

RESEARCH ARTICLE

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Do Exposure to Arsenic, Occupation and Diet Have Synergistic Effects on Prostate Cancer Risk?

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Abstract

Background: Diverse environmental exposures, as well as dietary and lifestyle factors, are associated with prostate cancer (PC) etiology; however little is known about joint interactive influences. The aim of this study was to analyse effects of diet combined with arsenic in drinking water and agricultural occupation on PC risk. **Methods:** A case-control study was conducted in Córdoba, Argentina (period 2008-2015) including 147 cases of PC and 300 controls. All subjects were interviewed about food consumption, socio-demographic and lifestyle characteristics. A sample of drinking water was taken to determine arsenic concentrations. Adherence scores to the Traditional Dietary Pattern were estimated, based on a principal component factor analysis. A two-level logistic regression model was fitted in order to assess effects of the Traditional Pattern, occupation and arsenic exposure on the occurrence of PC (outcome). Family history of PC was considered as a clustering variable. **Results:** PC risk was greatest in subjects with high adherence to the Traditional Pattern (OR 2.18; 95%IC 1.097–4.344). Subjects exposed to arsenic in drinking water above 0.01mg/l who simultaneously performed agricultural activities showed a markedly elevated PC risk (OR 5.07; 95%IC 2.074-12.404). Variance of the random effect of family history of PC was significant. **conclusion:** Diet, arsenic and occupation in agriculture exert significant effects on PC risk. Further efforts are necessary to analyse risk factors integrally, in order to achieve a better understanding of the complex causal network for PC in this multiple-exposure population.

Keywords: Prostate cancer- dietary patterns- arsenic- occupational exposure- Córdoba-Argentina

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Introduction

Prostate cancer (PC) is the second most common cancer in men worldwide (Ferlay et al., 2012). In Córdoba, Argentina, PC is the leading cause of cancer, with an age-standardized incidence rate of 37.20 per 100,000 person/year and with a non-random spatial distribution (PCRC, 2013; Díaz et al., 2010). Environmental and lifestyle factors seem to play a crucial role in PC development (Hunter and Reddy, 2013).

Arsenic toxicity is a recognized public health problem in Argentina. In the central region of the country, where Córdoba province is located, there is arsenic concentration in groundwater reaching up to 1.8 mg/L (Francisca and Carro-Perez, 2009). Numerous studies reveal an association between chronic arsenic exposure through drinking water and several chronic diseases including PC (Bardach et al., 2015). An ecological study carried out in Córdoba (Aballay et al., 2012) has shown increased incidence rates of PC in areas where groundwater contains arsenic above 0.01 mg/L, the maximum acceptable level for human intake (WHO, 2008).

Another public health concern in Argentina is the increasing population's exposure to agrochemicals due to the great expansion of the planted area. Particularly in Córdoba, the cultivated surface has almost tripled in the past two decades and pesticide exposure linked to agricultural production was evidenced (Lantieri et al., 2011). Pesticides are responsible for acute poisonings as well as for long term health effects as cancer occurrence. A possible association between PC development and pesticide exposure and/or agricultural occupations has been reported (Sanborn et al., 2007; Silva et al., 2016).

In addition to arsenic, pesticides and recognized carcinogens as cigarette smoke, other potentially carcinogenic compounds were identified. Workers in industries are also persistently exposed to numerous chemicals with carcinogenic potential (Hu et al., 2015).

Industrialization and globalization processes have produced transformations in food production systems with consequent changes in the population's diet. An increased intake of energy, fat, sugar and refined carbohydrates alongside a decreased consumption of

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fiber, polyunsaturated fatty acids and micronutrients, are associated with obesity and sedentary lifestyles, increasing the risk of cancer (Popkin et al., 2012). Epidemiological studies suggest that PC is associated with a western lifestyle and diets, including a high intake of fatty and processed meats, fats and dairy products. In contrast, a high intake of whole grains and foods containing vitamin E, lycopene and selenium may decrease PC risk (Nelson et al., 2014; Niclis et al., 2012).

