RESEARCH COMMUNICATION

Meat Consumption and Cancer Risk: a Case-control Study in Uruguay

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Abstract

Introduction: There is strong evidence that high meat intake increases the risk of colorectal cancer. However, for other cancer sites there is currently less convincing evidence. Methods: To further explore associations between meat intake and cancer risk we conducted a multisite case-control study of 11 cancer sites in Uruguay between 1996 and 2004, including 3,539 cancer cases and 2,032 hospital controls. We used unconditional logistic regression to estimate odds ratios and 95% confidence intervals of cancer associated with meat intake. Results: In the multivariable model there was a significant increase in the odds of cancers of the oral cavity and pharynx (OR=3.65, 95% CI: 2.21-6.01), esophagus (OR=3.36, 95% CI: 1.97-5.72), larynx (OR=2.91, 95% CI: 1.80-4.68), stomach (OR=2.19, 95% CI: 1.31-3.65), colorectum (OR=3.83, 95% CI: 2.37-6.20), lung (OR=2.17, 95% CI: 1.52-3.10), breast (OR=1.97, 95% CI: 1.04-3.75), prostate (OR=1.87, 95% CI: 1.08-3.21), bladder (OR=2.11, 95% CI: 1.20-3.72) and kidney (OR=2.72, 95% CI: 1.22-6.07) with high intake of red meat and similar findings were found for total meat. In addition, intake of beef and lamb were also associated with increased risk of several cancer sites. High intake of processed meat was associated with increased risk of cancers of the esophagus (OR=1.63, 95% CI: 1.08-2.47), larynx (OR=1.84, 95% CI: 1.21-2.78), stomach (OR=1.62, 95% CI: 1.07-2.44), colorectum (OR=2.15, 95% CI: 1.49-3.11), lung (OR=1.70, 95% CI: 1.28-2.25) and breast (OR=1.53, 95% CI: 1.01-2.30). Conclusion: Our results confirm earlier findings of increased risk of digestive tract cancers, but suggest that meat consumption also increases the risk of several other cancers.

Key Words: Diet - meat - cancer - epidemiology

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Introduction

The incidence rates of colorectal cancer and breast cancer in Uruguay are the highest among the South-American countries (Ferlay et al., 2002), with age-standardized rates of 39.6 and 63.1 per 100 000 persons per year, respectively. Rates of cancers of the larynx, esophagus, lung, prostate, bladder and kidney are also high, especially among men (Ferlay et al., 2002). While there is no doubt that smoking and high alcohol consumption contributes to the high rates of cancers of the lung, aerodigestive tract and some other cancers, there is increasing evidence that diet plays a major role in influencing cancer risk (World Cancer Research Fund/ American Institute for Cancer Research, 2007).

The Uruguayan diet is characterized by a low intake of fruits, vegetables and whole grains and by the highest per capita meat intake in the world (Speedy, 2003) and thus provides an interesting setting for investigating 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) and lung (Deneo-Pellegrini et al., 1996; De Stefani et al., 2002) with a high meat intake. Further, in a previous analysis we reported positive associations between a western dietary pattern high in red and processed meat and the risk of several cancers (De Stefani et al., 2009). Four multisite case-control studies conducted in Italy (Tavani et al., 2000; Levi et al., 2004), Canada (Hu et al., 2008) and in Uruguay (Aune et al., 2009) and a large American cohort study (Cross et al., 2007), similarly reported increased risk.

However, because the dietary questionnaire which was used in our previous study was rather short we were only able to adjust for a limited number of other dietary factors (Aune et al., 2009), thus residual confounding from other food groups and energy intake remained a concern. To further expand upon these findings we decided to explore the association between meat consumption and the risk of 11 cancers in a case-control study in Uruguay, with a more comprehensive dietary assessment than previously.

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Materials and Methods

Selection of cases

In the time period between 1996 and 2004 we conducted a multisite case-control study including cancers of the mouth and pharynx (n=283), esophagus (n=234), stomach (n=274), colon (n=176), rectum (n=185), larynx (n=281), lung (n=931), breast (n=461), prostate (n=345), bladder (n=255) and kidney (n=114). All the cases were <90 years old at diagnosis (age range 26-89 years, mean 63.6 years) and were drawn from the four major public hospitals of Montevideo. A total of 3,744 newly diagnosed and microscopically confirmed cancers were considered eligible for the study. In total, 205 patients refused the interview or were to ill for interview, leaving a final total of 3,539 cases included in the study (response rate 94.5%).

