Tobacco smoking patterns and differential food effects on prostate and breast cancers among smokers and nonsmokers in Córdoba, Argentina

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The aim of this study was to estimate the effect of diet on prostate and breast cancer (PC and BC) risks in smokers and nonsmokers and to explore the effect modification between smoking and dietary patterns. PC or BC incidence rates were assessed spatially according to tobacco exposure, age-adjusted standardization using lung cancer mortality as a proxy. Two case–control studies were carried out in Argentina (2008–2012). Participants were interviewed about their diet, smoking habits, and other lifestyle factors. Multilevel models were fitted including family history of cancer as the random intercept for the second level, and diet and lifestyle variables as covariates. Tobacco exposure was aggregated spatially. Family history of cancer significantly accounts for PC and BC. In smokers, high intake of fat meat increased PC and BC risks [odds ratio (OR) 1.56, 95% confidence interval (CI) 0.81–3.05 and OR 6.01, 95% CI 1.99–8.19, respectively]. PC and BC risks were also greater in smokers with high intakes of fatty foods (OR 1.95, 95% CI 1.09–3.50 and OR 24.2, 95% CI 0.82–7.21, respectively). Moderate intake of nonstarchy vegetables and risk of PC were inversely associated in nonsmokers (OR 0.55, 95% CI 0.20–1.48). In smoker women, BC risk was associated with sweet drink consumption (OR 2.96, 95% CI 1.10–7.92) and ethanol intake (OR 5.15, 95% CI 1.88–14.16). Spatial distributions of cancer incidence rates match those of tobacco exposure. Differential effects of diet on PC and BC risks were found in smokers and nonsmokers. *European Journal of Cancer Prevention* 23:310–318 © 2014 Wolters Kluwer Health | Lippincott Williams & Wilkins.

European Journal of Cancer Prevention 2014, **23**:310–318

Keywords: breast cancer, Córdoba, Argentina, diet, GLLAMM, prostate cancer, tobacco smoking

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Received 28 June 2013 **Accepted** 25 September 2013

Introduction

Carcinogenesis is related to biological, environmental, and lifestyle factors. Among these, dietary habits and tobacco smoking have been shown to modify some cancer risks (World Cancer Research Fund/American Institute for Cancer Research, 2007). In Argentina, breast and prostate cancers (BC and PC) are the most frequent cancers, with age-adjusted standardized incidence rates (ASIRs) of 74.0 and 58.8, respectively (Ferlay *et al.*, 2012). Córdoba is the second most populated province in Argentina. In this province, ASIRs among women are led by BC (ASIR 75.45), followed by cervix and digestive tract cancers, whereas in men, PC is the second incident cancer (ASIR 35.04), only preceded by lung cancer (Diaz *et al.*, 2009, 2010).

Tobacco smoking is a widespread source of exposure to known carcinogens and is associated with several types of cancer (IARC, 2004). Some of the chemical compounds in tobacco have been evaluated by IARC as showing 'sufficient evidence for carcinogenicity' in humans or in animal models (IARC, 2004). Among the chemicals in tobacco smoke, polycyclic aromatic hydrocarbons, and nicotine-derived nitrosamines have been identified as the most abundant genotoxic components (Hecht, 2006).

However, there is no convincing epidemiological evidence for an increased risk of PC and BC because of cigarette smoking. Although prospective epidemiological data support an association between habitual smoking and different subtypes of PC (Hickey *et al.*, 2001; Gong *et al.*, 2008) and BC (Iwasaki and Tsugane, 2011; Johnson *et al.*, 2011), many observational studies have failed to show such an association (Terry and Rohan, 2002; Butler *et al.*, 2009; Waters *et al.*, 2009). This is possibly because of the wide exposure of the population; nevertheless, tobacco smoke may act by modifying the effect of a second exposure agent, diet, on the risk of cancer (Dietrich *et al.*, 2003; Tomita *et al.*, 2011).