Recent studies on dietary patterns of Córdoba's population Niclis et al., (2015) showed Traditional Pattern (fatty red meats, processed meat, starchy vegetables, added sugars and sweets, fats and vegetable oils) as the most representative. High adherence to this pattern had a promoting effect for PC. However, it is not known whether PC occurrence is modified by this singularly risky dietary pattern coupled with other frequent exposures present in this population, such as occupational (industrial or agricultural) exposure and arsenic concentration in drinking water. Therefore, the purpose of this study was to analyse the effect of adherence to Traditional Pattern and the combined effect of arsenic in drinking water and occupational exposure to agricultural activity.

Material and Methods

Study Design

A case-control study was conducted from 2008 to 2015 by the GEECC (Group of Environmental Epidemiology of Cancer in Córdoba) in two areas of Córdoba province (Argentina) with different environmental levels of arsenic. The studied areas were defined according to data from measurements of groundwater supplies reported by Francisca (2009). Thus, the area of high arsenic exposure included counties of the south and southeast of Córdoba, while counties of north and west were considered into the low arsenic content area.

Cases (n=147) were men with an incident histologically confirmed diagnosis of PC (CIE-10 C61) identified in public and private health institutions throughout the province of Córdoba, and controls (n=300) were male of identical age (± 5 years) and geographical residence than cases. About two controls per case, chosen at random from the same neighbourhoods and time-period as cases, were included in the study after careful verification of the absence of any neoplastic or related diseases or other cultural, religious, or lifestyle conditions that generate long-term modification of diet. All participants signed an informed consent prior to their inclusion in the study. This case-control study was conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. It was approved by the Ethics Committee of the University of Córdoba, and registered at the Provincial Register of Health Research (RePIS N° 345).

Exposure Assessment

All subjects were interviewed by trained professionals with a structured questionnaire about socio-demographic characteristics, anthropometric variables, lifestyle

(physical activity, smoking, occupational history, diet, source of drinking water and time of exposure to well water consumption), personal medical history and family history of cancer. Dietary exposure was assessed with a validated food frequency questionnaire (FFQ) coupled with a validated photographic atlas based on standard portion sizes in Argentina. The FFQ focused on the five-year period before diagnosis for cases and before interview for controls. More details can be found in Niclis et al., (2015). At the time of interview, a sample of drinking water was taken for a further analysis of arsenic content. Water samples were taken at the subject's home in polyethylene bottles previously washed with nitric acid (10%) and rinsed with ultrapure water. The samples were then acidified with nitric acid (1%), filtered (0.45 μm) and refrigerated at 4°C until analysis. Atomic absorption spectrometry was employed to quantify arsenic content (Meza et al., 2004).

Statistical Analyses

A two-level logistic regression model was fitted in order to assess individual-level variable effects of dietary pattern, occupational exposure and arsenic concentration in drinking water, on PC occurrence (outcome). A random intercept was included to account the variability from the family history of the disease (Rabe-Hesketh and Skrondal, 2008). Family history of cancer (first degree family history of PC/first degree family history of other cancer/No family history of cancer) was proposed in order to consider the presence of a contextual aggregation estimated through a variance component. Effects of all individual-level covariates were considered fixed and their estimates expressed as odds ratios (ORs) for risk interpretation.

Dietary patterns were previously identified based on the intake of 24 food groups using a principal component factor analysis (Niclis et al., 2015). The first factor, called Traditional Pattern explain the greater variability of data and it is characterized by positive high loadings of fatty red meats, processed meat, starchy vegetables, added sugars and sweets, candies, fats and vegetable oils. Factor score, defined for all subjects by means of the weighted least-squares method, indicates the degree to which each subject's diet adheres to Traditional Pattern (Edefonti et al., 2009). This adherence score to the Traditional Pattern was included as a first-level covariate.