Selection of controls

In the same time period and in the same hospitals, 2,117 patients <90 years old (age range 23-89 years, mean 62.3 years) with non-neoplastic diseases not related to smoking, drinking and without recent changes in their diet were considered eligible for this study. Sixty seven patients refused the interview, leaving a final total of 2,032 controls (response rate 96.0%). These patients presented with the following diseases: eye disorders (21.2%), abdominal hernia (20.8%), injuries and accidents (19.1%), venous diseases (5.5%), acute appendicitis (5.5%), diseases of the skin (6.7%), hydatid cyst (5.0 %), urinary system diseases (4.7%) and various other conditions (11.5%). The controls were not matched to the cases for any factors.

Interviews and questionnaire

All the participants were administered a structured questionnaire by trained social workers, with interviews conducted in hospitals shortly after admittance. No proxy interviews were conducted. The questionnaire contained the following sections: 1) socio-demographic characteristics (age, sex, residence, education), 2) a complete occupational history based in their jobs and its duration, 3) self-reported height and weight five years before the date of the interview, 4) a history of cancer in first degree relatives, 5) a complete history of tobacco smoking (age at start, age of quit, number of cigarettes smoked per day, type of tobacco, type of cigarette, inhalation practices), 6) a complete history of alcohol intake (age at start, age of quit, number of glasses per day or week, type of alcoholic beverage), 7) a complete history of mate (a local herbal tea), coffee and tea consumption (age at start, age of quit, number of cups or liters ingested per day) and 8) a detailed food frequency questionnaire (FFQ) with 64 food items which covered the dietary intake one year before diagnosis. Although the FFQ has not been validated, it has been tested for reproducibility, the correlation coefficients between the two assessments being 0.67, 0.77 and 0.55 for total meat, red meat and processed meat, respectively (Ronco et al., 2006). Total meat included red meat, liver, processed meat and white meat. red meat was defined as fresh meat including beef and lamb, while processed meat included hot dogs, sausages, ham, salami, saucisson, mortadella, bacon and salted meat.

Statistical methods

We used unconditional logistic regression to estimate odds ratios and 95% confidence intervals (CIs) of cancer for increasing levels of meat intake. Cut-points were based on absolute intake with increments of 100 grams per day for all except processed meat where the increment was 30 grams per day. The multivariable model included the following covariates: age (continuous), sex (when applicable), residence (urban/rural), education (continuous), income (continuous), interviewer (categorical), smoking status (never, former, current), age at starting smoking (continuous), years since quitting smoking (continuous), cigarettes per day (continuous), duration of smoking (continuous), alcohol intake (0, 1-60, 61-120, 121-240, ≥241 ml/d), intake of grains (continuous), fatty foods including butter, eggs, custard and cake (continuous), fruits and vegetables (continuous), poultry (continuous), fish (continuous), mate drinking status (categorical), energy intake (continuous) and BMI (continuous). Poulty and fish were not included as covariates in the analysis of total meat.

Potential confounders were included in the

Table 1. Socio-demographic Characteristics and Selected Risk Factors among Cases and Controls (Values are means (standard deviations), except for sex (%))

Cancer	Number	Age (years)	Men (%)	Smoking (Cig./d)	Ethanol (ml/d)	Fruits, vegetables (g/d)	Meat (g/d)
Oral cavity	283	59.9 (9.7)	96.8	27.6 (15.9)	213.1 (222.5)	335.7 (155.3)	258.7 (108.7)
Esophagus	234	66.3 (10.3)	78.6	22.2 (18.8)	122.9 (195.7)	317.7 (146.6)	238.0 (99.8)
Larynx	281	62.1 (10.0)	97.5	32.6 (21.3)	194.0 (231.6)	327.8 (141.8)	265.0 (101.4)
Upper aerodigestive tract	798	62.5 (10.3)	91.7	27.8 (19.2)	179.9 (221.3)	327.6 (148.1)	254.9 (104.1)
Stomach	275	65.5 (11.2)	69.3	16.0 (17.7)	85.4 (140.2)	342.9 (143.9)	230.1 (99.2)
Colon	176	64.3 (11.9)	49.4	13.7 (19.0)	45.7 (127.1)	322.5 (153.7)	220.2 (92.0)
Rectum	185	66.3 (10.2)	68.6	14.8 (17.2)	70.3 (119.3)	335.0 (171.4)	235.1 (98.6)
Colorectum	361	65.3 (11.1)	59.3	14.2 (18.0)	58.3 (123.6)	328.9 (162.9)	227.8 (95.6)
Lung	931	62.0 (10.0)	94.0	31.6 (19.8)	135.9 (185.6)	317.8 (169.7)	232.6 (100.6)
Breast	461	59.7 (13.1)	0.0	4.1 (8.7)	12.1 (51.5)	282.5 (157.5)	198.1 (82.1)
Prostate	345	70.6 (7.3)	100.0	18.0 (18.5)	96.4 (165.9)	347.1 (163.8)	205.1 (94.3)
Bladder	254	66.9 (10.0)	88.2	19.3 (18.0)	83.7 (129.7)	348.5 (190.0)	220.2 (112.7)
Kidney	114	60.6 (11.8)	67.5	15.6 (16.3)	78.0 (162.8)	323.5 (163.6)	201.5 (103.8)
All cases	3,539	63.6 (11.0)	75.1	21.4 (20.1)	108.4 (176.6)	323.7 (162.6)	227.9 (100.7)
Controls	2,032	62.3 (12.8)	64.8	13.5 (15.8)	75.3 (147.4)	329.8 (156.0)	195.8 (87.1)

