Cancer Research and Oncology: Open Access
Received: Mar 01, 2016, Accepted: May 12, 2016, Published: May 17, 2016
Cancer Res Oncol, Volume 2, Issue 3
http://crescopublications.org/pdf/crooa/CROOA-2-015.pdf
Article Number: CROOA-2-015

Research Article Open Access

Meat Consumption and Risk of Colorectal Cancer: A Case-Control Study in Uruguay Emphasizing the Role of Gender

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Citation: Eduardo De Stefani, Paolo Boffetta, Alvaro L Ronco, Hugo Deneo-Pellegrini, María Mendilaharsu and Cecilia Silva (2016) Meat Consumption and Risk of Colorectal Cancer: A Case-Control Study in Uruguay Emphasizing the Role of Gender. Cancer Res Oncol 2: 015.

Abstract:

Background: To determine the role of meat consumption in the etiology of colorectal cancer, we conducted a case-control study among Uruguayan population in the time period 1996-2005.

Methods: The study included 361 cases and 1.907 controls, frequency matched on age, sex, and residence. Both series were drawn from the four major public hospitals in Montevideo, Uruguay. Unconditional multiple logistic regression was used to estimate odds ratios (ORs) and 95 % confidence intervals (95 % CIs) by quartiles of red meat, processed meat, poultry, and fish intakes.

Results: The highest vs. the lowest quartile of processed meat (OR = 3.31, 95 % CI 2.29-4.78), red meat (OR = 1.65, 95 % CI 1.15-2.38), and poultry (OR = 1.63, 95 % CI 1.16-2.29) was associated with increased risk of colorectal cancer, while intake of fish was inversely associated with risk of this malignancy (OR = 0.67, 95 % CI 0.47-0.95). Moreover, red meat, poultry and fish displayed significant interactions by sex.

Conclusions: This study suggests that red meat, processed meat, and poultry may play a role in the etiology of colorectal adenocarcinoma.

Keywords: Total meat; Red meat; Processed meat; Poultry; Fish.

Abbreviations: ORs: Odds Ratios; CIs: Confidence Intervals; FFQ: Food-Frequency Questionnaire.

Introduction

Colorectal cancer is the third maligncy in frequency among Uruguayan men and the second one among Uruguayan women, with age-standardized rates of 34.1 and 25.2 per 100,000 persons respectively [1]. According to the more recent monograph by the World Cancer Research Fund/American Institute for Cancer Research, red meat, processed meat, alcohol drinking and body fatness are convincing factors for the etiology of these cancers [2].

The recent monograph by the International Agency for Research on Cancer examined thoroughly epidemiologic studies on red and processed meat consumption and classified processed meat as group 1 (carcinogenic to humans), whereas red meat was classified as group 2A (probably carcinogenic to humans) [3]. Nevertheless, the summarized data from the quoted monograph still did not communicate differences in processed and red meat by sex or age group in patients afflicted by colorectal cancer. Moreover, ORs for types of processed meat were not specified [3].

Therefore, we decided to conduct a case-control study on colorectal adenocarcinoma and meat consumption, emphasizing the risks by sex, age, and types of processed meat, in a high risk country, like Uruguay.

Material and Methods

Selection of Cases

In the time period 1996-2005, all the patients with newly diagnosed and microscopically confirmed colorectal cancers were considered eligible for the study. In total 371 patients were eligible and 10 refused the interview, leaving a final number of 361 cases (response rate 97.3 %). There were 214 (59.3 %) men and 147 (40.7 %) women, aged 30 to 89 years. One-hundred and seventy six (176, 48.8 %) patients presented tumors localized in the colon and 185 (51.2 %) cases showed malignancies localized in the rectum. All the cases were drawn from the four major public health hospitals of Montevideo.

