Cancer Therapy Vol 7, 174-187, 2009

Meat consumption and cancer risk: a multisite case-control study in Uruguay

Research Article

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Key words: Meat, diet, food, cancer, epidemiology

Abbreviations: food frequency questionnaire, (FFQ); heterocyclic amines, (HCA); polycyclic aromatic hydrocarbons, (PAH); World Cancer Research Fund/American Institute for Cancer Research, (WCRF/AICR)

Received: 24 February 2009; Revised: 9 March 2009
Accepted: 12 March 2009; electronically published: April 2009

Summary

There is strong evidence that meat intake increases the risk of colorectal cancer. However, for other cancer sites there is currently less convincing evidence. To further explore the association between meat intake and cancer risk we conducted a case-control study of 26 cancer sites in Uruguay between 1988 and 2000, including 6892 cancer cases and 1832 hospital controls. Unconditional logistic regression was used to estimate multivariate adjusted odds ratios (ORs) and 95% confidence intervals of various cancers for intake of total meat, red meat, beef, lamb and processed meat. There was a statistically significant increase in the odds of cancers of the mouth and pharynx (OR=1.63), esophagus (OR=3.30), larynx (OR=1.85), stomach (OR=4.02), colorectum (OR=1.78), lung (OR=1.59), sarcomas (OR=2.27), prostate (OR=1.58), bladder (OR=1.68), kidney (OR=1.96), nervous system (OR=3.12), thyroid (OR=2.38) and of non-Hodgkin's lymphoma (OR=1.79), myeloma (OR=3.28) and all cancer sites combined (OR=1.61) with high intake of total meat and similar findings were found with red meat, beef and lamb. Intake of processed meat was associated with increased odds of cancers of the pharynx (OR=1.90), esophagus (OR=1.51), larynx (OR=2.03), stomach (OR=4.39), colorectum (OR=1.76), breast (OR=1.23), non-Hodgkin's lymphoma (OR=2.01), leukemia (OR=2.11) and with all cancer sites combined (OR=1.32). Our results confirm earlier findings of increased risk of gastrointestinal cancers with higher meat intake and suggest that meat consumption increases the risk of multiple other cancer sites.

I. Introduction

Previous studies have reported elevated cancer risks with a high intake of total meat, red meat and processed meat (World Cancer Research Fund/American Institute for Cancer Research, 2007). Although an increased risk of colorectal cancer is well established (Larsson and Wolk, 2006; World Cancer Research Fund/American Institute for Cancer Research, 2007) there are a number of other types of cancer where the current evidence suggest there may be an increased risk, including cancers of the esophagus, lung, stomach, pancreas, prostate and endometrium (World Cancer Research Fund/American Institute for Cancer Research, 2007). Uruguay is the country with the highest per capita meat consumption in the world (Speedy, 2003) and cancer rates are also very high. The age-standardised incidence-rates for cancers of the colorectum, lung, prostate and for all sites except non-melanoma skin cancer among men, are 39.6, 60.0, 46.6 and 320.4 per 100 000 persons per year, respectively (Ferlay et al, 2002). Among women rates of breast cancer and all cancer sites except non-melanoma skin cancer are also high with age-standardised incidence rates of 63.1 and 237.5 per 100,000 persons per year, respectively (Ferlay et al, 2002). Thus, Uruguay is an interesting setting for investigating the association between meat intake and cancer risk. Several previous studies conducted in this population suggested increased risk of multiple cancers including those of the upper aerodigestive tract (De Stefani et al, 1994, 1995, 1999; Oreggia et al, 2001), stomach (De Stefani et al, 1990, 1998a), colorectum (De Stefani et al, 1997a), breast (De Stefani et al, 1997b), kidney (De Stefani et al, 1998b), lung (Deneo-Pellegrini et al, 1996; De Stefani et al, 2002) and of non-Hodgkin's lymphoma (De Stefani et al, 1998c), with high meat intake. Further, in a previous analysis of dietary patterns and cancer risk we reported increased risk of several cancers with a western dietary pattern, with high loadings of red and processed meat (De Stefani et al, 2009). However, no systematic evaluation of meat consumption and cancer risk across multiple sites has previously been conducted in this population. Three multisite case-control studies, two in Italy (Tavani et al, 2000; Levi et al, 2004) and one in Canada (Hu et al, 2008), previously reported increased risk of several cancers with high meat intake. Recently the NIH-AARP Diet and Health cohort study also suggested increased risk of multiple cancers with high red and processed meat intake (Cross et al, 2007). To further expand upon these findings we decided to explore the association between meat consumption and cancer risk in a case-control study of 26 types of cancer in Uruguay.

II. Material and methods

In the time period between 1988 and 2000 we conducted a case-control study including cancers of the mouth (n=251), pharynx (n=243), esophagus (n=374), stomach (n=128), colon (n=177), rectum (n=200), pancreas (n=104), larynx (n=275), lung (n=1174), female breast (n=1607), cervix uteri (n=253), corpus uteri (n=82), ovary (n=83), prostate (n=376), testis (n=62), bladder (n=183), kidney (n=168), nervous system (n=64), thyroid (n=51) and sarcoma (n=147), melanoma (n=117), non-melanoma skin (n=390), Non-Hodgkin's lymphoma (n=199), Hodgkin's lymphoma (n=72), myeloma (n=46), leukemia (n=66) and all cancers combined (n=6892). The cases were between 20 and 89 years old and were admitted for diagnosis and treatment of a primary cancer in the Institute Nacional de Oncologia of Montevideo and completed a routine questionnaire on risk factors for cancer shortly after admittance. Of a total of 7142 eligible patients, 117 (1.6%) patients were too ill or deceased to participate and 133 (1.9%) patients refused the interview leaving a total of 6892 cases (response rate 96.5%).

In the same time period 1832 hospital controls (age 20-89 years) without malignancies were admitted to the institute. The controls were affected with the following disorders: oral diseases (n=99, 5.4%), acute peritonitis (n=87, 4.7%), respiratory disorders (n=105, 5.7%), skin diseases (n=82, 4.5%), male genital diseases (n=103, 5.6%), benign breast disease (n=286, 15.6%), female genital diseases (n=78, 4.3%), benign lesions (n=182, 9.9%), various other diseases (n=527, 28.8%) and some were healthy check-up controls (n=283, 15.5%). Of a total of 1902 eligible controls, 31 (1.6%) patients were too ill or deceased and 39 (2.1%) refused the interview, leaving a total of 1832 controls (response rate 96.3%). They served as a common control group for all groups of cases.

The questionnaire was administered by trained social workers and included questions on socio-demographic factors, occupational history, a history of cancer among 1st degree relatives, self-reported height and weight 5 years before admission, smoking history, alcohol intake (history and usual intake), mate intake (a local herbal tea), reproductive history (women) and a short food frequency questionnaire (FFQ). The FFQ, which has not been validated, included questions about the intake of fresh red meat (beef and lamb), processed meat, salted meat, milk and total vegetables and fruits. Total meat was defined as the sum of fresh red meat (beef and lamb), processed meat and salted meat. Results specifically for salted meat will be reported separately.

A. Statistical methods

Odds ratios of cancer for the middle and upper tertiles of the distribution of meat intake were estimated with unconditional logistic regression, using the lowest tertile as the referent group; the tertiles were based on functional cut-off points in servings per week. We used a multivariable model including the following covariates: age (continuous), sex (when applicable), residence (urban/rural), education (continuous), smoking status (never, former, current), cigarettes per day (continuous), age at starting smoking (continuous), age at quitting smoking (continuous), duration of smoking (continuous), current alcohol intake (continuous), intake of fruits and vegetables (continuous) and intake of milk (continuous). Analyses of breast, ovarian and endometrial cancers were also adjusted for age at menarche (continuous), age at menopause (continuous), number of pregnancies (continuous) and duration of lactation (continuous). The analysis of cervical cancer was also adjusted for age at first sexual intercourse (continuous) and number of pregnancies (continuous). Analyses with confounders treated as categorical variables yielded similar results to analyses with confounders as continuous variables. Potential confounders were included in the multivariate model mostly based on a review of the literature and from comparisons of cases vs. controls with student's t-test. Because of lack of information on weight and height in a large number of participants (>50%) we could not include these covariates in the overall analyses. However, we conducted sensitivity analyses restricted to those participants with information on height and weight to investigate whether these covariates altered the results for all cancer sites combined. Because of the possibility that benign breast disease and benign prostate hyperplasia may be intermediates between diet and breast and prostate cancer risk, respectively, we repeated these analyses with exclusion of these controls. For cancers of the mouth and pharynx, larynx, esophagus, upper aerodigestive tract combined and lung we conducted sensitivity analyses with exclusions of respiratory disease controls. Tests for linear trend were calculated by entering the categorical variables as continuous parameters in the models.