Table 2. Meat Intake in Relation to Cancer Risk (multivariate ORs and 95% CIs[1])

Cancer site		Total meat[2]		Red meat[3]		Beef[4]		Lamb[5]		Processed meat[6]	
		Cases	OR (95%CI)	Cases	OR (95%CI)	Cases	OR (95%CI)	Cases	OR (95%CI)	Cases	OR (95%CI)
Oral cavity /pharynx	1	38	1.00 (ref.)	70	1.00 (ref.)	94	1.00 (ref.)	126	1.00 (ref.)	47	1.00 (ref.)
	2	105	1.10 (0.71-1.69)	126	1.35 (0.94-1.93)	124	1.06 (0.76-1.47)	124	1.07 (0.80-1.43)	121	0.91 (0.62-1.34)
	3	140	1.92 (1.14-3.20)	87	3.65 (2.21-6.01)	65	2.06 (1.29-3.29)	33	3.60 (2.11-6.15)	115	1.31 (0.86-1.98)
	P_{trend}		0.003		<0.0001		0.011		0.002		0.13
Esophagus	1	41	1.00 (ref.)	71	1.00 (ref.)	98	1.00 (ref.)	111	1.00 (ref.)	45	1.00 (ref.)
	2	96	1.46 (0.96-2.21)	112	1.68 (1.18-2.41)	100	1.16 (0.84-1.60)	93	1.12 (0.82-1.52)	103	0.96 (0.65-1.39)
	3	97	2.66 (1.57-4.51)	51	3.36 (1.97-5.72)	36	1.87 (1.12-3.12)	30	2.94 (1.72-5.03)	86	1.63 (1.08-2.47)
	P_{trend}		<0.0001		<0.0001		0.036		0.003		0.014
Larynx	1	24	1.00 (ref.)	56	1.00 (ref.)	85	1.00 (ref.)	120	1.00 (ref.)	40	1.00 (ref.)
	2	124	1.81 (1.11-2.93)	145	1.64 (1.14-2.35)	132	1.13 (0.82-1.57)	131	1.17 (0.88-1.56)	114	1.03 (0.69-1.54)
	3	133	2.30 (1.33-3.97)	80	2.91 (1.80-4.68)	64	1.82 (1.15-2.87)	30	2.73 (1.59-4.69)	127	1.84 (1.21-2.78)
	P_{trend}		0.005		<0.0001		0.026		0.004		0.001
Upper aero-digestive tract	1	103	1.00 (ref.)	197	1.00 (ref.)	277	1.00 (ref.)	357	1.00 (ref.)	132	1.00 (ref.)
	2	325	1.43 (1.09-1.89)	383	1.61 (1.28-2.03)	356	1.16 (0.94-1.43)	348	1.13 (0.93-1.37)	338	0.93 (0.73-1.19)
	3	370	2.20 (1.56-3.09)	218	3.22 (2.30-4.50)	165	1.89 (1.35-2.62)	93	3.01 (2.06-4.39)	328	1.53 (1.17-2.01)
	P_{trend}		<0.0001		<0.0001		<0.0001		<0.0001		<0.0001
Stomach	1	53	1.00 (ref.)	89	1.00 (ref.)	107	1.00 (ref.)	147	1.00 (ref.)	46	1.00 (ref.)
	2	124	1.20 (0.82-1.75)	136	1.36 (0.98-1.89)	127	1.21 (0.88-1.65)	113	1.05 (0.79-1.39)	138	1.29 (0.89-1.86)
	3	98	1.64 (1.00-2.70)	50	2.19 (1.31-3.65)	41	1.70 (1.04-2.83)	15	1.50 (0.79-2.84)	91	1.62 (1.07-2.44)
	P_{trend}		0.016		0.004		0.053		0.36		0.026
Colon	1	37	1.00 (ref.)	71	1.00 (ref.)	76	1.00 (ref.)	117	1.00 (ref.)	33	1.00 (ref.)
	2	85	2.45 (1.55-3.88)	84	2.02 (1.35-3.01)	82	2.00 (1.36-2.93)	53	0.93 (0.64-1.33)	81	1.21 (0.78-1.87)
	3	54	4.38 (2.30-8.32)	21	3.26 (1.63-6.53)	18	3.13 (1.57-6.26)	6	0.87 (0.35-2.18)	62	2.52 (1.53-4.16)
	P_{trend}		<0.0001		<0.0001		<0.0001		0.62		<0.0001
Rectum	1	35	1.00 (ref.)	60	1.00 (ref.)	67	1.00 (ref.)	104	1.00 (ref.)	33	1.00 (ref.)
	2	82	1.82 (1.16-2.86)	85	1.87 (1.26-2.79)	88	1.96 (1.34-2.85)	69	1.20 (0.85-1.69)	87	1.16 (0.75-1.78)