Epidemiological studies have explored dietary habits in relation to cancer, and suggest that intake of certain foods, their cooking methods, and nutrient content are related to risks of PC and BC (World Cancer Research Fund/American Institute for Cancer Research, 2007). PC was associated with high intake of dairy products and fats,

0959-8278 © 2014 Wolters Kluwer Health | Lippincott Williams & Wilkins DOI: 10.1097/CEJ.0000000000000044

as well as dietary patterns characterized by high intakes of red and processed meat, processed foods, and lower vegetable consumption. In contrast, patterns that reduce the risk of PC include higher intakes of fish, cereals, pulses, and vegetables (Niclis *et al.*, 2012). Saturated fat and red meat intake have also been indicated as possible risk factors for BC, whereas healthy dietary patterns with abstention from alcohol, high intake of fiber and vegetables, and weight control were inversely linked to BC (Cappellani *et al.*, 2012). However, it is not known whether the effect of diet on PC and BC risk is modified by tobacco smoking. The main purpose of the present work was to estimate the dietary effects on risks of PC and BC in smokers and in nonsmokers and to determine the effect modification between smoking and dietary patterns.

Materials and methods

Data source

Córdoba province is located in the center of Argentina. Politically, it is divided into 26 counties, and according to the last census, it has 3 067 000 inhabitants [National Institute of Statistics and Censuses (INDEC), 2007].

Cancer incidence data from the year 2007 were compiled from the Córdoba Cancer Registry database, which includes information on age, sex, residence, and histopathologically confirmed diagnoses, classified according to the 10th International Classification of Diseases (ICD-10). Cancer mortality data from the year 2006 were obtained from the Córdoba Ministry of Health. Census data of the resident population of Córdoba province were obtained from the National Institute of Statistics and Census [National Institute of Statistics and Censuses (INDEC), 2007].

Case–control study

Data were obtained from two ongoing case–control studies being carried out in Córdoba. BC and PC case–control studies (BCCCS and PCCCS) began in 2008. Detailed descriptions of the design of these studies can be found in the study of Pou *et al.* (2012).

Cases were patients with incident, histologically confirmed BC (CIE-10 C50) or PC (CIE-10 C61), with no previous diagnosis of cancer, identified by the Córdoba Cancer Registry. Controls were of identical sex, age (± 5 years), and place of residence and were interviewed in the same time period as the cases. Participants were included as controls only after precise verification of the absence of any neoplasic or related condition. A total of 100 women with BC and 293 controls, and 135 men with PC and 282 controls were included. Before inclusion in the study, all participants signed an informed consent according to established bioethical norms. Both studies were approved by the Committee of Ethics in Health Research of the province of Córdoba.

Cases and controls were interviewed by nutritionists who were centrally trained and routinely supervised. The questionnaire, as used in several local epidemiological studies (Navarro *et al.*, 2003; Pou *et al.*, 2012; Román *et al.*, 2013), had sections asking about sociodemographic characteristics, anthropometric variables, lifestyle factors, personal medical history, and family history of cancer. Social status was defined on the bases of educational level and occupation of the head of the household. Occupational exposure to carcinogens (pesticides, paints, textiles, rubber, leather, automotive, carbon) was also considered. Information on tobacco smoking included smoking status (never smoker, former, or current smoker), type and average number of cigarettes smoked per day, and duration of smoking in years. To assess dietary exposure, a validated food frequency questionnaire was used (Navarro *et al.*, 2001). Food items were grouped to assess their potential role in PC and BC risk as dairy foods, lean meat, fat meat, nonstarchy vegetables, fruits, fats and oils, sweet drinks, and ethanol. Each food group was categorized as dichotomous variables with cutpoints based on the median value of controls' intake.

Spatial and statistical analysis

ASIRs (world standard population) were estimated per 10^{-5} inhabitant-years for BC and PC for each of the 26 counties. Because direct information on smoking history by area was not available, lung cancer age-adjusted standardized mortality rates (ASMRs) were used as a proxy for tobacco smoking as suggested by Pou *et al.* (2011) and others (Ezzati and Lopez, 2004; Best and Hansell, 2009).