Other individual-level variables included were arsenic concentration in drinking water (≥ 0.01 mg/L or < 0.01 mg/L), and occupational exposure (industry worker-agricultural worker-low risk worker). Subjects working in direct contact with some chemical recognized by the IARC as carcinogens, for at least 2 years, were defined as occupationally exposed to industry. Agricultural workers were defined as persons carrying out activities in rural areas related to agricultural production. The model was also adjusted by tobacco smoking (yes/no) and the continuous variables of age, body mass index (BMI), total energy intake and years of exposure to the drinking water measured.

The suitable model was selected according to

the Akaike information criterion (AIC). The intraclass correlation coefficient (ICC) and median OR (MOR) (Rabe-Hesketh and Skrondal, 2008) were calculated to quantify between-subject heterogeneity given covariates and residual heterogeneity between clusters (in terms of OR), respectively. All the analyses were performed using STATA 13.1 (StataCorp, 2013).

Results

This study included 147 cases (mean age 71 years, SE 8.5) and 300 controls (mean age 70 years, SE 8.6). Socio-demographic variables are described in Table 1. Cases and controls had similar distribution of socioeconomic status, smoking habit and energy intake. Most subjects showed overweight (BMI >24.9). High proportion of subjects (69.78%) smoked an average of 19.39 years (SE 18.61) (data not shown). The presence of family history of PC was more frequent among cases (p<0.001).

Table 2 shows the distribution of exposure variables stratified by areas of low and high arsenic content. Cases were more concentrated in higher category of

Traditional Pattern in the area of low arsenic exposure. In the area of high exposure to arsenic, a greater proportion of cases than controls had an agricultural occupation (p=0.003).

Daily water consumption was similar among cases and controls in both areas (mean 1,360 cc/day; SE 728.21). Regarding analysis of arsenic in drinking water, small proportion of samples with arsenic levels greater than 0.01 mg/L was found in area of low arsenic exposure. By contrast, concentrations higher than 0.01 mg/L were found in most samples in the area with the greatest exposure to arsenic. The mean of arsenic content in this area was 0.27 mg/L (SE 0.13) however, no differences were evidenced between cases and controls (data not shown).

The use of public drinking water supplies for at least 30 years was reported by 90% of participants. Also, more than 50% of the subjects reported having consumed groundwater at some time. The average years of consumption of groundwater was similar between cases and controls in the area of low arsenic exposure, while in the area of high arsenic exposure cases reported consume groundwater for a longer period than controls (p=0.019).

Table 1. Cases and Controls Characteristics According to Selected Variables and Prostate Cancer Risk Estimation from Logistic Regression Model

	Cases (n=147) n (%)	Controls (n=300) n (%)	OR ^a (95% CI) ^b
Age (years)			
≤60	17 (11.56)	40 (13.33)	-
61-70	48 (32.65)	109 (36.33)	1.04 (0.53 – 2.00)
71-80	63 (42.86)	115 (38.33)	1.29 (0.67 – 2.46)
≥81	19 (12.93)	36 (12.00)	1.24 (0.56 – 2.75)
Social status			
Low	49 (35)	108 (37)	-
Middle	55 (40)	103 (36)	1.20 (0.72 - 2.03)
High	34 (25)	77 (27)	1.23 (0.75 - 1.74)
Educational level			
Low	34 (23.13)*	47 (15.82)*	-
Middle	70 (47.62)	141 (47.47)	0.73 (0.43 – 1.23)
High	43 (29.25)	109 (36.70)	0.58 (0.33 – 1.05)
Body Mass Index			
≤ 24.9	34 (24.44)	84 (27.66)	-
25 – 29.9	87 (57.78)	150 (49.65)	1.43 (0.88 - 2.31)
≥ 30	26 (17.78)	66 (22.70)	0.97 (0.53 - 1.78)
Smoking Habit			
Non-smoker	51 (34.69)	92 (34.69)	-
Smoker	96 (65.31)	208 (69.33)	0.83 (0.54 - 1.26)
Energy Intake ^c			
Low	40 (27.21)	100 (33.33)	-
Middle	48 (32.65)	100 (33.33)	1.20 (0.72 – 1.98)
High	59 (40.14)	100 (33.33)	1.47 (0.91 – 2.40)
Family history of cancer			
None	62 (42.18)	155 (51.67)	-
Other cancer	60 (40.82)	129 (43.00)	1.16 (0.76 - 1.78)
Prostate cancer	25 (17.01) ^o	16 (5.33) ^o	3.90 (1.95 – 7.81)