	3	68	2.57 (1.43-4.62)	40	3.90 (2.13-7.15)	30	3.32 (1.83-6.02)	12	1.35 (0.66-2.77)	65	1.87 (1.15-3.04)
	P_{trend}		0.001		<0.0001		<0.0001		0.26		0.009
Colorectum	1	72	1.00 (ref.)	131	1.00 (ref.)	143	1.00 (ref.)	221	1.00 (ref.)	66	1.00 (ref.)
	2	167	2.05 (1.46-2.86)	169	1.96 (1.46-2.63)	170	1.98 (1.49-2.62)	122	1.04 (0.80-1.35)	168	1.18 (0.86-1.63)
	3	122	3.31 (2.10-5.23)	61	3.83 (2.37-6.20)	48	3.36 (2.08-5.42)	18	1.22 (0.68-2.21)	127	2.15 (1.49-3.11)
	P_{trend}		<0.0001		<0.0001		<0.0001		0.47		<0.0001
Lung	1	191	1.00 (ref.)	356	1.00 (ref.)	419	1.00 (ref.)	463	1.00 (ref.)	165	1.00 (ref.)
	2	394	1.35 (1.05-1.74)	383	1.13 (0.91-1.42)	377	1.08 (0.87-1.33)	395	1.11 (0.92-1.34)	453	1.17 (0.92-1.50)
	3	346	2.03 (1.44-2.87)	192	2.17 (1.52-3.10)	135	1.67 (1.17-2.39)	73	1.52 (1.01-2.29)	313	1.70 (1.28-2.25)
	P_{trend}		<0.0001		<0.0001		0.018		0.068		<0.0001
Breast	1	130	1.00 (ref.)	216	1.00 (ref.)	128/244	1.00 (ref.)	288/473	1.00 (ref.)	121	1.00 (ref.)
	2	237	1.85 (1.34-2.56)	212	1.84 (1.35-2.50)	135/189	1.28 (0.92-1.78)	125/178	1.31 (0.97-1.77)	228	0.92 (0.68-1.25)
	3	94	2.05 (1.23-3.42)	33	1.97 (1.04-3.75)	198/253	1.58 (1.11-2.24)	48/35	1.88 (1.12-3.15)	112	1.53 (1.01-2.30)
	P_{trend}		0.001		0.001		0.013		0.009		0.084
Prostate	1	93	1.00 (ref.)	125	1.00 (ref.)	151	1.00 (ref.)	164	1.00 (ref.)	86	1.00 (ref.)
	2	168	1.11 (0.80-1.54)	179	1.56 (1.15-2.13)	164	1.42 (1.07-1.90)	158	1.37 (1.05-1.78)	169	0.89 (0.66-1.21)
	3	84	1.03 (0.63-1.67)	41	1.87 (1.08-3.21)	30	1.54 (0.89-2.64)	23	1.49 (0.85-2.62)	90	0.95 (0.66-1.38)
	P_{trend}		0.85		0.001		0.024		0.023		0.82
Bladder	1	66	1.00 (ref.)	106	1.00 (ref.)	123	1.00 (ref.)	142	1.00 (ref.)	56	1.00 (ref.)
	2	114	1.25 (0.85-1.82)	101	1.10 (0.77-1.56)	92	1.02 (0.73-1.43)	94	1.23 (0.91-1.68)	121	1.01 (0.70-1.46)
	3	74	1.24 (0.72-2.14)	47	2.11 (1.20-3.72)	39	2.20 (1.28-3.79)	18	1.27 (0.68-2.37)	77	1.43 (0.93-2.20)
	P_{trend}		0.32		0.04		0.037		0.23		0.099
Kidney	1	37	1.00 (ref.)	53	1.00 (ref.)	56	1.00 (ref.)	68	1.00 (ref.)	31	1.00 (ref.)
	2	42	1.01 (0.59-1.70)	43	1.12 (0.68-1.84)	43	1.14 (0.71-1.84)	43	1.47 (0.96-2.25)	50	0.76 (0.46-1.23)
	3	35	1.90 (0.90-4.00)	18	2.72 (1.22-6.07)	15	2.53 (1.14-5.59)	3	0.77 (0.22-2.67)	33	1.23 (0.68-2.22)
	P_{trend}		0.47		0.06		0.073		0.29		0.52
Controls	1	632	(364/268 m/w)	622	(353/269)	1,093	(660/433)	1,197	(724/473)	123	(53/70)
	2	936	(633/303)	1017	(699/318)	790	(570/220)	754	(558/196)	1,418	(934/484)
	3	464	(349/115)	393	(294/99)	149	(116/33)	81	(64/17)	491	(359/132)