As the ASIRs were obtained related to the geographical locations, these series constitute spatial data. Thereafter, two statistical modeling approaches were used. First, a geographically weighted regression (GWR) model (Brunsdon *et al.*, 1996) was adjusted using PC and BC ASIRs as outcome, and male and female lung cancer ASMR and population density as covariates. This strategy is a method for exploring spatial nonstationarity of a regression relationship for spatial data by locally fitting a spatially varying coefficient regression model. Poisson distribution was chosen for the response using log as a link function. The latitude and longitude of the capital cities of counties were included to calculate the optimal bandwidth used in the estimation procedure. Second, a two-multilevel Poisson model (MPM-RI) (Rabe-Hesketh and Skrondal, 2008) was used assuming county classification as a random intercept and ASIRs for PC or BC as the response. This model was extended to a two-level model, also assuming a random coefficient for lung cancer ASMR (MPM-RIC). Because these are Poisson mixed models, estimated incidence rate ratios were obtained, taking into account county variability and slope in each county cluster.

After fitting both models, Moran's Index coefficients were computed for regression residuals to assess the remaining autocorrelation. Moran's Index was also obtained for each variable in the model. Under the null hypothesis of no spatial autocorrelation, Moran's Index has an expected value near zero. Moran's Index autocorrelation was computed and compared for residuals from each regression model.

To estimate the risk of PC and BC related to diet and tobacco exposure, odds ratios (ORs) and the corresponding 95% confidence intervals (CIs) were computed applying multilevel random intercept binomial models. Family history of cancer was included as a random intercept variable in the second level. A binomial random component, link function logit, and bio-socio-cultural variables and tobacco smoke variables in the linear predictor were first specified (Rabe-Hesketh and Skrondal, 2008). The model was then applied in smokers and nonsmokers separately, with age, BMI, total energy intake (as continuous variables), and food group intake (as categorical variables) in the linear predictor.

All analyses were carried out using Stata software, version 12.1 (StataCorp, 2011).

Results

Study population distribution of both PCCCS and BCCCS by selected demographic and lifestyle characteristics is summarized in Table 1. Family history of BC or PC was related to an increased risk of BC and PC, respectively. An elevated proportion of individuals of PCCCS reported being current or former smokers and maintained the habit over 15 years. The proportion of smoker women in BCCCS was lower.

Some differences in food consumption were observed between cases and controls from BCCCS. Women with BC had greater mean consumption of meats, fat and oils, and calories than controls ($P < 0.05$). Nevertheless, in PCCCS, any food group intake showed significant

Table 1 Distribution of selected demographic and lifestyle characteristics (PCCCS and BCCCS: Córdoba, Argentina)

	PCCCS		BCCCS	
	Cases [*n* (%)]	Controls [*n* (%)]	Cases [*n* (%)]	Controls [*n* (%)]
Total	135	282	100	293
Age				
≤60 years	16 (11.85)	39 (13.83)		
61–70 years	43 (31.85)	99 (35.11)		
71–80 years	58 (42.96)	110 (39.01)		
≥81 years	18 (13.33)	34 (12.06)		
≤50 years[a]			24 (24.0)	85 (29.0)
51–65 years			44 (44.0)	110 (37.5)
≥66 years			32 (32.0)	98 (33.5)
BMI				
≤24.9	33 (24.44)	78 (27.66)	40 (40.0)	145 (49.5)
25–29.9	79 (58.52)	140 (49.65)	38 (38.0)	90 (30.7)
≥30	23 (17.04)	64 (22.70)	22 (22.0)	58 (19.8)
Social status				
High	32 (23.70)	79 (28.01)	36 (36.0)	118 (40.3)
Medium	54 (40.00)	109 (38.65)	39 (39.0)	84 (28.7)
Low	49 (36.30)	94 (33.33)	25 (25.0)	91 (31.1)
Occupational exposure[c]				
No	90 (66.67)	208 (73.75)	90 (90.0)	277 (95.8)[b]
Yes	45 (33.33)	74 (26.25)	10 (10)	12 (4.5)
Calorie intake				
Low	37 (27.41)	94 (33.33)	15 (15.0)	98 (33.5)
Medium	45 (33.33)	94 (33.33)	28 (28.0)	98 (33.5)
High	53 (39.26)	94 (33.33)	57 (57.0)	97 (33.0)
Family history of cancer (prostate[c]/breast[c])				
No	117 (86.67)	269 (95.39)	84 (84.00)	242 (82.59)
Yes	18 (13.33)	13 (4.61)	16 (16.00)	51 (17.41)
Smoking habit				
Never smoker	46 (34.07)	86 (30.50)	64 (64.00)	176 (60.07)
Smoker ≤15 years	24 (17.78)	52 (18.44)	12 (12.00)	52 (17.75)
Smoker >15 years	65 (48.15)	144 (51.06)	24 (24.00)	65 (22.18)
Number of cigarettes				
Never smoker	44 (32.69)	86 (30.50)	64 (64.0)	176 (60.7)
≤10 cigarettes/day	36 (26.67)	83 (29.43)	30 (30.0)	85 (29.01)
11–20 cigarettes/day	36 (26.67)	79 (28.01)	5 (5.0)	24 (8.19)
>20 cigarettes/day	19 (14.07)	34 (12.06)	1 (1.0)	8 (2.70)