Selection of Controls

In the same time period and the same public health hospitals, patients with non-neoplastic diseases not related with tobacco smoking, alcohol drinking and without recent changes in their diets were considered as eligible for the study. We identified 1.966 patients and 59 of them refused the interview, leaving a final total of 1.907 controls (response rate 97.0 %). The patients presented the following conditions: eye disorders (521 patients, 27.3 %), abdominal hernia (413, 21.7 %), fractures (196, 10.3 %), varicose veins (140, 7.3 %), acute appendicitis (119, 6.2), injuries (117, 6.1 %), diseases of the skin (110, 5.8 %), hydatid cyst (84, 4.4 %), urinary stones (81, 4.3 %), blood disorders (64, 3.4 %), diseases of the bone (35, 1.8 %), and prostate hypertrophy (27, 1.4 %).

Interviews and Questionnaire

Both cases and controls were administered with a structured questionnaire by two trained social workers. All the interviews were conducted in the hospitals shortly after admittance. The questionnaire included the following sections: socio-demographics (age, sex, residence, education, monthly income, identification number), a complete history of occupation including the last four jobs and their duration, family history of colorectal cancer in the first-degree relatives (mother, father, sisters, brothers), self-reported height and weight 5 years before the date of the interview, a complete history of smoking (age of start, age of quit, number of cigarettes smoked per day, type of cigarette, type of tobacco, inhalation practices), a complete history of alcohol consumption (age of start, age of quit, number of glasses drunk per day, type of alcoholic beverage), a complete history of non-alcoholic beverages (*mate*, coffee, tea), menstrual and reproductive events, and a food frequency questionnaire (FFQ), which queried the usual intake of 64 foods items 5 years prior to diagnosis. This FFQ allowed the calculation of total energy intake and represented the usual diet of the Uruguayan population. Although the FFQ was not validated, it was tested for reproducibility. The correlation coefficients between the two diet assessments were 0.67 for total meat, 0.77 for red meat, 0.55 for processed meat, 0.60 for poultry, and 0.62 for fish [4].

Definition of Foods

We calculated the following items: (1) total meat (red meat, processed meat, poultry, and fish), (2) red meat (beef, lamb), (3) processed meat (bacon, sausage, *mortadella*, salami, *saucisson*, hot dog, and salted meat), (4) total white meat (poultry, fish), (5) poultry, and (6) fish. All the types of meat were log-transformed and energy-adjusted by the residuals method of Willett and Stampfer [5, 6]. Meat intake was categorized in quartiles according to the distribution of cases and controls.

Statistical Analysis

Relative risks, approximated by the odds ratios, were estimated by multiple unconditional logistical regressions [7]. Odds ratios of meat intake was estimated fitting the following model: age (continuous), sex (ordinal), residence (ordinal), education (categorical, 3 strata), monthly income (categorical, 3 strata), body mass index (categorical, 4 strata), smoking status (categorical, 3 strata), alcohol drinking (categorical, 4 strata), total energy intake (continuous), and total vegetables and fruits (continuous). Odds ratios for each type of control were fitted by multinomial (polynomial) regression taking as base category the more numerous conditions [8]. Heterogeneity was estimated by the likelihood ratio test, and *p*-value for trend was calculated as entering categorical variables as continuous in the model. Goodness of fit of each model was calculated by the Hosmer-Lemeshow statistic [9]. A two-tailed *p*-value of < 0.05 was considered to be statistical significant. All statistical analyses were carried out using Stata version 13.1 [10]. The study was approved by the Directors of the four hospitals involved in the Project.

Results

The distribution of cases and controls by sociodemographic variables and selected risk factors is shown in Table 1. Age, sex, residence, and education were rather similar among both groups of participants. Also smoking status and body mass index were similarly distributed. On the other hand, alcohol drinking was higher among cases compared with controls (*p*-value = 0.03).

Table 1: Distribution of cases and controls by socio-demographic variables and selected risk factors.