For comparison with other studies, we also analyzed meat consumption as a continuous variable and in this model, the unit of intake was set to 1 serving per day. Possible interactions between meat intake and age, sex, smoking status, alcohol intake, and intake of fruits, vegetables and milk, were assessed by including cross product terms in the multivariable models. We also investigated more extreme categorizations of meat intake to assess whether an effect is apparent only for very high intake of meat. A two-tailed P-value of <0.05 was considered to be statistically significant. All statistical tests were carried out using STATA version 9.2.

III. Results

The distribution of cases and controls according to socio-demographic variables and selected risk factors is shown in **Table 1**. Cancer cases were generally older and less educated, they also had higher intake of alcohol and tobacco, milk and total meat, but a similar intake of fruits and vegetables compared with the controls.

The adjusted odds ratios for meat groups are shown in **Table 2**. The risk of oral cancer was increased in the highest tertile of intake of red meat (OR=2.09; p for trend <0.0001) and beef (OR=2.20; p for trend <0.0001), while intake of total meat (OR=1.61; p for trend = 0.03), red meat (OR=1.71; p for trend = 0.007), beef (OR=1.69; p for trend = 0.003), lamb (OR=1.85; p for trend = 0.009) and processed meat (OR=1.90; p for trend = 0.004) was associated with increased risk of pharyngeal cancer. The distribution of cases and controls by intake of meats is shown in the **Supplementary Table**.

High intake of total meat (OR=1.85; p for trend =0.003), red meat (OR=1.65; p for trend = 0.01), beef (OR=1.79; p for trend = 0.001) and processed meat (OR=2.03; p for trend =0.003) was associated with increased risk of laryngeal cancer. Similarly, high intake of most meat groups was associated with 2-4 fold increases in the risk of cancers of the esophagus, upper aerodigestive tract and stomach. Exclusion of respiratory disease controls from these analyses did not materially alter these results. High intake of total meat (OR=1.78; p for trend <0.0001), red meat (OR=1.89; p for trend <0.0001), beef (OR=2.04; p for trend <0.0001) and processed meat (OR=1.76; p for trend <0.0001) was associated with an increased risk of colorectal cancer.

Table 1. Comparison of selected covariates among all cases and controls (values are means (SD), unless other is specified).

Variable	Cases	Controls	P
Age, years	61.7 (13.3)	55.0 (16.6)	<0.0001
Sex, n (%)			
Men	3692 (53.6)	742 (40.50)	
Women	3200 (46.4	1090 (59.50)	
Education, years	4.8 (3.1)	5.8 (3.5)	<0.0001
Smoking status, n (%)			
Never smoker	2529 (36.7)	747 (40.8)	
Former smoker	1527 (22.2)	352 (19.2)	
Current smoker	2836 (41.1)	733 (40.0)	
Cigarettes per day	15.5 (17.9)	12.4 (15.5)	<0.0001
Ethanol, ml/d	74.7 (153.4)	44.4 (115.6)	<0.0001
Fruits and vegetables, servings/week	6.4 (4.4)	6.5 (4.4)	0.12
Milk, servings/week	7.3 (5.5)	6.6 (5.5)	<0.0001
Total meat, servings/week	9.9 (6.2)	8.3 (5.6)	<0.0001

Table 2. Odds ratios, 95% confidence intervals of cancers with meat consumption[1].

Cancer site	Tertile[2]	Total meat	Fresh red meat	Beef	Lamb	Processed meat
Oral	1	1.00	1.00	1.00	1.00	1.00
	2	1.40 (0.93-2.10)	1.50 (1.00-2.24)	1.62 (1.08-2.42)	0.96 (0.58-1.58)	0.95 (0.61-1.49)
	3	1.53 (0.99-2.36)	2.09 (1.36-3.21)	2.20 (1.42-3.41)	0.99 (0.55-1.78)	0.99 (0.69-1.42)
	P_{trend}	0.083	<0.0001	<0.0001	0.98	0.96
	Serv/d[3]	1.16 (0.98-1.38)	1.41 (1.14-1.73)	1.57 (1.23-2.00)	0.89 (0.47-1.68)	0.62 (0.35-1.10)
Pharynx	1	1.00	1.00	1.00	1.00	1.00
	2	1.30 (0.88-1.93)	1.17 (0.81-1.70)	1.28 (0.89-1.84)	1.11 (0.66-1.88)	1.69 (1.01-2.84)
	3	1.61 (1.07-2.42)	1.71 (1.16-2.52)	1.69 (1.14-2.51)	1.85 (1.04-3.30)	1.90 (1.23-2.94)
	P_{trend}	0.028	0.007	0.003	0.009	0.004
	Serv/d	1.31 (1.11-1.55)	1.47 (1.20-1.80)	1.56 (1.22-1.99)	1.38 (0.81-2.35)	1.09 (0.67-1.77)
Oral, pharynx	1	1.00	1.00	1.00	1.00	1.00
	2	1.37 (1.02-1.86)	1.36 (1.01-1.82)	1.51 (1.13-2.01)	0.96 (0.66-1.39)	1.20 (0.84-1.70)
	3	1.63 (1.19-2.24)	1.97 (1.45-2.68)	2.08 (1.51-2.84)	1.28 (0.83-1.95)	1.27 (0.95-1.68)
	P_{trend}	0.005	<0.0001	<0.0001	0.073	0.10
	Serv/d	1.16 (1.02-1.31)	1.35 (1.16-1.57)	1.47 (1.23-1.77)	1.21 (0.79-1.85)	0.97 (0.59-1.59)