BCCCS, breast cancer case–control studies; PCCCS, prostate cancer case–control studies.
[a]In BCCCS, age was categorized into three categories.
[b]Four individuals of BCCCS did not answer this question.
[c]Significant crude odds ratio (OR) ($P < 0.05$). Occupational exposure was significant in BCCCS (OR 2.56, 95% CI 1.07–6.14). Family history of disease was significant in PCCCS (OR 3.18, 95% CI 1.51–6.71) and in BCCCS (OR 3.24, 95% CI 1.81–5.79).

differences between cases and controls. Men had higher meat intake than women, without significant differences between cases and controls. A high proportion of individuals consumed more than 100 g/day of meat (data not shown).

Moran's Indexes of 0.204 ($P<0.001$) and 0.043 ($P=0.024$) in men and women, respectively, indicated spatial autocorrelation for lung cancer mortality rates (Table 2). Total cancer incidence in men and women [Moran's Index $=-0.010$ ($P=0.228$) and -0.015 ($P=0.263$) for men and women, respectively] and PC and BC incidence rates [Moran's Index $=-0.022$ ($P=0.314$) and -0.005 ($P=0.188$) for men and women, respectively] showed no spatial autocorrelation.

GWR or MPM-RI models yielded similar results for PC and BC ASIRs related to population density and tobacco exposure (Table 3). When GWR or MPM-RI was fitted using lung cancer mortality rates, no significant effect was found of tobacco exposure on the incidence of PC. For BC, however, these effects were significant. When Moran's Index was estimated for residuals' distribution from both regression models, the results indicated null autocorrelation (Table 2).

As the random coefficient was not significant in the MPM-RIC model, only results for the MPM-RI model are shown (Table 3). The checking modeling analysis for MPM-RIC shows a better fit for MPM.

There was no statistically significant interaction between any food group and smoking habit either for BCCCS or for PCCCS. However, different effects on the risk of BC and PC were found among smokers and nonsmokers in relation to intake of some foods. From the two-level models, it was shown that having a family history of PC or BC constitutes significant clustering, which explains a non-negligible portion of the sample variability (variance 1.421, SE 0.178 in PC and variance 0.549, SE 0.325 in the BC model). This helps to improve the estimate's precision for food group intakes. In BCCCS, other reproduction-related variables such as nulliparity, breast-feeding practice, and premenopausal or postmenopausal status were not statistically significant and so were not considered in the model.

Table 2 Moran's Index for lung cancer SMR, breast and prostate ASIRs, and residuals of the GWR or MPM models

	Moran's Index	*P*-value
Male lung cancer SMR	0.204	<0.0001
Prostate		
ASIRs	−0.022	0.314
GWR residuals	−0.018	0.281
MPM residuals	−0.028	0.326
Female lung cancer SMR	0.043	0.024
Breast		
ASIRs	−0.005	0.188
GWR residuals	−0.056	0.371
MPM residuals	−0.096	0.083

ASIRs, age-adjusted standardized incidence rates; GWR, geographically weighted regression; MPM, multilevel Poisson model; SMR, standardized mortality ratio.