		Cases		Controls		
Variable	**Category**	**N°**	**%**	**N°**	**%**	**Global *p*-value**
Age (years)	30-39	6	1.7	34	1.9	0.94
	40-49	35	9.7	181	9.5	
	50-59	62	17.2	341	17.9	
	60-69	109	30.2	614	32.2	
	70-79	123	34.1	610	32.0	
	80-89	26	7.2	124	6.5	
Sex	Men	214	59.3	1136	59.6	0.92
	Women	147	40.7	771	40.4	
Residence	Montevideo	184	51.0	993	52.1	0.70
	Other counties	197	49.0	914	47.9	
Education (yrs)	0-4	195	54.0	1014	53.2	0.89
	5-6	122	33.8	643	33.7	
	7+	44	12.2	250	13.1	
Income	<143	149	41.3	717	37.6	0.72

(US dollars)				
	144+	150 41.5	755 39.6	
	Missing	62 17.2	435 22.8	
Body mass index (kg/m2)	<23.1	92 25.5	459 24.1	0.65
	23.2-25.4	90 27.4	491 25.7	
	25.5-28.1	87 24.1	462 24.2	
	28.2+	83 23.0	495 26.0	
Smoking status	Never smokers	149 41.3	834 43.7	0.62
	Former smokers	98 27.1	514 27.0	
	Current smokers	114 31.6	559 29.3	
Alcohol drinking	Never drinkers	194 53.7	988 51.8	0.03
(ml/ethanol)	1-60	74 20.5	481 25.2	
	61-120	44 12.2	260 13.7	
	121+	49 13.6	178 9.3	
N° patients		361 100.0	1907 100.0	

Odds ratios of colorectal cancer for types of meat are shown in Table 2. Colorectal cancer was positively associated with processed meat (OR 3.31, 95 % CI 2.29-4.78, *p*-value for trend <0.0001), red meat (OR 1.65, 95 % CI 1.15-2.38, *p*-value = 0.02), and poultry intakes (OR 1.63, 95 % CI 1.16-2.29, *p*-value = 0.05). On the other hand, fish intake was inversely associated with colorectal cancer risk (OR 0.67, 95 % CI 0.47-0.95, *p*-value = 0.04).

Table 2: Odds ratios of colorectal cancer for meat consumption [a].

Type of meat	**Grams/day**	**Cases/Controls**	**OR**	**95 % CI**
Total meat	<127.9	45/522	1.0	reference
	128.0-178.0	93/474	2.42	1.65-3.56
	178.1-233.2	106/451	2.68	1.83-3.91
	233.3+	117/450	2.92	1.99-4.27
		p-value for trend	<0.0001	
Red meat	<85.5	59/508	1.0	reference
	85.6-150.0	107/460	1.85	1.30-2.63

	150.1-170.0	99/468	1.77 1.24-2.52
	170.1+	96/471	1.65 1.15-2.38
		p-value for trend	0.02
Processed meat	<7.1	47/520	1.0 reference
	7.2-17.8	94/473	2.20 1.50-3.22
	17.9-35.5	88/479	2.07 1.41-3.05
	35.6+	132/435	3.31 2.29-4.78
		p-value for trend	<0.0001
Total white meat	<7.9	81/486	1.0 reference
	8.0-16.9	97/470	1.28 0.92-1.78
	17.0-28.1	91/476	1.21 0.86-1.71
	28.2+	92/475	1.27 0.90-1.79
		p-value for trend	0.24
Poultry	<3.9	74/493	1.0 reference
	4.0-11.2	113/454	1.58 1.17-2.21
	11.3-16.9	67/500	1.03 0.71-1.47
	17.0+	107/460	1.63 1.16-2.29
		p-value for trend	0.05
Fish	0	104/463	1.0 reference
	0.1-5.5	98/469	0.98 0.71-1.34
	5.6-12.0	97/470	0.95 0.69-1.30
	12.1+	62/505	0.67 0.47-0.95
		p-value for trend	0.04

[a] Multivariate ORs adjusted for age, sex, residence, education, monthly income, body mass index, smoking status, alcohol drinking, total energy, and total fruit and vegetables intake.