*Proportion values significantly different (p ≤ 0.1), ^oProportion values significantly different (p ≤ 0.05), ^aCrude odds ratio ^bConfidence interval, ^cCategories based on tertiles of intake in controls.

Table 2. Distribution of Traditional Pattern, Occupational Exposure and Mean Value of Arsenic Concentration in Water Samples, Stratified by Areas of Low and High Arsenic Content

	Area of low arsenic exposure		Area of high arsenic exposure	
	Cases (n=107)	Controls (n=218)	Cases (n=40)	Controls (n=82)
	n(%) or mean (SD)	n(%) or mean (SD)	n(%) or mean(SD)	n(%) or mean(SD)
Traditional Pattern				
Tertile I	29 (27.10)	80 (36.70)	10 (25.00)	20 (24.39)
Tertile II	27 (25.23)	66 (30.28)	13 (32.50)	34 (41.46)
Tertile III	51 (47.66) ^o	72 (33.03) ^o	17 (42.50)	28 (34.15)
Occupational Exposure				
Low risk worker	69 (64.49)	164 (75.23)	21 (52.50)	59 (71.58)
Rural worker	13 (12.15)	17 (7.80)	18 (45.00) ^o	13 (15.85) ^o
Industry worker	25 (23.36)	37 (16.97)	1 (2.50)	10 (12.20)
Drinking water				
As concentration in drinking water				
≤ 0.01mg/L	105 (98.13)	215 (98.62)	8 (20.00)	10 (12.20)
> 0.01 mg/L	2 (1.87)	3 (1.38)	32 (80.00)	72 (87.80)
Time of consumption of public drinking water supplies (years)				
Mean (SD)	56.23 (18.47)	53.07 (18.95)	48.89 (19.23)	54.01 (12.87)
Time of consumption of groundwater (years)				
Mean (SD)	22.40 (14.01)	24.04 (16.86)	28.46 (20.13) ^o	19.98 (13.90) ^o

^oProportion values significantly different (p ≤ 0.05)

No differences were observed in the volume of water consumed daily between cases and controls.

Table 3 shows the results of the modelling approach. A promoting effect of Traditional Pattern on PC risk was observed (OR 2.18; 95%IC 1.097–4.344). Exposure to arsenic higher than 0.01 mg/L in drinking water combined with occupational exposure in rural workers showed a synergistic effect on PC risk as evidenced by a multiplicative risk with respect to the sum of the effects of each factor individually. The exposure time to drinking water measured was positively associated to PC occurrence. An increase of 2% in PC risk was observed for each year of water consumption (OR 1.02; 95%IC 1.001–1.031).

The accuracy of estimates increased when variability was captured within cancer family history categories. Thus, 10% of the variability of those estimated risks is captured when grouping by cancer family history (intra-class correlation coefficient equal to 0.104). Subjects with a family history of PC have more than twice the chance of developing the disease than those without that condition (MOR 2.65).

Discussion

Some issues regarding cancer aetiology were studied in Córdoba (Argentina), a province with a particular risk scenario. An increased PC risk was found in subjects with higher adherence to the Traditional Pattern which combines foods rich in fat, starch and sugars. Besides, subjects consuming water with arsenic concentration above 0.01 mg/L and those who were exposed to agricultural work showed a higher risk of PC than those

who did not have both conditions simultaneously.