Table 4 shows that intakes of nonstarchy vegetables over 200 g/day were associated inversely with a risk of PC in nonsmokers (OR 0.55, 95% CI 0.20–1.48), whereas in smokers, there was no association. Smokers with high intakes of fat meat had an increased risk of PC (OR 1.56, 95% CI 0.81–3.05) and BC (OR 6.01, 95% CI 1.99–8.19) (Table 5). Higher intakes of fat and oils showed a positive association in smokers of both PCCCS and BCCCS (OR 1.95, 95% CI 1.09–3.50 and OR 2.42, 95% CI 0.82–7.21). An increased risk of BC has been observed in smoker women whose consumption of sweet drinks exceeded 200 ml/day (OR 2.96, 95% CI 1.10–7.92). A moderate positive association with the risk of BC was found in nonsmoker women who consumed ethanol over 5 g/day (OR 2.13, 95% CI 1.07–4.54). This association was stronger in smoker women (OR 5.15, 95% CI 1.88–14.16).

Discussion

Tobacco exposure and the incidence of BC and PC are not distributed randomly in Córdoba; moreover, the distribution of the former may influence the latter as tobacco showed just a fixed effect. This suggests a possible matched pattern between tobacco exposure and incidence. Risk analysis showed that dietary factors had differential effects among smokers and nonsmokers on PC and BC.

Diaz *et al.* (2009, 2010) have already shown that the pattern of cancer incidence in Córdoba is not random. Its aggregate pattern could possibly match that of tobacco exposure when assessed through lung cancer mortality. Thus, this widespread habit could be masking tobacco's effect on the risk of cancer. However, two kinds of exposures could be derived: one because of habit and environment in smokers and other because of only environmental exposure in nonsmokers. Also, smoking habit could be acting as a baseline variable, modifying the effect of food intake in both subpopulations (smokers and nonsmokers) either in BCCCS or in PCCCS.

Clinical and epidemiological studies have suggested a strong association between chronic inflammation and cancer (Coussens and Werb, 2002; Shacter and Weitzman, 2002; Dobrovolskaia and Kozlov, 2005; Fox and Wang, 2007; Ray, 2007). The oxidant–antioxidant imbalance generated by cigarette smoke can promote inflammation (Foronjy and D'Armiento, 2006). There are several inflammation mediators such as histamine, serotonin, prostaglandins, reactive oxygen species, and cytokines. As proinflammatory cytokines influence the tumor microenvironment, promote cell growth and survival, and angiogenesis, tumor cell proliferation and progression are facilitated (Karin and Greten, 2005; Karin, 2006; Das, 2008; Comba *et al.*, 2010). Cigarette smoke

Table 3 Global risks of total, prostate, and breast cancers by tobacco smoking and population density accounting for territorial location in Córdoba

Sex	Cancer	IRR_1 (SE)	*P*-value	Moran Index[a] (*P*-value)[b]	IRR_2	*P*-value	Moran Index[a] (*P*-value)[b]
Male	Total						
	Lung SMR	1.001136 (0.0003386)	0.001	0.015 (0.090)	1.001240 (0.000667)	0.063	0.030 (0.044)
	Density	1.000093 (0.0000287)	0.001		1.000095 (0.000062)	0.127	
	Prostate						
	Prostate ASIR	1.002146 (0.0005932)	–[c]	–	1.002274 (0.001167)	0.051	0.007 (0.126)
	Density	1.000105 (0.0000285)	–[c]		1.000107 (0.000060)	0.072	
Female	Total						
	Lung SMR	1.000326 (0.0012397)	0.793	−0.040 (0.498)	1.00053 (0.0022995)	0.818	−0.032 (0.421)
	Density	1.000167 (0.0000287)	0.000		1.00017 (0.0000610)	0.005	
	Breast						
	Lung SMR	1.000189 (0.0000587)	0.001	–	1.000189 (0.000110)	0.085	0.058 (0.008)
	Density	1.000171 (0.0000286)	–[c]		1.000174 (0 .00006)	0.002	

ASIRs, age-standardized incidence rates; IRR_1, according to geographical weighted regression model; IRR_2, according to GLLAMM; SMR, standardized mortality ratio.
[a]Moran's Index for model residuals.
[b]$P < 0.05$ refutes the hypothesis of a nonspatial autocorrelation.
[c]Convergence not achieved.