Odds ratios of colorectal cancer for types of meat, stratified by gender, are shown in Table 3. Among men, total meat (OR 3.92, 95 % CI 2.31-6.65, *p*-value for trend <0.0001), red meat (OR 2.30, 95 % CI 1.38-3.84, *p*-value = 0.002), processed meat (OR 2.31, 95 % CI 1.42-3.96, *p*-value = 0.002), and poultry (OR 2.08, 95 % CI 1.32-3.28, *p*-value = 0.006) were positively associated with colorectal cancer. On the other hand, women displayed high risks for total meat (OR 2.13, 95 % CI 1.17-3.86, *p*-value = 0.008), and processed meat intakes (OR 5.44, 95 % CI 3.03-9.76, *p*-value < 0.0001). Fish consumption displayed an inverse association for colorectal cancer among women (OR 0.40, 95 % CI 0.23-0.68, *p*-value = 0.0004). There was a significant heterogeneity by sex for red meat intake (p = 0.01), poultry (p = 0.01), and fish consumption (p = 0.003).

Table 3: Odds ratios of colorectal cancer stratified by sex.

Sex					
	Men		**Women**		
Type of meat	**OR**	**95 % CI**	**OR**	**95 % CI**	***p*-value heterogeneity**
Total meat	1.0	reference	1.0	reference	
	2.89	1.65-5.07	2.10	1.22-3.62	
	3.09	1.79-5.33	2.43	1.41-4.19	
	3.92	2.31-6.65	2.13	1.17-3.86	
	<0.0001		0.008		0.31
Red meat	1.0	reference	1.0	reference	
	1.88	1.11-3.19	2.02	1.24-3.82	
	2.54	1.52-4.25	1.23	0.73-2.08	
	2.30	1.38-3.84	1.17	0.65-2.11	
	0.002		0.92		0.01
Processed meat	1.0	reference	1.0	reference	
	1.74	1.05-2.88	3.06	1.69-5.53	
	1.67	1.01-2.77	2.82	1.52-5.23	
	2.31	1.42-3.76	5.44	3.03-9.76	
	0.002		<0.0001		0.37
Total white meat	1.0	reference	1.0	reference	
	1.80	1.18-2.74	0.68	0.39-1.18	
	2.23	1.44-3.45	0.48	0.27-0.83	
	1.47	0.91-2.36	0.86	0.51-1.46	
	0.04		0.56		0.0003
Poultry	1.0	reference	1.0	reference	
	2.08	1.36-3.19	0.90	0.52-1.55	
	1.74	1.08-2.80	0.43	0.24-0.78	
	2.08	1.32-3.28	0.97	0.57-1.64	
	0.006		0.60		0.01
Fish	1.0	reference	1.0	reference	
	1.30	0.86-1.96	0.68	0.40-1.16	
	1.52	0.99-2.34	0.54	0.34-0.88	

	1.04	0.64-1.68	0.40	0.23-0.68	
	0.56		0.0004		0.003

[a] Multivariate ORs adjusted for age, residence, education, monthly income, body mass index, smoking status, alcohol drinking, total energy, and total fruit and vegetables intake.

Odds ratios of colorectal cancer for types of processed meat are shown in Table 4. Bacon (OR 0.73, 95 % CI 0.58-0.93), sausage (OR 1.00, 95 % CI 0.85-1.18), salami (OR 1.12, 95 % CI 0.98-1.27), *saucisson* (OR 0.90, 95 % CI 0.74-1.10), and ham (OR 1.01, 95 % CI 0.88-1.17) were not associated with colorectal cancer among men. On the contrary, *mortadella* (OR 1.13, 95 % CI 1.01-1.28), hot dog (OR 1.33, 95 % CI 1.16-1.53), and salted meat (OR 1.31, 95 % CI 1.07-1.37) were positively associated with risk of colorectal carcinoma in males. On the other hand, women showed positive associations of hot dog (OR 1.46, 95 % CI 1.26-1.69), ham (OR 1.44, 95 % CI 1.25-1.66), and salted meat (OR 1.40, 95 % CI 1.18-1.66) with colorectal adenocarcinoma. Furthermore, ham consumption showed a significant heterogeneity by gender.

Table 4: Odds ratios of types of processed meat by gender [a].

