancer sites for processed meat consumption\textsuperscript{a,b,c,d,e}

| Cancer site                        | OR (95% CI) | P-value |
|-----------------------------------|------------|---------|
|                                   | I \leq 1.4 | II 11.5–28.2 | III 28.3+ |
| Oral/pharynx                      | 1.0        | 1.21 (0.79–1.87) | 1.42 (0.95–2.13) | 0.07 |
| Esophagus                         | 1.0        | 1.25 (0.81–1.94) | 1.67 (1.08–2.60) | 0.02 |
| Stomach                           | 1.0        | 2.05 (0.90–4.68) | 3.02 (1.40–6.52) | 0.004 |
| Stomach/rectum                    | 1.0        | 1.60 (1.02–2.49) | 1.93 (1.25–2.98) | 0.003 |
| Colan                             | 34/844     | 62/844 | 80/844 | 0.0001 |
| Rectum                            | 1.0        | 1.76 (0.94–3.32) | 2.01 (1.07–3.76) | 0.03 |
| Rectum/colon                      | 1.0        | 2.25 (1.19–4.23) | 3.53 (1.93–6.46) | <0.0001 |
| Colon/rectum                      | 75/844     | 127/844 | 159/844 | 0.0001 |
| Larynx                            | 47/844     | 85/844 | 140/844 | <0.0001 |
| UADT                              | 154/844    | 248/844 | 396/844 | <0.0001 |
| Lung                              | 176/844    | 310/844 | 434/844 | <0.0001 |
| Breast                            | 127/844    | 161/844 | 173/844 | 0.0001 |
| Prostate                          | 75/844     | 134/844 | 136/844 | 0.002 |
| Bladder                           | 54/844     | 98/844 | 103/844 | 0.001 |
| Kidney                            | 29/844     | 38/844 | 47/844 | 0.07 |
| Urinary tract                     | 83/844     | 136/844 | 150/844 | 0.02 |
| All sites                         | 734/844    | 121/844 | 157/844 | <0.0001 |

Abbreviations: CI = confidence interval; OR = odds ratio. *Multivariate adjusted for age, residence, body mass index, smoking status, smoking cessation, number of cigarettes smoked per day among current smokers, alcohol drinking, mate consumption, total energy, total vegetables and fruits, total white meat, and red meat intakes. \textsuperscript{1}Number of cases and controls by intake of processed meat (both sexes). \textsuperscript{2}Men. \textsuperscript{3}Women. \textsuperscript{4}Cancer of the upper aerodigestive tract (oral, pharynx, esophagus, larynx).  

**DISCUSSION**

According to our study, processed meat intake was positively associated with cancers of the esophagus, stomach, colon, rectum, larynx, lung, breast, prostate, and urinary bladder. Therefore, processed meat could be said to act as a multiorgan carcinogen among humans (World Cancer Research Fund/American Institute for Cancer Research, 2008).

Moreover, our study replicates the findings of previous reports (Larsson et al, 2006; Cross et al, 2007; Santarelli et al, 2008), which strongly suggest that processed meat consumption was associated with an increased risk of gastric and colorectal cancers.

The mechanisms of processed meat are somehow conflictive, but ham, salt (mainly for gastric cancer), aromatic amines, nitrates, and nitrosamines are strong candidates for explaining the effect of cured meats (Santarelli et al, 2008) in the process of carcinogenesis.

Oesophageal cancer, mainly the squamous cell histologic type, has been positively associated with the consumption of air-dried and salted lamb through the presence of nitrosamines. In our report, oesophageal carcinoma displayed an increased risk of 96%, which was highly significant.

Gastric cancer was strongly associated with intake of processed meat, mainly with mortadella, sausisson, hot dog, and ham. All these types of processed meat are high in salt, an enhancing chemical in gastric carcinogenesis (Correa et al, 1985; Chen et al, 1990; Nazario et al, 1993). The comprehensive meta-analysis by Larsson et al (2006) analysed all the studies dealing with stomach cancer and processed meat, both case–control and cohort, and they concluded that processed meat is possibly a strong carcinogen in this organ. Several studies also concluded that processed meat is a possible agent in gastric carcinogenesis (De Stefani et al, 2001, 2004; Boeing et al, 1991; Larsson et al, 2006).

According to the prospective study by Cross et al (2007), processed meat increases significantly the risk of developing colorectal cancer. Their findings have been replicated in numerous studies on colorectal cancer and processed meat intake (Goldbohm et al, 1994). According to a study by Goldbohm et al (1994), an intake of > 20 g per day of processed meat was associated with an increased risk of 72% for colorectal carcinoma.

Lung cancer has been considered as directly associated with meat intake. In the present study, lung cancer displayed an increased risk of 88% for consumption of processed meat. When lung cancer risk was examined for the components of the processed meat group, there was significant increase in risk for mortadella, salami, hot dog, ham, and salted meat intakes. Not all studies found an increase in risk of lung cancer. In the EPIC prospective study, Linseisen et al (2011) only found a modest increase of lung cancer for processed meat intake. On the other hand, Lam et al (2009) reported a significant increase...
in the risk of lung cancer of 71% for weekly consumption of processed meat.

Female breast cancer is the higher malignancy among Uruguayan women with an ASIR of 116 persons per 100,000 (Parkin et al., 2002). In fact, this rate is the highest in the world (Parkin et al., 2002). Studies conducted in Uruguay reported elevated risks for red meat intake (Ronco et al., 1996; De Stefani et al., 1997; Ronco et al., 2006). In the present study, breast cancer showed an increased risk of 82% for high intake of processed meat. In a study by Pala et al. (2009), postmenopausal women afflicted with breast cancer showed an increased risk of 13% (P = 0.06), whereas the study by Aune et al. (2009) displayed an increased risk of 53% for consumption of processed meat among women afflicted with breast cancer.

Prostate cancer is the second malignancy in frequency among Uruguay men, following lung cancer (Parkin et al., 2002).
According to the report by the World Cancer Research Fund (World Cancer Research Fund/American Institute for Cancer Research, 2008), processed meat intake has a suggestive role among those men afflicted with this malignancy. In the present study, patients with prostate cancer showed an increased risk of 72% per 28 g per day. Sinha et al (2009) studied the risk of advanced prostate cancer and found an increased risk of 32% per 25 g per 1000 cal. Thus, our findings replicate those reported by Sinha et al (2009).

In our study, bladder cancer showed a significant increased risk for both sexes with a magnitude similar to that observed for prostate cancer. In a prospective study by Michaud et al (2006), frequent consumption of bacon was positively associated with a relative risk of 2.1 (P-value for trend = 0.006). Furthermore, this association was stronger among never smokers. On the contrary, in our study bacon intake was inversely associated with the risk of bladder cancer. This difference could be explained by the low consumption of bacon among the Uruguayan population (mean intake of bacon: 1.1 g daily). On the contrary, we found rather elevated risks for bladder cancer in our study, directly associated with the intake of hot dogs, ham, and salted meat.

Like other case–control studies, the present study is subject to several potential biases, such as selection bias and recall bias. Nevertheless, the Uruguayan population is mainly unaware of the potential danger of a high consumption of processed meat. This also applies to interviewers. Our study has several strengths. In the first place, the statistical power of the study is a strength. Second, all the cases were microscopically validated by expert pathologists. Finally, the high response rate for cases and controls is another significant strength of the study.

In summary, we conducted a sizeable case–control study on the role of processed meat consumption in several cancer sites. The results were consistently associated with an elevation in risk for most cancer sites, suggesting that processed meat consumption could be a possible risk factor for various cancer sites.

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Conflict of interest

The authors declare no conflict of interest.

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