Table 4 Risk for prostate cancer by smoking habits for different food groups considering a family history of prostate cancer as a covariate or as a clustering variable

	Prostate cancer					
	All		Nonsmoker		Smoker	
	Cases (%)	OR (95% CI)	Cases (%)	OR (95% CI)	Cases (%)	OR (95% CI)
Dairy products (g/day)						
< 200	65	1	34	1	46	1
≥ 200	35	1.01 (0.64–1.59)	66	1.24 (0.51–2.99)	54	1.03 (0.60–1.75)
Lean meat (g/day)						
< 120	56	1	68	1	68	1
≥ 120	44	0.76 (0.48–1.19)	32	1.19 (0.51–2.75)	32	0.97 (0.55–1.69)
Fat meat (g/day)						
< 200	59	1	61	1	57	1
≥ 200	41	1.32 (0.77–2.28)	39	1.42 (0.50–3.98)	43	1.56 (0.81–3.05)
Nonstarchy vegetables (g/day)						
< 200	56	1	59	1	68	1
≥ 200	44	0.66 (0.43–1.03)	41	0.55 (0.20–1.48)	32	1.03 (0.58–1.83)
Fruits (g/day)						
< 200	44	1	40	1	42	1
≥ 200	56	1.35 (0.87–2.09)	60	1.18 (0.52–2.71)	58	1.42 (0.83–2.42)
Fat and oils (g/day)						
< 30	56	1	54	1	54	1
≥ 30	44	1.56 (0.96–2.54)	46	1.11 (0.45–2.76)	46	1.95 (1.09–3.50)
Sweet drinks (ml/day)						
< 250	61	1	59	1	61	1
≥ 250	39	1.10 (0.67–1.79)	41	0.97 (0.41–2.31)	39	1.30 (0.72–2.34)
Ethanol (g/day)						
< 20	53	1	57	1	50	1
≥ 20	47	0.71 (0.44–1.15)	43	0.73 (0.29–1.83)	50	0.72 (0.41–1.28)

OR, multilevel analyses include age, BMI, total energy intake, dairy products, lean meat, fatty meat, nonstarchy vegetables, fruits, total fat, sweet drinks, and ethanol as covariates, with family history of prostate cancer as a level 2 variable (clustering variable).
CI, confidence interval; OR, odds ratio.

exposure affects the differentiation of monocytic cells, modifying its morphology and stimulating the expression and secretion of several cytokines (Lerner *et al.*, 2009). Also, these changes may be accompanied by impairment in the inflammatory response of macrophages. Impairment in monocytic differentiation is likely to decrease the contribution of macrophages toward host defense and may predispose cells to malignant transformation (Sica and Bronte, 2007). Interference with monocytic cell differentiation together with an increase in proinflammatory activity may play a role in the carcinogenic effect of smoking exposure. Moreover, oxidants can promote chromatin remodeling, which facilitates the expression of proinflammatory genes (Foronjy and D'Armiento, 2006). It is possible that low-grade chronic inflammation caused by cigarette smoking provides an inflammatory platform that may increase an individual's vulnerability to other risk factors such as diet (Das, 2010).

Table 5 Risk for breast cancer by smoking habits for different food groups considering a family history of breast cancer as a covariate or as a clustering variable