Sex					
	Men		**Women**		
Types of processed meat	**OR**	**95 % CI**	**OR**	**95 % CI**	**Heterogeneity**
Bacon	0.73	0.58-0.93	0.74	0.54-1.02	0.88
Sausage	1.00	0.85-1.18	1.12	0.93-1.36	0.43
Mortadella	1.13	1.01-1.28	1.12	0.95-1.32	0.41
Salami	1.12	0.98-1.27	1.03	0.86-1.24	0.09
Saucisson	0.90	0.74-1.10	0.98	0.71-1.35	0.92
Hot dog	1.33	1.16-1.53	1.46	1.26-1.69	0.79
Ham	1.01	0.88-1.17	1.44	1.25-1.66	0.002
Salted meat	1.21	1.07-1.37	1.40	1.18-1.66	0.07

[a] Multivariate ORs adjusted for age, residence, education, monthly income, body mass index, smoking status, alcohol drinking, total energy, and total fruit and vegetables intake.

Odds ratios of colon adenocarcinoma for types of meat, stratified by sex, are shown in Table 5. Fish consumption showed an inverse association with colon carcinoma (OR 0.32, 95 % CI 0.16-0.65) among women and the interaction fish*sex was significant. The other meat types did not displayed significant heterogeneity.

Table 5: Odds Ratios of Colon Adenocarcinoma by Gender [a].

Colon adenocarcinoma					
Sex					
	Men		Women		
Type of meat	**OR**	**95 % CI**	**OR**	**95 % CI**	***p*-value heterogeneity**
Total meat	1.0	reference	1.0	reference	
	4.11	1.69-9.97	1.98	1.01-3.88	
	4.28	1.80-10.2	2.08	1.05-4.12	
	4.21	1.77-9.99	2.55	1.25-5.20	
	0.003		0.01		0.61
Red meat	1.0	reference	1.0	reference	
	2.02	0.92-4.41	2.17	1.20-3.93	
	2.66	1.24-5.72	1.18	0.62-2.28	
	2.21	1.02-4.77	1.17	0.56-2.43	
	0.051		0.99		0.08
Processed meat	1.0	reference	1.0	reference	
	1.67	0.80-3.57	3.34	1.53-7.30	
	1.26	0.59-2.70	3.70	1.68-8.17	
	2.09	1.03-4.25	6.52	3.04-13.9	
	0.08		<0.0001		0.43
Total white meat	1.0	reference	1.0	reference	
	2.04	1.10-3.80	0.78	0.39-1.55	
	2.45	1.29-4.65	0.61	0.31-1.20	
	1.11	0.52-2.37	0.89	0.46-1.73	
	0.41		0.71		0.01
Poultry	1.0	reference	1.0	reference	
	2.28	1.21-4.28	1.04	0.51-2.11	
	1.96	0.99-3.89	0.62	0.29-1.30	
	1.62	0.80-3.27	1.31	0.67-2.57	
	0.24		0.52		0.08
Fish	1.0	reference	1.0	reference	
	1.16	0.62-2.17	0.80	0.43-1.49	

	1.76	0.95-3.26	0.55	0.30-0.98	
	0.96	0.46-1.98	0.32	0.16-0.65	
	0.61		0.001		0.01

[a] Multivariate ORs adjusted for age, residence, education, monthly income, body mass index, smoking status, alcohol drinking, total energy, and total fruit and vegetables intake.

Odds ratios of rectal cancer for meat intake, stratified by sex, are shown in Table 6. Only poultry showed a significant interaction with sex, showing higher risks among men (OR 2.40) compared with women (OR 0.61).

Table 6: Odds Ratios of Rectal Adenocarcinoma by Gender [a].