Esophagus	1	1.00	1.00	1.00	1.00	1.00
	2	1.70 (1.16-2.51)	1.55 (1.08-2.22)	1.56 (1.10-2.18)	1.59 (0.96-2.63)	1.18 (0.80-1.76)
	3	3.30 (2.22-4.89)	2.95 (2.03-4.28)	2.80 (1.92-4.07)	2.72 (1.56-4.74)	1.51 (1.09-2.08)
	P_{trend}	<0.0001	<0.0001	<0.0001	<0.0001	0.006
	Serv/d	1.74 (1.52-1.99)	1.91 (1.61-2.27)	2.08 (1.70-2.56)	3.08 (1.96-4.83)	1.85 (1.29-2.67)
Larynx	1	1.00	1.00	1.00	1.00	1.00
	2	1.37 (0.93-2.04)	1.36 (0.94-1.95)	1.31 (0.91-1.87)	1.33 (0.79-2.23)	2.01 (1.22-3.32)
	3	1.85 (1.23-2.77)	1.65 (1.12-2.42)	1.79 (1.22-2.64)	1.52 (0.86-2.70)	2.03 (1.31-3.13)
	P_{trend}	0.003	0.011	0.001	0.12	0.003
	Serv/d	1.38 (1.18-1.61)	1.50 (1.24-1.83)	1.68 (1.33-2.12)	1.04 (0.61-1.76)	1.43 (0.94-2.19)
Upper aerodigestive tract	1	1.00	1.00	1.00	1.00	1.00
	2	1.62 (1.29-2.04)	1.53 (1.23-1.91)	1.59 (1.28-1.97)	1.31 (0.97-1.76)	1.33 (1.02-1.73)
	3	2.33 (1.82-2.97)	2.34 (1.85-2.96)	2.40 (1.89-3.05)	1.81 (1.29-2.54)	1.47 (1.19-1.83)
	P_{trend}	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
	Serv/d	1.37 (1.25-1.51)	1.54 (1.36-1.73)	1.69 (1.47-1.94)	1.50 (1.07-2.12)	1.44 (0.99-2.09)
Stomach	1	1.00	1.00	1.00	1.00	1.00
	2	2.09 (1.10-3.98)	1.54 (0.85-2.78)	1.49 (0.83-2.67)	1.99 (0.81-4.90)	2.37 (1.03-5.43)
	3	4.02 (2.09-7.74)	3.70 (2.04-6.73)	3.66 (2.01-6.65)	2.80 (1.03-7.60)	4.39 (2.17-8.90)
	P_{trend}	<0.0001	<0.0001	<0.0001	0.025	<0.0001
	Serv/d	1.97 (1.62-2.40)	2.08 (1.60-2.70)	2.18 (1.59-2.99)	4.47 (2.37-8.44)	3.75 (2.44-5.75)
Colon	1	1.00	1.00	1.00	1.00	1.00
	2	1.31 (0.85-2.03)	1.53 (0.99-2.36)	1.45 (0.94-2.24)	1.32 (0.73-2.39)	2.11 (1.21-3.68)
	3	1.87 (1.14-3.06)	1.99 (1.20-3.30)	2.00 (1.19-3.35)	1.53 (0.72-3.26)	2.10 (1.30-3.39)
	P_{trend}	0.019	0.008	0.001	0.29	0.002
	Serv/d	1.41 (1.16-1.72)	1.48 (1.16-1.90)	1.57 (1.18-2.08)	1.27 (0.50-3.24)	1.65 (0.98-2.76)
Rectum	1	1.00	1.00	1.00	1.00	1.00
	2	1.29 (0.84-1.97)	1.26 (0.83-1.91)	1.42 (0.93-2.16)	1.36 (0.75-2.44)	1.10 (0.65-1.86)
	3	1.64 (1.03-2.63)	1.70 (1.06-2.72)	1.92 (1.18-3.13)	1.12 (0.53-2.35)	1.60 (1.07-2.39)
	P_{trend}	0.056	0.031	0.001	0.93	0.01
	Serv/d	1.29 (1.07-1.55)	1.35 (1.08-1.71)	1.53 (1.18-2.00)	0.68 (0.26-1.76)	1.85 (1.16-2.94)
Colorectal	1	1.00	1.00	1.00	1.00	1.00
	2	1.29 (0.97-1.72)	1.37 (1.04-1.81)	1.43 (1.08-1.88)	1.32 (0.91-1.91)	1.54 (1.05-2.26)
	3	1.78 (1.29-2.45)	1.89 (1.37-2.61)	2.04 (1.47-2.83)	1.32 (0.82-2.13)	1.76 (1.28-2.40)
	P_{trend}	<0.0001	<0.0001	<0.0001	0.28	<0.0001
	Serv/d	1.30 (1.13-1.49)	1.36 (1.14-1.63)	1.51 (1.23-1.85)	0.93 (0.51-1.69)	1.57 (0.93-2.66)
Pancreas	1	1.00	1.00	1.00	1.00	1.00
	2	0.87 (0.49-1.55)	0.96 (0.55-1.69)	0.92 (0.53-1.62)	1.83 (0.71-4.67)	1.08 (0.55-2.10)
	3	1.32 (0.72-2.43)	1.44 (0.77-2.67)	1.36 (0.72-2.56)	2.19 (0.75-6.40)	1.34 (0.78-2.28)
	P_{trend}	0.38	0.28	0.25	0.14	0.23
	Serv/d	1.30 (1.02-1.66)	1.31 (0.96-1.78)	1.28 (0.89-1.83)	1.69 (0.65-4.42)	1.74 (0.94-3.22)
Lung	1	1.00	1.00	1.00	1.00	1.00
	2	1.26 (1.00-1.58)	1.28 (1.03-1.59)	1.29 (1.04-1.60)	1.33 (0.97-1.82)	1.33 (1.01-1.74)
	3	1.59 (1.24-2.03)	1.68 (1.32-2.14)	1.66 (1.30-2.12)	1.91 (1.33-2.75)	1.24 (0.99-1.56)
	P_{trend}	<0.0001	<0.0001	<0.0001	<0.0001	0.11
	Serv/d	1.30 (1.18-1.44)	1.43 (1.26-1.62)	1.36 (1.17-1.58)	1.45 (0.99-2.13)	1.22 (0.92-1.62)
Sarcomas	1	1.00	1.00	1.00	1.00	1.00
	2	1.55 (0.94-2.54)	1.39 (0.86-2.25)	1.34 (0.83-2.16)	1.00 (0.54-1.84)	1.92 (1.10-3.35)
	3	2.27 (1.31-3.91)	2.18 (1.27-3.73)	2.08 (1.20-3.60)	1.03 (0.46-2.29)	1.55 (0.96-2.52)
	P_{trend}	0.004	0.004	0.001	0.94	0.16
	Serv/d	1.60 (1.31-1.96)	1.72 (1.33-2.23)	1.77 (1.26-2.49)	1.28 (0.47-3.44)	1.15 (0.62-2.12)

Melanoma	1	1.00	1.00	1.00	1.00	1.00
	2	0.89 (0.55-1.44)	0.92 (0.57-1.49)	0.98 (0.61-1.58)	1.24 (0.62-2.49)	1.51 (0.84-2.72)
	3	0.93 (0.52-1.68)	0.96 (0.52-1.76)	0.92 (0.49-1.74)	0.87 (0.33-2.28)	1.14 (0.69-1.88)
	P_{trend}	0.79	0.87	0.86	0.63	0.82
	Serv/d	0.93 (0.71-1.22)	0.94 (0.67-1.30)	0.97 (0.64-1.46)	0.64 (0.17-2.42)	0.76 (0.34-1.69)
Non-melanoma skin	1	1.00	1.00	1.00	1.00	1.00
	2	1.14 (0.85-1.54)	1.03 (0.77-1.38)	1.06 (0.79-1.42)	1.11 (0.75-1.64)	1.69 (1.19-2.41)
	3	1.20 (0.85-1.69)	1.23 (0.88-1.74)	1.36 (0.96-1.92)	1.23 (0.75-2.02)	1.32 (0.98-1.79)
	P_{trend}	0.38	0.26	0.023	0.40	0.21
	Serv/d	1.08 (0.93-1.26)	1.17 (0.97-1.41)	1.15 (0.92-1.45)	0.82 (0.42-1.57)	1.02 (0.66-1.57)
Breast	1	1.00	1.00	1.00	1.00	1.00
	2	1.10 (0.92-1.33)	1.06 (0.88-1.26)	1.02 (0.86-1.23)	1.16 (0.91-1.46)	1.27 (0.98-1.64)
	3	1.19 (0.93-1.52)	1.38 (1.06-1.79)	1.36 (1.04-1.78)	1.65 (1.12-2.43)	1.23 (1.01-1.51)
	P_{trend}	0.15	0.034	0.059	0.016	0.067
	Serv/d	1.06 (0.94-1.20)	1.16 (0.99-1.35)	1.15 (0.97-1.36)	1.71 (0.84-3.48)	1.10 (0.72-1.68)
Cervix uteri	1	1.00	1.00	1.00	1.00	1.00
	2	1.11 (0.81-1.54)	1.12 (0.82-1.54)	1.08 (0.79-1.48)	1.29 (0.83-2.00)	0.84 (0.54-1.31)
	3	1.39 (0.94-2.05)	1.59 (1.05-2.39)	1.57 (1.04-2.38)	1.53 (0.80-2.92)	0.94 (0.67-1.31)
	P_{trend}	0.10	0.04	0.06	0.20	0.83
	Serv/d	1.19 (0.99-1.43)	1.40 (1.11-1.76)	1.45 (1.13-1.86)	1.67 (0.67-4.14)	0.71 (0.41-1.23)
Corpus uteri	1	1.00	1.00	1.00	1.00	1.00
	2	0.73 (0.43-1.25)	0.54 (0.31-0.93)	0.50 (0.29-0.87)	0.83 (0.45-1.53)	1.30 (0.63-2.66)
	3	1.17 (0.62-2.20)	1.36 (0.70-2.61)	1.41 (0.73-2.73)	1.02 (0.37-2.83)	1.37 (0.77-2.44)
	P_{trend}	0.91	0.95	0.94	0.84	0.31
	Serv/d	0.94 (0.66-1.33)	1.04 (0.67-1.61)	1.11 (0.69-1.78)	0.29 (0.02-3.57)	1.01 (0.29-3.50)
Ovary	1	1.00	1.00	1.00	1.00	1.00
	2	1.23 (0.73-2.07)	1.10 (0.66-1.84)	1.24 (0.74-2.06)	1.40 (0.69-2.90)	1.57 (0.77-3.21)
	3	0.89 (0.43-1.83)	1.16 (0.56-2.41)	1.00 (0.45-2.20)	1.59 (0.55-4.61)	1.34 (0.73-2.46)
	P_{trend}	0.95	0.66	0.77	0.37	0.45
	Serv/d	0.92 (0.65-1.31)	0.99 (0.65-1.53)	0.99 (0.62-1.58)	1.02 (0.15-6.85)	0.74 (0.21-2.60)
Prostate	1	1.00	1.00	1.00	1.00	1.00
	2	1.25 (0.88-1.78)	1.33 (0.95-1.87)	1.44 (1.03-2.02)	1.08 (0.69-1.68)	0.98 (0.64-1.49)
	3	1.58 (1.08-2.30)	1.42 (0.99-2.06)	1.56 (1.08-2.28)	1.02 (0.61-1.69)	1.06 (0.76-1.48)
	P_{trend}	0.018	0.072	0.022	0.99	0.71
	Serv/d	1.17 (1.00-1.37)	1.17 (0.97-1.42)	1.25 (0.99-1.56)	0.99 (0.58-1.69)	1.11 (0.70-1.77)
Testis	1	1.00	1.00	1.00	1.00	1.00
	2	1.46 (0.74-2.91)	1.16 (0.61-2.21)	1.50 (0.78-2.88)	1.55 (0.58-4.19)	1.53 (0.66-3.56)
	3	2.04 (1.00-4.18)	1.89 (0.97-3.68)	2.08 (1.03-4.20)	2.48 (0.83-7.43)	1.44 (0.70-2.94)
	P_{trend}	0.051	0.05	0.037	0.059	0.40
	Serv/d	1.33 (0.99-1.79)	1.51 (1.05-2.15)	1.56 (1.03-2.36)	1.94 (0.77-4.86)	1.00 (0.43-2.30)
Bladder	1	1.00	1.00	1.00	1.00	1.00
	2	1.17 (0.76-1.82)	0.98 (0.64-1.49)	1.00 (0.66-1.51)	1.64 (0.86-3.13)	1.75 (1.07-2.86)
	3	1.68 (1.06-2.66)	1.76 (1.14-2.72)	1.71 (1.10-2.65)	1.89 (0.92-3.88)	1.22 (0.79-1.88)
	P_{trend}	0.029	0.012	0.007	0.071	0.75
	Serv/d	1.36 (1.13-1.64)	1.45 (1.15-1.83)	1.41 (1.07-1.86)	1.52 (0.81-2.85)	1.18 (0.67-2.08)
Kidney	1	1.00	1.00	1.00	1.00	1.00
	2	1.47 (0.90-2.38)	1.33 (0.82-2.15)	1.33 (0.82-2.14)	1.18 (0.61-2.28)	1.57 (0.95-2.60)
	3	1.96 (1.16-3.33)	2.43 (1.45-4.06)	2.47 (1.46-4.15)	1.80 (0.84-3.87)	1.21 (0.79-1.86)
	P_{trend}	0.019	0.001	<0.0001	0.099	0.63
	Serv/d	1.47 (1.22-1.78)	1.81 (1.43-2.30)	1.84 (1.33-2.53)	2.11 (1.00-4.45)	0.73 (0.38-1.43)