	Breast cancer					
	All		Nonsmoker		Smoker	
	Cases (%)	OR (95% CI)	Cases (%)	OR (95% CI)	Cases (%)	OR (95% CI)
Dairy products (g/day)						
<200	46	1	72	1	66	1
≥200	54	0.88 (1.052–1.47)	28	0.65 (1.01–1.02)	34	1.03 (0.35–2.96)
Lean meat (g/day)						
<120	66	1	61	1	61	1
≥120	34	0.69 (0.41–1.18)	39	0.98 (0.48–2.04)	39	0.62 (0.19–1.44)
Fat meat (g/day)						
<200	75	1	47	1	30	1
≥200	25	1.11 (0.55–2.22)	53	1.18 (0.57–2.43)	70	6.01 (1.99–8.19)
Nonstarchy vegetables (g/day)						
<200	49	1	33	1	19	1
≥200	51	0.88 (0.53–1.45)	67	0.66 (0.31–1.38)	81	0.96 (036–2.55)
Fruits (g/day)						
<200	52	1	76	1	72	1
≥200	48	0.74 (0.44–1.23)	24	0.69 (0.32–1.47)	28	0.90 (3.14–2.58)
Fat and oils (g/day)						
<30	62	1	44	1	28	1
≥30	38	1.26 (0.71–2.26)	56	0.74 (0.36–1.49)	72	2.42 (0.82–7.21)
Sweet drinks (ml/day)						
<200	41	1	55	1	41	1
≥200	59	1.84 (1.15–3.28)	45	1.35 (0.68–2.69)	59	2.96 (1.10–7.92)
Ethanol (g/day)						
<5	61	1	69	1	47	1
≥5	39	2.67 (1.54–4.73)	31	2.13 (1.07–4.54)	53	5.15 (1.88–14.16)

OR, multilevel analyses include age, BMI, total energy intake, dairy products, lean meat, fatty meat, nonstarchy vegetables, fruits, total fat, sweet drinks, and ethanol as covariates, with a family history of breast cancer as a level 2 variable (clustering variable).
CI, confidence interval; OR, odds ratio.

In this study, when food group intake was assessed separated by smokers and nonsmokers, nonstarchy vegetables were observed to be protective against PC in nonsmokers individuals. Nonstarchy vegetables are an important source of such antioxidants as carotenoids, selenium, and vitamins C and E (World Cancer Research Fund/American Institute for Cancer Research, 2007). Antioxidants may suppress signal molecules involved in the survival of cancer cells, thus inhibiting their proliferation (Loo, 2003; Willcox *et al.*, 2004). Antioxidant requirements depend on an individual's exposure to endogenous and exogenous reactive oxygen species. As cigarette smoking results in increased cumulative exposure to these compounds, it seems logical that smokers would have an increased requirement for antioxidant nutrients (Kelly, 2002). Recent studies support the inverse relationship between dietary fiber and the risk of PC and BC, but the mechanisms responsible are still unclear (Park *et al.*, 2009; Taburn *et al.*, 2012). Dietary fiber contains a unique blend of bioactive components with recognized health benefits, including slowly digestible energy, resistant starches, vitamins, minerals, phytochemicals, and antioxidants (Lattimer and Haub, 2010). The effects of phytochemicals, increased nutrient content, and digestive properties are believed to be the mechanisms responsible for the beneficial effects of dietary fibers on the treatment and prevention of obesity and diabetes, thus indirectly helping to reduce the risk of several cancers (Lattimer and Haub, 2010).

Meat and saturated fat intake has been associated positively with the risk of BC (Kolonel, 2001; Alexander *et al.*, 2010; Cappellani *et al.*, 2012). In this study, eating more than 200 g/day of fat meat and consumption of fat and oils above 30 g/day showed higher risk in smokers of BCCCS and PCCCS. According to Neuhouser *et al.* (2007), associations may vary by host factors including family history and smoking (Neuhouser *et al.*, 2007). Overconsumption of dietary fats is associated with excess body weight and adipose storage, indirectly increasing the risk of cancer (World Cancer Research Fund/American Institute for Cancer Research, 2007). Also, higher intake of n-6 fatty acids relative to n-3 fatty acids has been related to increased production of leukotrienes, thromboxanes, and other inflammatory and tumorigenic factors (Thiébaut *et al.*, 2009; Comba *et al.*, 2010).

In this study, high consumption of sweet drinks was associated with the risk of BC. In agreement, it has been suggested that frequent intake of foods with an elevated glycemic index may lead to insulin resistance. This may increase insulin-related growth factors (IGFs) and estrogen secretion, which were associated with the risk of BC (Tavani *et al.*, 2006; Bradshaw *et al.*, 2009).