Arsenic is a widely distributed natural toxic metalloid with substantial impacts on Public Health. A large area of Argentina has high arsenic concentrations in groundwater derived from the mineralogical composition of quaternary loess sediments (Francisca and Carro-Perez, 2009). About 4 million inhabitants, nearly 10% of the national population, live in affected areas. Long-term consumption of arsenic in drinking water was associated with various chronic diseases (Bardach et al., 2015; Villamil-Lepori, 2015). Epidemiological studies reported a positive association between arsenic levels in drinking water and PC mortality and incidence rates and suggest a dose-response relationship (Nordstrom, 2002; Straif et al., 2009; Hughes et al., 2011; Nuñez et al., 2016). A prospective study in US provides evidence regarding PC mortality at low-moderate arsenic levels in rural communities (García-Esquinas et al., 2013). Our results showed that 90% of the residents in the southeast counties drink water containing arsenic above 0.01 mg/L, thus exceeding the limit values established by international organizations (WHO, 2008). The Argentine Food Code (NAMFMT, 2007) allows different values in areas with naturally high arsenic content and in 2007 established a period of 5 years to reduce levels to 0.01mg/L. However, this last provision was modified in 2012 to extend the deadline until the end epidemiological study carried out by governmental institutions.

Our study indicated no significant differences between cases and controls in current arsenic exposure status. However, when the habitually consumed water source was analysed, we observed a greater proportion of

Table 3. Prostate Cancer Risk Estimates from Multilevel Logistic Model Including Scored Dietary Patterns, Interaction Terms of Arsenic Concentration in Drinking Water and Risk Occupation, and other Individual-level Covariates

Measures of association	OR (95%CI)	p value
Interactions: arsenic in drinking water x occupational exposure		
Arsenic \leq 0.01 mg/l x Low risk worker ^o	-	-
Arsenic \leq 0.01 mg/l x Rural worker	1.96 (0.89 - 4.33)	0.094
Arsenic \leq 0.01 mg/l x Industry worker	1.43 (0.77 - 2.63)	0.256
Arsenic $>$ 0.01 mg/l x Low risk worker	0.64 (0.33 - 1.23)	0.175
Arsenic $>$ 0.01 mg/l x Rural worker	5.07 (2.07 - 12.40)	0.000
Arsenic $>$ 0.01 mg/l x Industry worker	0.48 (0.09 - 2.41)	0.352
Traditional Dietary Pattern [†]		
Tertile I ^o	-	-
Tertile II	1.03 (0.58 - 1.84)	0.907
Tertile III	2.18 (1.09 - 4.34)	0.026
Smoking Habit		
Non-smoker ^o	-	-
Smoker	0.89 (0.57 - 1.41)	0.637
Body Mass Index	0.98 (0.92 - 1.04)	0.505
Total Energy Intake	0.99 (0.99 - 1.01)	0.731
Time of exposure to measured drinking water	1.02 (1.01 - 1.03)	0.030
Age	1.01 (0.98 - 1.03)	0.610

Multilevel model adjusted by age, body mass index, energy intake, years of exposure to drinking water (as continuous variables) and smoking habit (never smoker - smoker), [†]Tertiles of dietary pattern score. ^oReference, OR, odds ratio, SE standard error.

cases that sometime had consumed groundwater and for a longer exposure time than controls. These results support the evidence that a long exposure period is required to develop the disease. Arsenic may contribute to carcinogenesis in exposed populations due to its ability to increase oxidative stress and genotoxic damage (Ren et al., 2011).

In our work, we found an increased PC risk in agricultural workers, a fraction of the population highly vulnerable to the toxic effects of pesticide exposure. Indeed, a population-based study of terrestrial pesticide applicators in Córdoba showed a significant burden of diseases related to their occupational exposure to pesticides (Butinof et al., 2015).