[1]Adjusted for: age, sex (when applicable), residence, education, income, interviewer, smoking status, cigarettes per day, duration of smoking, age at starting, years since quitting, alcohol, dairy foods, grains, fatty foods (butter, eggs, custard, cake), fruits and vegetables, fish, poultry (except total meat), mate drinking, BMI and energy intake. Red meat, beef and lamb were adjusted for processed meat and vice versa. [2]Total meat, cut-off: 0-<150, 150-<250, 250-686.8 g/d, median: 108.3, 191.9, 306.3 g/d. [3]Red meat: 0-<150, 150-<250, 250-600 g/d, and: 85.5, 160.3, 300.2 g/d. [4]Beef, (men, all): 0-<150, <150-<250, 250-524.8 g/d, and: 85.5, 150, 300 g/d. (women): 0-<90, 90-<150, 150-524.8, and: 64.1, 117.5, 171 g/d. [5]Lamb, (men, all): 0, >0-<100, 100-524.8 g/d, and: 0, 7.4, 150 g/d. (women): 0,>0-<50, 50-524.8, and: 0, 4.9, 96.2. [6]Processed meat: 0-10, >10-40, >40-258.8 g/d and median: 3.7, 22.1, 63.9 g/d.

multivariate models based on review of the literature and from comparisons of cases vs. controls or whethe.r they altered the risk estimate by 10% or more. Tests for linear trend were calculated by entering the categorical variables as continuous parameters. A two-tailed P-value of <0.05 was considered statistically significant. All statistical tests were carried out using STATA version 9.2.

Results

Selected socio-demographic characteristics and risk factors among cases and controls are shown in Table 1. The multivariate adjusted odds ratios for types of meat and the various cancers are shown in Table 2.

Compared with the controls, the cases were in general

older and smoked more and had a higher intake of alcohol and total meat, but a lower intake of fruits and vegetables.

High total meat consumption was strongly associated with risk of cancers of the oral cavity and pharynx (OR=1.92, 95% CI: 1.14-3.20; p_{trend}=0.003), esophagus (OR=2.66, 95% CI: 1.57-4.51; p_{trend}<0.0001), larynx (OR=2.30, 95% CI: 1.33-3.97; p_{trend}=0.005), upper aerodigestive tract (OR=2.20, 95% CI: 1.56-3.09; p_{trend}<0.0001), stomach (OR=1.64, 95% CI: 1.00-2.70; p_{trend}=0.02), colorectum (OR=3.31, 95% CI: 2.10-5.23; p_{trend}<0.0001), lung (OR=2.03, 95% CI: 1.44-2.87; p_{trend}<0.0001) and breast cancer (OR=2.05, 95% CI: 1.23-3.42; p_{trend}=0.001) (Table 2). There was no significant association with prostate (OR=1.03, 95% CI: 0.63-1.67; p_{trend}=0.85), bladder (OR=1.24, 95% CI: 0.72-2.14; p_{trend}=0.32) or kidney cancer (OR=1.90, 95% CI: 0.90-4.00; p_{trend}=0.47).