Rectal adenocarcinoma					
Sex					
	Men		**Women**		
Type of meat	**OR**	**95 % CI**	**OR**	**95 % CI**	***p*-value heterogeneity**
Total meat	1.0	reference	1.0	reference	
	2.35	1.16-4.76	2.38	1.03-5.51	
	2.61	1.23-5.14	3.02	1.32-6.89	
	3.87	2.04-7.35	1.51	0.57-4.03	
	<0.0001		0.20		0.08
Red meat	1.0	reference	1.0	reference	
	1.84	0.94-3.63	1.87	0.89-3.91	
	2.55	1.31-4.93	1.26	0.57-2.80	
	2.48	1.30-4.76	1.19	0.49-2.89	
	0.005		0.88		0.22
Processed meat	1.0	reference	1.0	reference	
	1.80	0.94-3.45	2.95	1.25-6.95	
	2.07	1.09-3.93	1.91	0.73-4.98	
	2.49	1.34-4.66	4.71	2.04-10.9	
	0.005		0.001		0.33
Total white meat	1.0	reference	1.0	reference	
	1.62	0.95-2.78	0.61	0.27-1.38	
	2.09	1.20-3.63	0.33	0.14-0.78	

	1.68	0.94-2.99	0.84	0.39-1.79	
	0.04		0.60		0.01
Poultry	1.0	reference	1.0	reference	
	1.94	1.13-3.33	0.78	0.36-1.66	
	1.58	0.85-2.94	0.25	0.10-0.64	
	2.40	1.38-4.18	0.61	0.28-1.33	
	0.006		0.08		0.02
Fish	1.0	reference	1.0	reference	
	1.42	0.85-2.35	0.51	0.21-1.22	
	1.32	0.76-2.29	0.56	0.28-1.14	
	1.10	0.61-2.01	0.52	0.24-1.11	
	0.72		0.09		0.08

[a] Multivariate ORs adjusted for age, residence, education, monthly income, body mass index, smoking status, alcohol drinking, total energy, and total fruit and vegetables intake.

Discussion

Our study found elevated risks of colorectal cancer among high consumers of total meat, red meat and processed meat. We also found an elevated risk of colorectal carcinoma for poultry intake among men.

Previous ecological studies have reported positive associations between dietary practices and colorectal cancer risk [11-13]. Although case-control studies reported increased risks for red and processed meat [14-22], most of the positive evidence comes from prospective studies [23-36]. Thus, red meat and processed meat may increase the risk of colorectal adenocarcinoma. The mechanisms involved in processed meat effect have been studied in detail in the study of Santarelli et al. [37]. Among others, high-fat diets, the formation of heterocyclic amines, the formation of *N*-nitroso compounds, and the effect of heme iron have been implicated in colorectal carcinogenesis [37, 38].

Red meat is rich in vitamin B6, vitamin B12, and calcium [39]. These nutrients could display a protective role against the effect of red meat and processed meat in colorectal carcinogenesis [39].

Concerning red meat, our study showed elevated risks among men, but not among women. Also, poultry and fish were associated with higher risks among men compared with women. These differences by sex resulted in a significant heterogeneity for these types of meat. According with Alexander and Cushing [40], several prospective studies showed sex differences for red meat intake. More precisely, red meat was possitively associated with men participants, whereas women displayed null or inverse associations for this type of meat.

Our study also showed higher risks among elderly subjects compared with young ones. Nevertheless, this difference was non significant. Therefore, age did not appear to be a major covariant in colorectal cancer.

The present study has both limitations and strengths. One limitation is the possibility of recall bias given the retrospective nature of exposure assessment. The participants in this study were mostly of low socioeconomic status, with little knowledge about the role diet plays in colorectal cancer risk. Also, a high meat intake is not considered an unhealthy dietary habit in the Uruguayan population and this should also have limited any possibility of recall bias. Another limitation of our study is the possibility of selection bias. Although difficult to exclude, we tried to prevent it by frequency-matching cases and controls on age and residence. Selection of hospital controls is another potential source of bias in case-control studies.

However, when we repeated the analyses excluding each one of the types of controls, the results were similar. Measurement error in the assessment of diet by use of an inadequate FFQ is another possible limitation of our study. Among the strengths is the complete microscopic report of all cases, which was performed by pathologists with particular expertise in colorectal adenocarcinoma, and the very high response rate, both for cases and controls.

In summary, we performed a case-control study on meat consumption and colorectal adenocarcinoma. It is important to emphasize the role of gender, since red meat, poultry, and fish were markedly different among men and women.

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