Nervous system	1	1.00	1.00	1.00	1.00	1.00
	2	1.64 (0.76-3.53)	1.97 (0.92-4.21)	2.18 (1.01-4.70)	1.28 (0.48-3.37)	1.79 (0.74-4.31)
	3	3.12 (1.40-6.97)	3.79 (1.69-8.50)	3.97 (1.73-9.11)	1.75 (0.55-5.63)	1.80 (0.85-3.80)
	Ptrend	0.006	0.001	<0.0001	0.33	0.15
	Serv/d	1.39 (1.01-1.91)	1.81 (1.23-2.66)	2.02 (1.26-3.23)	1.09 (0.25-4.74)	0.66 (0.22-1.98)
Thyroid	1	1.00	1.00	1.00	1.00	1.00
	2	1.28 (0.60-2.71)	1.82 (0.85-3.88)	1.54 (0.73-3.26)	1.47 (0.49-4.42)	0.42 (0.17-1.03)
	3	2.38 (1.07-5.31)	2.17 (0.90-5.26)	2.33 (0.98-5.50)	3.05 (0.87-10.72)	0.73 (0.41-1.29)
	P_{trend}	0.039	0.083	0.071	0.064	0.83
	Serv/d	1.11 (0.92-1.34)	1.04 (0.84-1.30)	1.54 (0.91-2.60)	1.55 (0.36-6.58)	1.24 (0.63-2.41)
Lymphomas	1	1.00	1.00	1.00	1.00	1.00
	2	1.27 (0.93-1.74)	1.52 (1.13-2.06)	1.46 (1.08-1.97)	1.33 (0.88-2.01)	1.73 (1.13-2.65)
	3	1.87 (1.33-2.64)	1.95 (1.37-2.76)	1.93 (1.36-2.75)	1.81 (1.09-3.00)	2.01 (1.41-2.86)
	P_{trend}	0.006	<0.0001	<0.0001	0.019	<0.0001
	Serv/d	1.27 (1.09-1.48)	1.37 (1.14-1.66)	1.48 (1.19-1.83)	1.24 (0.68-2.27)	1.40 (0.79-2.48)
Non-Hodgkin's lymphoma	1	1.00	1.00	1.00	1.00	1.00
	2	1.33 (0.86-2.04)	1.87 (1.21-2.88)	1.69 (1.10-2.59)	1.46 (0.78-2.72)	1.74 (1.03-2.94)
	3	1.79 (1.11-2.88)	2.02 (1.22-3.35)	1.85 (1.11-3.09)	2.03 (0.97-4.25)	2.01 (1.30-3.11)
	P_{trend}	0.025	0.005	0.003	0.052	0.004
	Serv/d	1.26 (1.05-1.52)	1.40 (1.12-1.76)	1.39 (1.02-1.89)	1.45 (0.64-3.25)	0.94 (0.52-1.68)
Hodgkin's disease	1	1.00	1.00	1.00	1.00	1.00
	2	1.15 (0.68-1.92)	1.09 (0.67-1.75)	1.16 (0.71-1.87)	1.43 (0.71-2.87)	2.10 (0.86-5.15)
	3	1.48 (0.83-2.64)	1.09 (0.61-1.95)	1.34 (0.75-2.39)	0.97 (0.38-2.50)	2.15 (1.00-4.63)
	P_{trend}	0.19	0.77	0.42	0.74	0.065
	Serv/d	1.09 (0.77-1.53)	1.09 (0.71-1.66)	1.22 (0.85-1.75)	0.32 (0.07-1.46)	1.02 (0.47-2.19)
Myeloma	1	1.00	1.00	1.00	1.00	1.00
	2	1.33 (0.55-3.23)	1.10 (0.47-2.61)	1.16 (0.50-2.71)	0.85 (0.32-2.27)	1.24 (0.43-3.62)
	3	3.28 (1.34-8.00)	3.55 (1.52-8.31)	3.47 (1.47-8.21)	2.07 (0.67-6.40)	2.07 (0.89-4.78)
	P_{trend}	0.01	0.005	0.003	0.16	0.058
	Serv/d	1.82 (1.31-2.53)	2.14 (1.38-3.31)	2.29 (1.34-3.93)	2.61 (0.78-8.71)	1.27 (0.43-3.71)
Leukemia	1	1.00	1.00	1.00	1.00	1.00
	2	0.87 (0.45-1.69)	0.99 (0.51-1.90)	1.06 (0.55-2.04)	1.61 (0.61-4.22)	1.99 (0.84-4.73)
	3	1.55 (0.77-3.16)	1.70 (0.82-3.51)	1.87 (0.89-3.91)	1.27 (0.37-4.38)	2.11 (1.01-4.44)
	P_{trend}	0.25	0.18	0.092	0.83	0.058
	Serv/d	1.52 (1.13-2.06)	1.40 (0.95-2.07)	1.49 (0.92-2.41)	0.89 (0.20-4.01)	2.75 (1.40-5.38)
All sites	1	1.00	1.00	1.00	1.00	1.00
	2	1.19 (1.05-1.35)	1.19 (1.05-1.34)	1.20 (1.06-1.36)	1.24 (1.05-1.47)	1.36 (1.15-1.62)
	3	1.61 (1.38-1.88)	1.71 (1.46-1.99)	1.73 (1.48-2.03)	1.63 (1.31-2.03)	1.32 (1.15-1.51)
	P_{trend}	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
	Serv/d	1.24 (1.16-1.34)	1.35 (1.23-1.47)	1.41 (1.27-1.56)	1.41 (1.07-1.88)	1.12 (0.92-1.36)

[1] Adjusted for: age, sex (when applicable), education, residence, smoking status, cigarettes per day, age at starting smoking, years since quitting smoking, duration of smoking, type of tobacco, alcohol intake, fruits and vegetables and milk. Results for breast, ovarian and uterine corpus cancers were also adjusted for age at menarche, age at menopause, number of pregnancies and lactation while results for cervical cancer were adjusted for age at first sexual intercourse and number of pregnancies.