High intake of red meat was significantly associated with risk of cancers of the oral cavity and pharynx (OR=3.65, 95% CI: 2.21-6.01; p_{trend}<0.0001), esophagus (OR=3.36, 95% CI: 1.97-5.72; p_{trend}<0.0001), larynx (OR=2.91, 95% CI: 1.80-4.68; p_{trend}<0.0001), upper aerodigestive tract (OR=3.22, 95% CI: 2.30-4.50; p_{trend}<0.0001), stomach (OR=2.19, 95% CI: 1.31-3.65; p_{trend}=0.004), colorectum (OR=3.83, 95% CI: 2.37-6.20; p_{trend}<0.0001), lung (OR=2.17, 95% CI: 1.52-3.10; p_{trend}<0.0001), breast (OR=1.97, 95% CI: 1.04-3.75; p_{trend}=0.001), prostate (OR=1.87, 95% CI: 1.08-3.21; p_{trend}=0.001), bladder (OR=2.11, 95% CI: 1.20-3.72; p_{trend}=0.04) and kidney (OR=2.72, 95% CI: 1.22-6.07; p_{trend}=0.06) (Table 2).

Beef intake was associated with increased risk of cancers of the mouth and pharynx (OR=2.06, 95% CI: 1.29-3.29; p_{trend}=0.01), esophagus (OR=1.87, 95% CI: 1.12-3.12; p_{trend}=0.04), larynx (OR=1.82, 95% CI: 1.15-2.87; p_{trend}=0.03), upper aerodigestive tract (OR=1.89, 95% CI: 1.35-2.62; p_{trend}<0.0001), stomach (OR=1.70, 95% CI: 1.04-2.83; p_{trend}=0.05), colorectum (OR=3.36, 95% CI: 2.08-5.42; p_{trend}<0.0001), lung (OR=1.67, 95% CI: 1.17-2.39; p_{trend}=0.02), breast (OR=1.58, 95% CI: 1.11-2.24; p_{trend}=0.01), prostate (OR=1.54, 95% CI: 0.89-2.64; p_{trend}=0.02), bladder (OR=2.20, 95% CI: 1.28-3.79; p_{trend}=0.04) and kidney (OR=2.53, 95% CI: 1.14-5.59; p_{trend}=0.07) (table 2).

Intake of lamb was associated with increased risk of cancers of the oral cavity and pharynx (OR=3.60, 95% CI: 2.11-6.15; p_{trend}=0.002), esophagus (OR=2.94, 95% CI: 1.72-5.03; p_{trend}=0.003), larynx (OR=2.73, 95% CI: 1.59-4.69; p_{trend}=0.004), upper aerodigestive tract (OR=3.01, 95% CI: 2.06-4.39; p_{trend}<0.0001), lung (OR=1.52, 95% CI: 1.01-2.29; p_{trend}=0.07), breast (OR=1.88, 95% CI: 1.12-3.15; p_{trend}=0.009) and prostate (OR=1.49, 95% CI: 0.85-2.62; p_{trend}=0.02), while no associations were apparent for stomach (OR=1.50, 95% CI: 0.79-2.84; p_{trend}=0.36), colorectal (OR=1.22, 95% CI: 0.68-2.21; p_{trend}=0.47), bladder (OR=1.27, 95% CI: 0.68-2.37; p_{trend}=0.23) or kidney cancer (OR=0.77, 95% CI: 0.22-2.67; p_{trend}=0.29) (Table 2).

High intake of processed meat was associated with increased risk of cancers of the esophagus (OR=1.63, 95% CI: 1.08-2.47; p_{trend}=0.01), larynx (OR=1.84, 95% CI: 1.21-2.78; p_{trend}=0.001), upper aerodigestive tract (OR=1.53, 95% CI: 1.17-2.01; p_{trend}<0.0001), stomach (OR=1.62, 95% CI: 1.07-2.44; p_{trend}=0.03), colorectum (OR=2.15, 95% CI: 1.49-3.11; p_{trend}<0.0001), lung (OR=1.70, 95% CI: 1.28-2.25; p_{trend}<0.0001) and breast (OR=1.53, 95% CI: 1.01-2.30; p_{trend}=0.08). No significant association was found with cancers of the oral cavity and pharynx (OR=1.31, 95% CI: 0.86-1.98; p_{trend}=0.13), prostate (OR=0.95, 95% CI: 0.66-1.38; p_{trend}=0.82), bladder (OR=1.43, 95% CI: 0.93-2.20; p_{trend}=0.10) or kidney (OR=1.23, 95% CI: 0.68-2.22; p_{trend}=0.52) (Table 2).

Discussion

In this large hospital-based case-control study we found increased risk of multiple cancers with high 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; World Cancer Research Fund/American Insitute for Cancer Research, 2007; Aune et al., 2009). Three previous meta-analyses showed an elevated risk of colorectal cancer with higher meat intake (Sandhu et al., 2001; Norat et al., 2002; Larsson and Wolk, 2006) and in the most recent report from the World Cancer Research Fund/American Institute for Cancer Research from 2007 (WCRF/AICR), the evidence that red and processed meat increases colorectal cancer risk was judged to be convincing (World Cancer Research Fund/American Insitute for Cancer Research, 2007).