In relation to ethanol intake, this study shows a strong promoter effect on the risk of BC in smoker and nonsmoker women. Alcohol consumption has been linked to the risk of BC. Several researches support the hypothesis that regular lifetime alcohol intake is a significant risk factor for BC (Wu *et al.*, 2012) and that ethanol acts as a weak cumulative breast carcinogen and may also be a tumor promoter (Brooks and Zakhari, 2013).

As found in this study, it has been suggested that a western lifestyle characterized by a high dietary intake of animal protein, saturated fats, and rapidly digestible carbohydrates, combined with low physical activity, is associated with increased risks of many cancers including BC and PC. At least in part, these increases could be mediated by alterations in the metabolism of insulin and IGFs (Kaaks, 2004). Both insulin and IGF-1 stimulate anabolic processes and can promote tumor development by inhibiting apoptosis and stimulating cell proliferation (Allen *et al.*, 2007). Dietary factors are recognized as determinants of circulating IGF-1, and thus changes in diet may influence serum IGF-1 concentrations (Wolk, 2005).

Some methodological issues need to be considered. As the coefficient of autocorrelation was significant in the present work, two analytic strategies were tested: to capture variability because of autocorrelation, a random component was included in the multilevel model (MPM-RI), and then, for a more in-depth analysis, a random coefficient was also included (MPM-RIC), but this was not significant. Hence, other unknown variability sources may exist.

Selection bias may still be present in our data as the probability of being included in the sample may be slightly different in different areas of Córdoba province because of its geographical extension. However, sensitivity analysis shows that our estimates are robust (Tumas *et al.*, 2013). Information bias is another issue in observational studies. However, the food frequency questionnaire has been validated and misclassification of dietary exposure would not be of concern. Finally, our results have shown robustness in several studies (Cappellani *et al.*, 2012; Niclis *et al.*, 2012), providing very parsimonious and biologically consistent estimates.

To estimate the risk of PC and BC related to diet and tobacco exposure, we applied a multilevel model with family history of PC or BC as a random intercept variable in the second level. Even though this variable has only two categories, it has been included in the model because of large evidence respecting this antecedent on the risk of PC and BC. The model was applied in smokers and nonsmokers separately with age, BMI, total energy intake, and food group intake as linear predictors. It would have been appropriate to include an interaction term. However, it would be not acceptable to increase the number of parameters for this sample size.

In Argentina, recent studies have reported the magnitude of the public health and economic impact of this habit (Pichon-Riviere *et al.*, 2011). Scientific evidence on lifestyle factors, such as smoking and diet, in relation to the risk of BC and PC, identifies some modifiable risk factors that might be recommended to change to decrease the risk for these common cancer sites. For this purpose, it is important to consider the differential modulatory effect of tobacco smoking and diet on the risk of cancer found in the present study, coupled with the fact that nonsmokers usually show healthier eating behavior including higher consumption of fruits, vegetables, and fiber than smokers (Dallongeville *et al.*, 1998; Phillips *et al.*, 2000; McEligot *et al.*, 2009). It would seem that the smoking habits would both enhance the promoting effect of diet and minimize its protecting effect. Thus, in addition to measures intended to reduce tobacco use, nutritional guidelines and other preventive measures should be designed according to population characteristics, taking into account the exposure to carcinogen.

The present work adds new knowledge about the differential effects of food groups on risks of PC and BC in smokers and nonsmokers in our population. It also introduces the possibility of matched spatial distributions of cancer incidence rates and tobacco exposure.

Acknowledgements

María Dolores Román, Camila Niclis, and Natalia Tumas received fellowships from the National Scientific and Technical Research Council (CONICET). All authors received financial support from two grants provided by the National Agency of Science and Technology (FONCyT Grant PICT 2008-1814 and PICT-O 2005-36035) and the Córdoba University Secretary for Science and Technology (SECyT-UNC, Grant 05/H207).

The authors are grateful to the Statistics Department, Córdoba Provincial Health Ministry, for allowing them to use the mortality database. They also thank Córdoba Cancer Registry for providing the 2005 incidence rates databases.

Conflicts of interest

There are no conflicts of interest.

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