[2] Cut-off points and medians for tertiles:
Total meat, ≤ 5, 5-11, >11 times per week, medians: 3, 7.9, 15.9 times/wk. Red meat (fresh): ≤ 4, 4.02-9, >9 times per week, medians: 2.2, 7.1, 14.1 times/wk. Beef: ≤ 3, 3.02-7, >7 times per week, medians: 2, 7, 14 times/wk. Lamb: 0, 0.02-1, >1 time per week, medians: 0, 0.5, 3 times/wk. Processed meat: 0, 1/year-1/month, >1/month, medians: 0, 1/month, 1/week.

[3] Serv/d = analysis on a continuous scale, for an intake of 1 serving per day.

Most indicators of meat intake were not associated with pancreatic cancer, with the exception of an association for total meat on a continuous scale (OR=1.30).

High intake of total meat (OR=1.59; p for trend <0.0001), red meat (OR=1.68; p for trend <0.0001), beef (OR=1.66; p for trend <0.0001) and lamb (OR=1.91; p for trend <0.0001) was associated with increased risk of lung cancer, while an association with processed meat was not statistically significant (OR=1.24; p for trend =0.11).

High intake of total meat, red meat and beef was associated with a two-fold increased risk of sarcomas, but such an association was not observed with melanoma and non-melanoma skin cancer.

High intake of red meat (OR=1.38; p for trend =0.03), beef (OR=1.36; p for trend =0.06), lamb (OR=1.65; p for trend = 0.02) and processed meat (OR=1.23; p for trend = 0.07) was associated with increased risk of breast cancer, but such an association was not observed for total meat. Exclusion of controls with a diagnosis of benign breast disease did not alter these results (results not shown).

Similarly, high intake of red meat (OR=1.59; p for trend = 0.04) and beef (OR=1.57; p for trend = 0.06) was associated with increased risk of cervical cancer, but no association was observed between any type of meat and cancers of the corpus uteri and the ovaries. High intake of total meat (OR=1.58; p for trend = 0.02) and beef (OR=1.56; p for trend = 0.02) was significantly associated with risk of prostate cancer, while intake of total meat (OR=2.04; p for trend = 0.05), red meat (OR=1.89; p for trend = 0.05) and beef (OR=2.08; p for trend =0.04) was associated with testicular cancer risk. The results for prostate cancer were unaltered when we excluded controls with a diagnosis of benign prostate hyperplasia from the analysis (results not shown).

A high intake of total meat (OR=1.68; p for trend = 0.03), red meat (OR=1.76; p for trend = 0.01) and beef (OR=1.71; p for trend = 0.007) was associated with increased risk of bladder cancer; the same pattern was observed for kidney cancer risk (total meat: OR=1.96; p for trend = 0.02), red meat: OR=2.43; p for trend =0.001 and beef: OR=2.47; p for trend <0.0001) and risk of cancer of the nervous system (total meat: OR=3.12; p for trend =0.006), red meat: OR=3.79; p for trend =0.001 and beef: OR=3.97; p for trend <0.0001), while high intake of total meat (OR=2.38; p for trend = 0.04) was associated with elevated risk of thyroid cancer.

High intake of total meat (OR=1.87; p for trend = 0.006), red meat (OR=1.95; p for trend <0.0001), beef (OR=1.93; p for trend <0.0001), lamb (OR=1.81; p for trend = 0.02) and processed meat (OR=2.01; p for trend <0.0001) was associated with increased risk of all lymphomas combined; similar findings were found for non-Hodgkin's lymphoma and myeloma, but not for Hodgkin's disease. An association was suggested between leukemia risk and high intake of processed meat (OR=2.11; p for trend = 0.058) and total meat (OR=1.52) on a continuous scale, but not with other types of meat.

High intake of total meat (OR=1.61; p for trend <0.0001), red meat (OR=1.71; p for trend <0.0001), beef (OR=1.73; p for trend <0.0001), lamb (OR=1.63; p for trend <0.0001) and processed meat (OR=1.32; p for trend <0.0001) was associated with increased risk of all cancer sites included in the study combined. When we restricted the latter analysis to the participants with information on height and weight, inclusion of height and weight or BMI as additional covariates did not alter the results. We repeated the analyses of total meat, red meat and beef with more extreme cut-points to see whether extremes of intake yielded stronger results (**Figure 1**). There was a stronger association with this categorisation than using our original cut-off points with ORs of 2.04 to 2.31 for the highest category compared with the lowest, and this was also the case for most of the individual cancer sites (results not shown), however the effect estimates for several of the sites became rather unstable with considerably wider confidence intervals.

Age modified the association between total and red meat consumption and risk of all cancer sites combined (p for interaction 0.004 and 0.01 for total and red meat, respectively), with stronger ORs among younger persons (<40 years, OR=2.02, 95% CI: 1.32-3.10 for high intake of total meat and 1.83, 95% CI: 1.19-2.81 for high intake of red meat), than among middle-aged (40-60 years, corresponding ORs=1.64, 95% CI: 1.26-2.12 and 1.70, 95% CI: 1.31-2.21) and elderly (>60 years, corresponding ORs=1.44, 95% CI: 1.16-1.79 and 1.58, 95% CI: 1.27-1.96) (**Table 3**). Smoking modified the association between total meat intake and risk of all cancer sites combined with weaker ORs among never smokers (OR=1.43, 95% CI: 1.12-1.83) and former smokers (OR=1.55, 95% CI: 1.11-2.15) than among current smokers (OR=1.82, 95% CI: 1.42-2.34, p for interaction = 0.02), but a similar interaction was not observed between smoking and high intake of red and processed meat (**Table 3**). Further, when smoking-related cancers and non-smoking related cancers were analysed separately there were no significant interactions between total, red or processed meat intake and smoking (results not shown). Sex, alcohol intake and intake of fruits and vegetables and milk did not significantly modify the effect of meat intake on risk of all cancer sites combined (p for all comparisons ≥0.09). The increased risks with total meat, red meat and processed meat persisted among the group of never smokers, non-drinkers of alcohol and in most subgroups with respect to age, sex, intakes of fruit and vegetables and milk. With stepwise addition of each of the confounders to the age and sex-adjusted results it was observed that adjustment for smoking explained most of the attenuation of the OR for lung cancer and upper aerodigestive tract cancers, but this attenuation was relatively small for all cancer sites combined (results not shown).

IV. Discussion

In this large hospital-based case-control study we found increased risk of multiple cancers with intake of total meat, red meat, beef, lamb and processed meat.

The cancer site which has been most investigated previously in relation to meat intake is colorectal cancer and our finding of an elevated risk with higher intake is consistent with previous studies (De Stefani et al, 1997a; Singh and Fraser, 1998; Norat et al, 2005; Cross et al,