Our finding of an elevated risk of oral and pharyngeal cancer with higher intake of total, red meat, beef and lamb is consistent with some (Levi et al., 1998; Franceschi et al., 1999; Aune et al., 2009), but not all previous case-control studies (Zheng et al., 1992). Our findings suggested a strong increase in the risk of esophageal cancer with meat intake and is in line with recent case-control (Navarro Silvera et al., 2008; Aune et al., 2009) 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 Insitute for Cancer Research, 2007). We found increased risk of laryngeal cancer with all meat groups. Five (De Stefani et al., 1999; Oreggia et al., 2001; Bosetti et al., 2002; Sapkota et al., 2008; Aune et al., 2009) of six case-control studies (De Stefani et al., 1999; Tavani et al., 2000; Oreggia et al., 2001; Bosetti et al., 2002; Sapkota et al., 2008; Aune et al., 2009) and one cohort study (Cross et al., 2007) of red meat intake and laryngeal cancer found RRs of 1.2 or higher, although two of these were not statistically significant (Cross et al., 2007; De Stefani et al., 1999), while one case-control study reported a slight inverse association (Tavani et al., 2000). Processed meat intake was associated with increased risk of laryngeal cancer with RRs of 1.2 or higher in nine (Sokic et al., 1994; Esteve et al., 1996; De Stefani et al., 1999; Bosetti et al., 2002; Pisa and Barbone, 2002; Levi et al., 2004;

Cross et al., 2007; Sapkota et al., 2008; Aune et al., 2009) of the eleven previous studies (Sokic et al., 1994; Rogers et al., 1995; Esteve et al., 1996; De Stefani et al., 1999; Oreggia et al., 2001; Bosetti et al., 2002; Pisa and Barbone, 2002; Levi et al., 2004; Cross et al., 2007; Sapkota et al., 2008;Aune et al., 2009) (one of these was a cohort (Cross et al., 2007)), but only in four studies (Sokic et al., 1994; Bosetti et al., 2002; Levi et al., 2004; Aune et al., 2009) were the results statistically significant. Meat intake was associated with increased risk of upper aerodigestive tract cancers in line with some case-control studies which found increased risks with total and red meat (De Stefani et al., 1998c; Aune et al., 2009) and processed meat (Levi et al., 2004; Aune et al., 2009), but in contrast with another study (Tavani et al., 2000).

High meat intake was associated with increased risk of stomach cancer in this study consistent with our previous report (Aune et al., 2009). A previous meta-analysis of 10 cohort studies and 19 case-control studies found evidence that processed meat was associated with increased stomach cancer risk (Larsson et al., 2006) and our results provides further support for these findings. A large European cohort study found increased stomach cancer risk with higher intake of total, red and processed meat (Gonzalez et al., 2006), but a recent American cohort did not confirm these findings (Cross et al., 2007). The WCRF/AICR report stated that there was limited suggestive evidence that processed meats increases risk of stomach cancer (World Cancer Research Fund/ American Insitute for Cancer Research, 2007).

Lung cancer risk was elevated with higher intake of all meat groups in line with several previous studies (Deneo-Pellegrini et al., 1996; Alavanja et al., 2001; De Stefani et al., 2002; Cross et al., 2007; Hu et al., 2008; Aune et al., 2009; Lam et al., 2009) 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 Insitute for Cancer Research, 2007).

We found moderate to strong increases in the risk of breast cancer with intake total meat, red meat, beef, lamb and processed meat. Two previous meta-analyses of meat consumption and breast cancer risk found evidence of increased risk (Boyd et al., 1993; 2003) and the more recent one, based on 22 case-control studies and 9 cohort studies, found a summary RR of 1.17 (95% CI: 1.06-1.29) for high vs. low total meat intake (Boyd et al., 2003). However, a pooled analysis of seven cohort studies reported no association (Missmer et al., 2002). Some more recent studies have also found conflicting results, with some case-control (Kruk, 2007; Bessaoud et al., 2008; Aune et al., 2009) and cohort studies (Cho et al., 2006; Taylor et al., 2007; Egeberg et al., 2008) reporting positive associations while others found no association (Holmes et al., 2003; Cross et al., 2007; Kabat et al., 2007).

There was a trend toward a higher risk of prostate cancer with intake of red meat, beef and lamb, but not with other meats in this study. Previous studies of meat intake and prostate cancer have provided conflicting results with some cohorts showing positive associations (Gann et al., 1994; Le Marchand et al., 1994), while other case-control (Tavani et al., 2000) and cohort studies (Neuhouser et al., 2007; Park et al., 2007) found no association. Some cohort 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 Insitute for Cancer Research, 2007).