The current food production model and some processes related to demographic and industrialization changes and urbanization have a major impact on population lifestyle and dietary patterns (Popkin et al., 2012). The latest stage of the nutritional transition shows a marked tendency to a high intake of fat and refined carbohydrates and a low intake of vegetables and fiber. The dietary patterns approach is being applied in Nutritional Epidemiology to gather the numerous dietary variables into a single exposure measure. In this study, a high adherence to the dietary pattern characterized by fat and processed meat and starchy vegetables was associated with an increased PC risk. This pattern was the most representative of this population and it is consistent with the dominant food culture in Argentina. The strong representation of red meat as dominant group in the dietary pattern of both, in general and by gender Argentinean population, was also reported by other studies (Pou et al., 2014).

Several epidemiological studies have associated PC risk with a high intake of red meat processed meats, as well as roasted meat with crust formation during high temperature cooking (Sinha et al., 2009; Joshi et al., 2012). PC development may be associated with meat consumption due to the greater intake of animal fat would increase testosterone levels. Testosterone promotes cell proliferation, activation of oncogenes and inactivation of tumor suppressor genes (Tewari et al., 2012). Red meats are also an important source of zinc, an essential mineral that has been studied as a possible risk modulator of various cancers (Gray et al., 2005). Some cellular mechanisms were proposed by which zinc might prevent the occurrence of malignant transformation in prostate cells, including cell cycle suppression and apoptosis of cancer cells (Ho et al., 2011). However, others argue that a high zinc intake is associated with an increased PC risk, possibly because it is essential for the synthesis of testosterone (Zang et al., 2009).

Some studies have shown that some cooking methods with high temperatures, habitually used in Argentina such as grilling, frying or barbecue, generates heterocyclic compounds with carcinogenic activity (Sinha et al., 2009; Reartes et al., 2016)

Other elements of Traditional Pattern are starchy vegetables. High intakes of potatoes and sweet potatoes as well as cereals, refined flour and bread or crackers have been reported as promoters of PC. High starch and low dietary fiber containing in this foods, giving them a high glycemic index, which could justify the observed increased risk by promoting hyperglycemia, hyperinsulinemia (Drake et al., 2012). Insulin acts as a growth factor per se and induces the secretion of other

growth factors such as IGF-1 (insulin growth factor 1), a cell proliferation promoter and apoptosis inhibitor of normal and malignant cells. Insulin may also modify the metabolism of sex hormones causing imbalances of the prostate gland environment (Pollak et al., 2008). The same effects are true for sugar, sweets and candies, also components of the Traditional Pattern, containing high concentration of simple sugars absorbed rapidly in the gastrointestinal tract.

The dietary pattern approach address study of diet as a construct resulting from the combination of its components, beyond the effect on PC risk of each isolated food or food group. Moreover, multilevel models are a powerful tool to assess individual and clusters of individual adherence to a dietary pattern together with socio-demographic variables, without losing other clustered or contextual characteristics in the study population.

In the present study, as in others with similar design, the major limitation is the possibility of selection and recall bias. However, the sensitivity analysis performed previously (Nclis et al., 2015) based on the possibility of the mentioned systematic errors, showed no major evidence of influence of bias. Another possible bias can occur from underreporting of family history of PC leading to misclassification (Moradzadeh et al., 2015).

In this study family history of PC was self reported, and unfortunately we had not access to medical records, pathology reports or cancer registries to be used as gold standards for measure validation. However the questionnaire was applied by centralized trained interviewers so reducing recall bias of family history in both, cases and controls.

The main contribution of this work is the joint study of some risk factors for PC, the most common malignant disease in the Argentinean male population. The province of Córdoba has a scenario which combines exposures to natural and anthropic contaminants that appear to encourage its promoting effect of PC development when presented simultaneously. Also, population of Córdoba adheres to cultural dietary habits that have been associated with an increased risk of developing cancer. Efforts were made to analyze integrally factors assessed at individual and higher levels of population aggregation, in order to achieve a better understanding of the complex causal network of PC in this multiply-exposed population.

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