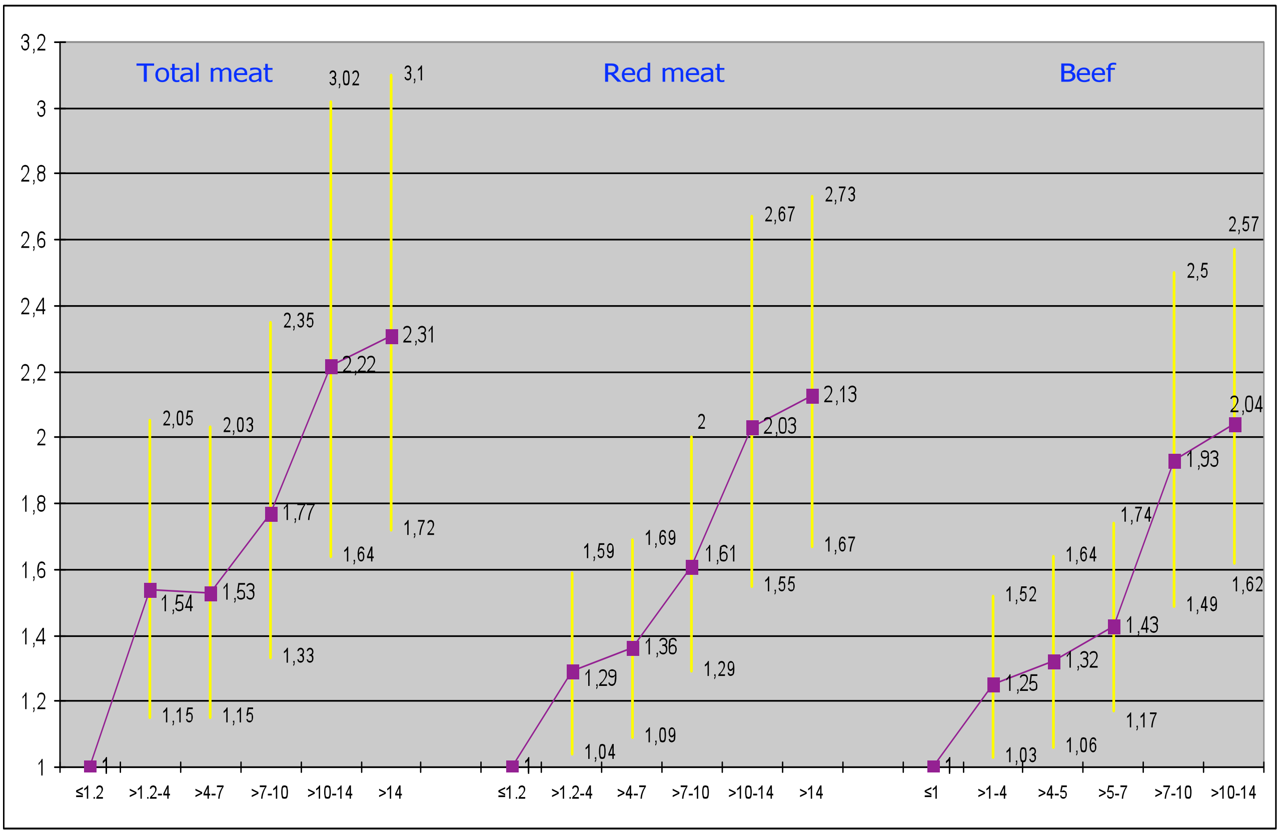

Figure 1. Odds ratios (squares) and 95% confidence intervals (yellow lines) for risk of all cancer sites combined with more extreme ranges of intake of total meat, red meat and beef (x-axis shows servings per week) with adjustment for confounders listed in footnote to **Table 2**. Medians of meat intake in each category: Total meat: 1, 3, 5.5, 8.2, 11.2 and 17 servings/week; red meat: 1, 3, 5.2, 8, 11 and 15 servings/week and beef: 1, 3, 5, 7, 9.3 and 14 servings/week.

Table 3. Odds ratios and 95% CIs for meat consumption and all cancer sites combined in strata of covariates.

All sites		**Total meat**		**Red meat**		**Processed meat**	
		2	3	2	3	2	3
Age	≤40 yrs	1.27 (0.90-1.80)	2.02 (1.32-3.10)	1.19 (0.85-1.67)	1.83 (1.19-2.81)	2.28 (1.35-3.85)	1.56 (1.04-2.33)
	>40-60 yrs	1.22 (0.98-1.52)	1.64 (1.26-2.12)	1.14 (0.92-1.41)	1.70 (1.31-2.21)	1.28 (0.95-1.71)	1.35 (1.07-1.70)
	>60 yrs	1.13 (0.94-1.36)	1.44 (1.16-1.79)	1.18 (0.98-1.41)	1.58 (1.27-1.96)	1.27 (1.01-1.60)	1.27 (1.05-1.53)
Sex	Men	1.16 (0.94-1.44)	1.69 (1.34-2.13)	1.21 (0.99-1.49)	1.67 (1.34-2.09)	1.34 (1.03-1.75)	1.21 (0.98-1.50)
	Women	1.22 (1.04-1.43)	1.46 (1.18-1.80)	1.16 (0.99-1.36)	1.70 (1.36-2.12)	1.35 (1.08-1.69)	1.39 (1.16-1.65)
Fruits,	≤median	1.15 (0.95-1.39)	1.70 (1.37-2.11)	1.12 (0.94-1.35)	1.71 (1.38-2.12)	1.44 (1.14-1.82)	1.40 (1.15-1.70)
vegetables	>median	1.23 (1.03-1.47)	1.50 (1.21-1.86)	1.25 (1.06-1.49)	1.67 (1.34-2.09)	1.31 (1.03-1.68)	1.24 (1.03-1.50)
Milk	≤median	1.16 (0.99-1.36)	1.59 (1.31-1.94)	1.16 (1.00-1.35)	1.80 (1.47-2.20)	1.34 (1.08-1.66)	1.27 (1.07-1.50)
	>median	1.25 (1.00-1.56)	1.63 (1.27-2.08)	1.24 (1.00-1.54)	1.56 (1.21-2.00)	1.42 (1.08-1.88)	1.40 (1.12-1.75)
Smoking	Never	1.17 (0.97-1.41)	1.43 (1.12-1.83)	1.28 (1.06-1.53)	1.75 (1.35-2.26)	1.20 (0.93-1.56)	1.26 (1.03-1.55)
	Former	1.21 (0.90-1.63)	1.55 (1.11-2.15)	1.19 (0.89-1.59)	1.51 (1.09-2.10)	1.09 (0.74-1.59)	1.20 (0.87-1.64)
	Current	1.24 (1.00-1.55)	1.82 (1.42-2.34)	1.07 (0.87-1.33)	1.66 (1.30-2.12)	1.83 (1.37-2.44)	1.50 (1.20-1.88)
Alcohol	Nondrinker	1.20 (1.03-1.40)	1.59 (1.31-1.92)	1.22 (1.05-1.41)	1.73 (1.42-2.12)	1.36 (1.10-1.66)	1.38 (1.17-1.62)
	1-120 drinks/yr	1.30 (0.96-1.75)	1.70 (1.23-2.34)	1.22 (0.91-1.62)	1.70 (1.25-2.31)	1.37 (0.94-2.00)	1.16 (0.85-1.57)
	121+ drinks/yr	0.97 (0.60-1.58)	1.48 (0.91-2.41)	1.01 (0.66-1.57)	1.54 (0.98-2.42)	1.40 (0.80-2.46)	1.37 (0.89-2.11)

2007; World Cancer Research Fund/American Institute for Cancer Research, 2007). Previous meta-analyses showed an elevated risk of colorectal cancer with higher meat intake (Norat et al, 2002; Larsson and Wolk, 2006) and in the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) report from 2007, the evidence that red and processed meat increases colorectal cancer risk was judged to be convincing (World Cancer

Research Fund/American Institute for Cancer Research, 2007).

Our finding of an elevated risk of oral and pharyngeal cancer with higher intake of red meat and beef is consistent with some (Levi et al, 1998; Franceschi et al, 1999), but not all previous case-control studies (Zheng et al, 1992). We did not find an elevated risk of oral cancer with higher processed meat intake as some case-control studies have indicated (Levi et al, 1998; Levi et al, 2004), but we did find a positive association with risk of pharyngeal cancer. Our findings suggested a strong increase in the risk of esophageal cancer with all meat groups and is in line with recent case-control (Navarro Silvera et al, 2008) and cohort studies (Gonzalez et al, 2006; Cross et al, 2007) and the WCRF/AICR report which found limited suggestive evidence for an association with both red and processed meat (World Cancer Research Fund/American Institute for Cancer Research, 2007). Most previous studies reported elevated risks of laryngeal cancer with higher intake of red and/or processed meat (Bosetti et al, 2002; Cross et al, 2007; Sapkota et al, 2008) and our study provides further support for these findings.

Stomach cancer risk was strongly associated with meat intake in this study. A previous meta-analysis found evidence that processed meat was associated with increased stomach cancer risk (Larsson et al, 2006b) and our results support these findings. The large European EPIC-study found increased stomach cancer risk with higher intake of total, red and processed meat (Gonzalez et al, 2006), but a recent American cohort could not confirm these findings (Cross et al, 2007). We found little association between meat intake and pancreatic cancer in line with some (Stolzenberg-Solomon et al, 2002; Michaud et al, 2003), but not all studies (Tavani et al, 2000; Nothlings et al, 2005; Larsson et al, 2006a; Cross et al, 2007). However, the statistical power of our study was not adequate to detect a moderate increase in risk of pancreatic cancer.

Lung cancer risk was elevated with higher intake of total meat, red meat, beef, lamb and processed meat, in line with several studies (Deneo-Pellegrini et al, 1996; Alavanja et al, 2001; De Stefani et al, 2002; Cross et al, 2007; Hu et al, 2008) and the recent WCRF/AICR report which stated that there was limited suggestive evidence for an adverse effect of red and processed meat on lung cancer risk (World Cancer Research Fund/American Institute for Cancer Research, 2007). Given the strong association between tobacco smoking and lung cancer, however, a residual confounding effect of this habit cannot be completely excluded.

We found an elevated risk of sarcoma with intake of most meats, but another study found no association (Tavani et al, 1997). A limited number of previous studies of meat intake and melanoma and non-melanoma skin cancer are consistent with our general findings of no association (Veierod et al, 1997; Davies et al, 2002).