We found positive associations between meat intake and bladder cancer risk. These results are in line with some case-control (Tavani et al., 2000; Hu et al., 2008; Aune et al., 2009) and cohort studies (Steineck et al., 1988; Mills et al., 1991; Lumbreras et al., 2008), but not all (Augustsson et al., 1999; Garcia-Closas et al., 2007). A few studies reported positive associations with the intake of processed meat (Cross et al., 2007; Hu et al., 2008) and bacon (Wilkens et al., 1996; Michaud et al., 2006). Red meat and beef intake was associated with kidney cancer risk, consistent with some case-control studies (Maclure and Willett, 1990; Chow et al., 1994; Boeing et al., 1997;Hsu et al., 2007;Aune et al., 2009), but not all (Augustsson et al., 1999; Tavani et al., 2000).

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 in meats. Higher intake of fat increases the formation of secondary bile acids which are carcinogenic in the colon and rectum (Nagengast et al., 1995) and may increase estrogen and androgen levels in plasma (Forman, 2007), decrease immune function (Kelley et al., 1992) and could increase the risk of overweight and obesity, a risk factor for several different cancer sites (World Cancer Research Fund/American Insitute 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 Insitute for Cancer Research, 2007).

Other possible mechanisms include heterocyclic amines (HCA) and polycyclic aromatic hydrocarbons (PAH) formed 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 the formation of DNA adducts and have been shown to induce several cancers in animals (Ohgaki et al., 1984).

Processed meats contain nitrite and nitrate which may be converted to carcinogenic nitrosamines (Lijinsky, 1987). Some processed meats contain added salt which is a suspected risk factor for stomach cancer (World Cancer Research Fund/American Insitute for Cancer Research, 2007). Higher heme-iron intake may increase the risk of gastrointestinal cancers due to genotoxic effects on colonic cells (Glei et al., 2006) and by increasing the endogenous formation of N-nitroso compounds (Cross et al., 2003; Lunn et al., 2007). Some cohort studies found increased risk of colorectal cancer with intake of heme-iron (Larsson et al., 2005; Balder et al., 2006).

Our study has several potential limitations; as with any case-control study we cannot rule out the possibility of recall or selection biases. If the controls either consume

or report their meat consumption differently than the general population biased results would occur. However, the mean red meat intake among the controls in this study (145.5 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, but also including Argentina and Paraguay (reference no. 67 in (Norat et al., 2002)). Participation rates were very high, thus minimizing the potential for selective participation according to lifestyle practices. Selection of hospital controls is another potential source of bias, however the diseases of the controls selected in this study were unrelated to dietary factors and the controls were without recent changes in their diet. Recall bias is a potential problem in case-control studies because of the retrospective assessment of diet. Nevertheless, the participants in this study were generally of low socioeconomic status, with little knowledge about the role of diet and meat intake in affecting cancer risk and this is likely to apply even more for the less common cancers.

Meat intake is not considered an unhealthy dietary habit in this population and this should have reduced the possibility for recall bias, but we cannot exclude the possibility that it may have been present. Further, we cannot exclude the possibility of residual confounding by unknown or unmeasured factors. We were not able to adjust for physical activity which is an important risk factor for several cancer sites, however, other studies found that the association between meat intake and cancer risk remained significant even after adjustment for physical activity, suggesting that confounding from physical activity does not fully explain the findings (Dai et al., 2002; Cross et al., 2007; Taylor et al., 2007; Bessaoud et al., 2008; Hu et al., 2008). Also, we found that adjustment for other food groups strengthened rather than weakened the association between meat intake and cancer risk. Nevertheless, other unmeasured variables could still confound some of our findings. 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 rather strong ORs found in our study probably reflect the very high meat intake in this population, compared with other populations. 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/d for men and 86 and 12 g/d for women in the highest and lowest quintiles, respectively (Cross et al., 2007). In contrast, in this study the mean red meat intake in the highest and lowest category of intake among controls was 300 and 86 g/d, respectively, a 2-3 fold higher intake than in the European and American studies. In the present study we confirm our previous findings an elevated risk of several cancers with a high meat intake (Aune et al., 2009), but in a study with more comprehensive dietary assessment and adjustment for dietary confounders than previously.

In conclusion, our findings provide further evidence that high meat intake increases cancer risk and suggest that multiple cancer sites may be linked to high meat intake. Reducing meat intake may be an important modifiable risk factor for several types of cancer.

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