We found a significant increase in breast cancer risk with intake of red meat, beef and lamb and a marginally significant increase with intake of processed meat, but not with total meat. These results are not entirely consistent with a previous study from this population which found strong increases in the risk with higher total and red meat intake (De Stefani E. et al, 1997b). A previous meta-analysis of meat consumption and breast cancer risk including 22 case-control studies and 9 cohort studies found evidence of increased risk (Boyd et al, 2003), while a pooled analysis of seven cohort studies found no association (Missmer et al, 2002). More recent studies have also found conflicting results, with some case-control (Kruk, 2007; Bessaoud et al, 2008) and cohort studies (Cho et al, 2006; Taylor et al, 2007; Egeberg et al, 2008) reporting positive associations while others reported no association (Cross et al, 2007; Kabat et al, 2007). In our study high intake of red meat and beef were associated with increased risk of cervical cancer, but we did not find any associations between meat intake and cancers of the uterus or ovaries. A previous meta-analysis of 9 case-control studies and one cohort study found a positive association between total and red meat intake and endometrial cancer (Bandera et al, 2007) in contrast to our null findings. A review of the literature suggested that meat intake was associated with increased risk of ovarian cancer (Schulz et al, 2004), but recent cohorts found mixed results (Kiani et al, 2006; Cross et al, 2007; Schulz et al, 2007). Recent studies found positive associations between intake of meat (Ghosh et al, 2008) or processed meat (Cross et al, 2007) and cervical cancer, but the evidence is limited (World Cancer Research Fund/American Institute for Cancer Research, 2007).

In this study high intake of total meat and beef was positively associated with risk of prostate cancer and high intake of total meat, red meat and beef was associated with increased risk of testicular cancer. Previous studies of meat intake and prostate cancer have provided conflicting results with some showing a positive association (Gann et al, 1994; Le Marchand L. et al, 1994), while others found no association (Tavani et al, 2000; Park et al, 2007). Some studies reported positive associations with advanced or metastatic prostate cancers, but not with total prostate cancer (Michaud et al, 2001; Cross et al, 2007). The WCRF/AICR report stated that there was limited suggestive evidence that processed meat increases prostate cancer risk (World Cancer Research Fund/American Institute for Cancer Research, 2007). Few studies have previously investigated meat intake and testicular cancer with some reporting positive associations (Sigurdson et al, 1999; Hu et al, 2008) while others reported no association (Bonner et al, 2002).

We found positive associations between intake of total meat, red meat and beef and bladder cancer risk, in line with some (Steineck et al, 1988; Mills et al, 1991; Tavani et al, 2000; Hu et al, 2008; Lumbreras et al, 2008), but not all previous studies (Augustsson et al, 1999). We also found positive associations between total meat, red meat and beef and kidney cancer risk, also consistent with some (Chow et al, 1994; Maclure and Willett, 1990; De Stefani et al, 1998b; Hsu et al, 2007), but not all studies (Augustsson et al, 1999; Tavani et al, 2000).

Higher intake of total meat, red meat and beef was associated with increased risk of nervous system cancers, while only total meat was associated with thyroid cancer risk. A previous meta-analysis of 9 studies found increased risk of brain cancers with intake of processed meat (Huncharek et al, 2003) while the results have been mixed for thyroid cancer (Tavani et al, 2000; Cross et al, 2007).

In our study intake of all types of meat was associated with increased risk of lymphomas and similar results were apparent for non-Hodgkin's lymphoma and myeloma, but not with Hodgkin's disease. Other studies have also reported positive associations between total meat or red meat intake and non-Hodgkin's lymphoma (Chiu et al, 1996; Zhang et al, 1999), but most studies reported no association (Talamini et al, 2006; Cross et al, 2007; Hu et al, 2008). A few previous studies found increased risk of myeloma with intake of red meat (Tavani et al, 2000) or processed meat (Cross et al, 2007), while others reported no association (Hosgood, III et al, 2007; Brown et al, 2001). Total and processed meat intake was associated with increased risk of leukemia in line with a few case-control studies of childhood (Petridou et al, 2005; Sarasua and Savitz, 1994) or adulthood leukemia (Hu et al, 2008), but in contrast to prospective studies (Ross et al, 2002; Cross et al, 2007).

All the meat groups were associated with increased risk of all cancer sites combined. It should be noted that our estimate for all cancer sites (included in this study) combined is not equal to an effect on total cancer incidence because we did not have information on several cancer sites and because the distribution of cancers in this study is not representative of that of the Uruguayan population.

Several potential mechanisms could explain the association between meat intake and increased cancer risk. A detrimental effect of meat intake on cancer risk has often been attributed to the content of saturated fat and cholesterol. High intake of fat increases the formation of secondary bile acids which are carcinogenic in the colon and rectum (Nagengast et al, 1995); it may also increase estrogen and androgen levels in plasma (Forman, 2007) and may lead to obesity, an established risk factor for several different cancer sites (World Cancer Research Fund/American Institute for Cancer Research, 2007). However, the epidemiological evidence for dietary fat and cancer risk is weaker than that for meat for several cancer sites (World Cancer Research Fund/American Institute for Cancer Research, 2007).

Other possible mechanisms of meat-induced carcinogenesis include formation of heterocyclic amines (HCA) and polycyclic aromatic hydrocarbons (PAH) during cooking and grilling of meats, nitrite and nitrate in processed meats and the heme-iron content of red meat. HCAs are known to increase free radical formation and oxidative stress which can induce DNA adducts and mutations (Cross and Sinha, 2004). They have been shown to induce several cancers in animals, including cancers of the liver, lung, stomach, colorectum and breast and sarcomas (Ohgaki et al, 1984; Lijinsky, 1987; Snyderwine, 2002).

Processed meats contain nitrite and nitrate which can be converted to nitrosamines which in turn are multi-organ carcinogens in animals (Lijinsky, 1987). Some processed meats contain added salt, a suspected risk factor for stomach cancer (World Cancer Research Fund/American Institute for Cancer Research, 2007) and one study reported increased risk of gastroesophageal reflux, an established risk factor for esophageal adenocarcinoma with higher intake of salted meat (Nilsson et al, 2004). Higher intake of heme-iron, but not organic iron, may increase the risk of gastrointestinal cancers by increasing the endogenous formation of N-nitroso compounds (Cross et al, 2003; Lunn et al, 2007) and some studies found increased risk of colorectal cancer with intake of heme-iron (Larsson et al, 2005; Balder et al, 2006). Heme-iron may increase oxidative stress and the formation of lipid peroxidation products, such as 1,4-dihydroxynonane mercapturic acid and 8-iso-prostaglanding-$F_2\alpha$, which have been associated with preneoplastic lesions in the colon of rats (Pierre et al, 2006). In addition, animal experiments suggest that higher iron intake may enhance the development of breast tumours (Diwan et al, 1997) and the formation of lung tumours (Yano et al, 1994). Higher body iron stores or dietary iron intake have been associated with increased risk of colorectal, lung and liver cancer in epidemiological studies (Knekt et al, 1994; Polesel et al, 2007). Because of limitations in the dietary assessment in this study we were not able to further address the issues of dietary fat, cooking mutagens, preservatives or heme-iron intake.

Our study has several potential limitations; as with any case-control study we cannot rule out the possibility of recall or selection biases. The finding of elevated risks of multiple cancers with weak or limited prior evidence could be interpreted to suggest that selection bias may be present. If the controls either consume or report their meat consumption differently than the general population biased results may occur. However, the mean red meat intake among the controls in this study (140 grams per day (g/d)) is similar to the estimated mean intake of 145 g/d (168 g/d and 122 g/d among men and women, respectively) in dietary surveys from the same region, including Argentina and Paraguay (reference no. 67 in (Norat et al, 2002)). The participation rates were very high and similar among cases and controls suggesting that response bias due to different participation rates has been minimized. Selection of hospital controls is another potential source of bias. Because some of the controls (benign breast disease, benign prostate hyperplasia and benign diseases) might be intermediates between diet and cancer risk we conducted sensitivity analyses with exclusions of these controls for these cancers and in the overall analysis, but the results were similar. Further, exclusion of oral and respiratory disease controls did not materially alter the results for cancers of the upper aerodigestive tract or lung.

Recall bias is a potential problem in case-control studies because of the retrospective assessment of diet. The possible link between meat intake and cancer risk is mostly unknown to the general population in Uruguay and the participants in this study were generally of low socioeconomic status, with minimal knowledge about the role of diet in affecting cancer risk. Meat intake is not considered an unhealthy dietary habit in this population and these points should make recall bias less likely. Nevertheless, we cannot exclude the possibility that recall bias could explain some of our findings. The short food frequency questionnaire that was used is an additional limitation of this study and we were only able to adjust for the intake of some dietary factors that may affect cancer risk, such as fruits, vegetables and milk in the multivariable analysis. We were not able to adjust for energy intake, BMI or physical activity because of missing or incomplete information on these variables. When we restricted the analysis of all cancer sites combined to those participants with complete information on weight and height, further adjustment for height and weight or BMI did not alter the results. Further, adjustment for BMI and other food groups in another study currently under way from the same population appeared to strengthen rather than weaken the results (unpublished results) and in several previous publications from the Uruguayan population the results for meat intake appeared to be independent of BMI and energy intake (Deneo-Pellegrini et al, 1996; De Stefani et al, 1997a,b, 1999; Oreggia et al, 2001). Thus, we believe our findings may not be subject to substantial confounding by these variables. Also, other studies found that the association between meat intake and cancer risk remained significant even after adjustment for physical activity (Cross et al, 2007; Hu et al, 2008; Bessaoud et al, 2008; Taylor et al, 2007; Norat et al, 2005). We cannot exclude the possibility of residual confounding by smoking or unknown or unmeasured factors (e.g. use of aspirin, other medications or infections). However, the finding that meat intake was associated with increased risk of cancer even among the group of never smokers and non-drinkers suggest that residual confounding by smoking or alcohol intake is not likely to explain the results. Also, the finding that the results persisted in most other subgroups when stratified suggests that meat intake may be an independent risk factor for cancer. For some sites, we may have had too low power to detect significant associations due to the small number of cases. Since we investigated meat intake and multiple cancers, some of our findings may have been due to chance.

Our study has several strengths as well; the high meat intake and the relatively large dietary variation in the Uruguayan population increased the power to detect significant associations. The large number of cancer sites available gave us the chance to investigate the relationship between meat intake and several cancers which have been minimally examined previously. Our finding of a dose-response relationship between meat consumption and increased cancer risk and that more extreme exposure increases the risk further, suggest that our findings are real and that there is a biological gradient underlying the risk. Also, future investigations may want to pay attention to the categorisation of intakes and evaluate whether more extremes of dietary intake (both at the lower and higher end) leads to stronger results. The stronger results for some cancers (e.g. esophagus and stomach) observed in this population as compared to studies conducted in North America and Europe may reflect the higher meat intake in Uruguay than in other countries. For example, in the European EPIC-cohort, the mean red meat intake in the highest quartile and the lowest quartile was 84.6 and 34.3 g/d for men, and 52.9 and 22.6 g/d for women, respectively (Gonzalez et al, 2006). In the NIH-AARP Diet and Health Study the mean red meat intake in the highest and the lowest quintile was 67.0 and 12.0 g/1000 kcal/d for men and 54.7 and 7.8 g/1000 kcal/d for women, respectively, which amount to an absolute intake of approximately 135 and 24 g/day for men and 86 and 12 g/d for women in the highest and lowest quintiles, respectively (Cross et al, 2007). In contrast, the mean red meat intake in the highest and lowest tertile among controls was 295.5 g/d and 49.7 g/d in this study (assuming a 150 gram serving size), suggesting a 2-3 fold higher intake in this population than in these other studies. However, when assessed on a continuous scale the OR per serving per day is comparable with the results from several studies from European and North-American countries (Tavani et al, 2000; Norat et al, 2005; Gonzalez et al, 2006; Navarro Silvera et al, 2008), suggesting that the high ORs observed in the categorical analysis in this study may be explained by the high intake in this population. Our findings therefore underscore the importance of having a large dietary variation within the population so the contrasts between extreme categories are large enough to detect a difference in risk.

In a previous study we found that a western dietary pattern with high loadings of red and processed meat was positively associated with a number of cancers (De Stefani et al, 2009), which is consistent with our present findings for meat. Collectively, these results suggest that meat intake may account for part of the association between the western dietary pattern and cancer risk, although other factors in the western dietary pattern also may be important.

V. Conclusion

Our results confirm earlier findings of an increased risk of gastrointestinal cancers with high meat intake, but also suggest that meat consumption may increase the risk of several other cancers. While a prospective cohort study in this population could more definitely establish the causal nature of the observed associations by ruling out some potential biases inherent in the case-control study design, our findings provide further evidence for an unfavourable effect of meat intake upon cancer risk and suggest that meat intake increases the risk of multiple cancer sites. Reducing meat consumption might be an important modifiable risk factor for several types of cancer and may remove a relatively large proportion of the cancer burden in a population characterized by a high intake of meat such as this one.

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Supplementary Table. Distribution of cases and controls.

Cancer site	Tertile	Total meat	Fresh red meat	Beef	Lamb	Processed meat
Oral	1	37	37	35	23	50
	2	109	10	118	168	46
	3	105	111	98	60	155
Pharynx	1	36	45	44	17	27
	2	98	90	107	149	44
	3	109	108	92	77	172
Oral, pharynx	1	73	82	79	40	77
	2	207	193	225	317	90
	3	214	219	190	137	327
Esophagus	1	37	49	51	19	60
	2	136	141	162	241	67
	3	201	184	161	114	247
Larynx	1	31	40	41	14	27
	2	106	111	120	181	55
	3	138	124	114	80	193
Upper aerodigestive tract	1	141	171	171	73	164
	2	449	445	507	739	212
	3	553	527	465	331	767
Stomach	1	14	21	22	6	9
	2	52	46	50	92	18
	3	62	61	56	30	101
Colon	1	45	47	48	19	24
	2	76	81	83	132	40
	3	56	49	46	26	113
Rectum	1	46	52	48	19	34
	2	86	84	93	153	30
	3	68	64	59	28	136
Colorectal	1	91	99	96	38	58
	2	162	165	176	285	70
	3	124	113	105	54	249
Pancreas	1	27	29	30	6	19
	2	38	39	42	77	18
	3	39	36	32	21	67
Lung	1	169	196	202	62	180
	2	466	465	524	760	234
	3	539	513	448	352	760
Sarcomas	1	30	37	38	18	22
	2	64	61	64	110	35
	3	53	49	45	19	90
Melanoma	1	39	43	42	13	23
	2	50	49	54	94	27
	3	28	25	21	10	67
Non-melanoma skin	1	104	119	116	44	72
	2	169	159	169	275	97
	3	117	112	105	71	221
Breast	1	581	649	643	224	364
	2	718	693	714	1241	323
	3	308	265	250	142	920
Cervix uteri	1	76	86	86	27	62
	2	113	109	111	202	39

	3	64	58	56	24	152
Corpus uteri	1	36	42	42	15	18
	2	27	22	22	60	16
	3	19	18	18	7	48
Ovary	1	28	32	30	9	16
	2	41	37	42	67	19
	3	14	14	11	7	48
Prostate	1	78	87	85	41	80
	2	159	166	181	257	68
	3	139	123	110	78	228
Testis	1	11	15	12	4	7
	2	27	22	27	45	12
	3	24	25	23	13	43
Bladder	1	34	42	43	10	31
	2	70	62	71	129	50
	3	79	79	69	44	102
Kidney	1	34	39	39	16	30
	2	74	65	70	116	39
	3	60	64	59	36	99
Nervous system	1	11	11	10	6	9
	2	27	28	31	47	13
	3	26	25	23	11	42
Thyroid	1	12	12	13	4	9
	2	19	24	23	36	7
	3	20	15	15	11	35
Lymphomas	1	73	77	78	29	42
	2	134	145	151	233	59
	3	110	95	88	55	216
Non-Hodgkin's lymphoma	1	46	43	46	17	27
	2	86	99	102	144	38
	3	67	57	51	38	134
Hodgkin's disease	1	18	23	21	6	8
	2	32	32	33	61	14
	3	22	17	18	5	50
Myeloma	1	9	11	11	6	7
	2	16	14	16	28	7
	3	21	21	19	12	32
Leukemia	1	20	21	20	6	9
	2	23	24	26	53	14
	3	23	21	20	7	43
All sites	1	1609	1828	1818	651	1224
	2	2882	2826	3055	4918	1370
	3	2401	2238	2019	1323	4298
Controls (males/ females)	1	567 (168/399)	651 (195/456)	646 (201/445)	231 (68/163)	409 (140/269)
	2	833 (333/500)	801 (314/487)	842 (336/506)	1383 (525/858)	321 (132/189)
	3	432 (241/191)	380 (233/147)	344 (205/139)	218 (149/69)	1102 (470/632)