Eur J Nutr
DOI 10.1007/s00394-013-0627-2

ORIGINAL CONTRIBUTION

Dietary patterns and risk of urinary tract tumors: a multilevel analysis of individuals in rural and urban contexts

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Received: 21 May 2013 / Accepted: 16 November 2013

Abstract

Introduction Bladder cancer is the fourth most frequently diagnosed malignancy in males in Córdoba, Argentina. The evidence regarding an association between urinary tract tumors and dietary factors still remains controversial. Argentina has particular dietary habits, which have already been associated with cancer occurrence.

Purposes (a) To estimate the association of typical dietary patterns in Argentina on the occurrence of urinary tract tumors and (b) to assess the urban–rural context of residence and cancer occurrence dependency.

Methods A case–control study of urinary tract tumors ($n = 123$, 41/82 cases/controls) was performed in Córdoba Province (Argentina), 2006–2011. A two-level logistic regression model was fitted, taking into account rural–urban residence. An exhaustive probabilistic sensitivity analysis (bias analysis) was performed.

Results Southern Cone pattern, characterized by red meat, starchy vegetables and wine consumptions (OR 1.75 high versus low level of adherence to the pattern), and a medium adherence to a high-sugar drinks pattern, with high loadings for soft drinks (OR 2.55), were associated with increasing risk of urinary tract tumors. High adherence to the latter pattern was inversely associated (OR 0.72). The occurrence of urinary tract tumors was also linked to place of residence (urban–rural), explaining more than 20 % of outcome variability and improving the above risk estimations.

Conclusions A high intake of red meat, starchy vegetables and wine, and a moderate intake of high-sugar drinks seem to be associated with increased risk of urinary tract tumors, with differences related to the context of residence.

Keywords Urinary tract tumor · Dietary patterns · Multilevel model · Argentina

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Introduction

Bladder cancer is the sixth most common type worldwide [1] and the fourth most commonly diagnosed in men in Córdoba Province (Argentina) [2]. Transitional cell carcinoma of the bladder comprises approximately 90 % of urinary tract tumors (UTT). The urothelium lining the urinary tract (pelvis, ureter and bladder) is exposed to catabolites and pollutants often excreted in urine, such as carcinogens, those from tobacco smoke or other environmental sources, which may be harmful compounds linked to the pathogenesis of UTT [3]. While smoking and some chemical exposures (i.e., to aromatic amines or inorganic arsenic in drinking water) are well-established risk factors for UTT [4, 5], evidence for the effect of some dietary components is still controversial. Argentina presents particular dietary habits, such as an unusually high consumption of red meat, mainly barbecued, a frequent wine consumption and a low fiber intake [6, 7]. According to the last data reported in the Food Balance Sheets, of the Food and Agriculture Organization (FAO), consumption of bovine meat, wine and vegetables is around 54.1, 25.8 and 64.7 kg/capita/year, respectively, in Argentina [8]. Referred to alcoholic drinks, this country has traditionally been among those with the highest per capita production of wine [9] and, in consequence, shows high levels of consumption. In Córdoba, it was also reported that the most commonly consumed alcoholic beverage is wine [7], and it was estimated a mean consumption of meat and meat products around 280 g/day [6]. So, all the above constitute an interesting scenario to perform studies on the field of nutritional epidemiology of cancer.

In cancer research, diet has usually been described in terms of nutrients or foods. However, the focus of nutritional epidemiology has recently turned to dietary patterns, which better represent the complexity of dietary practices [10]. The dietary-pattern-based approach enables the integration of several dietary exposures into a single one, consequently simplifying interpretation, addressing the issue of nutrient collinearity [11] and being more related to dietary recommendations [12].

Several studies concerning dietary patterns and cancer risk have been carried out in recent years [10, 11, 13], but few in South America were related to UTT [14, 15]. The pioneer study was carried out in Uruguay [14], identifying two dietary patterns associated with bladder cancer, "Sweet Beverages" and "Western" patterns. Andreatta et al. [15], using multiple correspondence analysis, identified two main dietary patterns in Córdoba city population: the "prudent" one, linked to controls, and the "Western" pattern, which was associated with UTT. The main dietary patterns for Córdoba Province were described differently, using mainly principal component factor analysis, now including rural areas [13]. "Southern Cone," with the highest consumption of red meat, wine and starchy vegetables, "high-sugar drinks" and "prudent" (fruit–non-starchy vegetables–dairy foods) were the three patterns associated with colorectal cancer [13].

Other factors than individual exposures of risk, such as several context-level determinants, may be included. Interestingly, a non-random geographical pattern was observed for bladder cancer incidence in Córdoba, Argentina [2, 16], suggesting that some environmental factors may well be linked to the distribution pattern. Thus, it must be recognized that several sources of variability of the response variable (disease occurrence) occur at different levels.

The aims of this work were: (a) to estimate the association of dietary patterns previously identified in Córdoba [13] on UTT occurrence and (b) to assess the urban–rural context of residence and cancer occurrence dependency.

Subjects and methods

Study design

We conducted a case–control study of UTT ($n = 123$, 41/82 cases/controls) in Córdoba Province, Argentina. Cases were subjects diagnosed with transitional cell carcinoma, epidermoid carcinoma or adenocarcinoma of urothelium (C65–68), histologically confirmed, between 2006 and 2011, identified at the major hospitals of Córdoba and included in the Córdoba Tumour Registry. Two controls per case were randomly chosen with the same place of residence, age (±5 years) and gender group. Cases and controls had no other neoplastic pathology than UTT in cases, or related diseases, or long-term modifications of diet linked to life style, social or religious conditions.

The study was approved by the Ethics Committee of the School of Medical Sciences, Córdoba University (Argentina), and was performed in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments. All persons gave their informed consent prior to inclusion in the study. Details that might disclose the identity of the subjects under study have been omitted.

Data

A structured questionnaire was used, including auto-reported information on sociodemographic characteristics, occupational data (special section to industrial workers), smoking and alcohol-drinking habits, physical activity, anthropometric measures, family and personal history of diseases, and dietary behaviors. Particularly, dietary exposure was investigated using a food frequency questionnaire (FFQ) on 127 food items, supported by a photographical atlas, both validated [17, 18]. An at-home face-to-face interview was conducted by specially trained interviewers. The FFQ was focused on the 5-year period before the date of interview (for controls) or diagnosis (for cases).

Data about the place of residence of case or control subjects were categorized as rural or urban, with rural being towns with up to 10,000 inhabitants.

Statistics

In order to assess individual-level variable effects such as dietary patterns on the outcome (occurrence of UTT), taking into account rural–urban context, a two-level logistic regression model [19] was proposed. We assumed a hierarchical structure in the data: Subjects (level 1) clustered into a contextual dimension (level 2). Three dietary patterns are included as first-level covariates: the Southern Cone pattern, high-sugar drinks pattern and prudent pattern [13]. These dietary patterns were previously identified in Córdoba population through a principal component factor analysis (PCFA) [13]. Factor 1 (labeled as Southern Cone pattern) was characterized by positive high loadings of red meat, wine and starchy vegetables, explaining 20 % of the total variance of the model. Secondly, high-sugar drinks pattern showed high loadings for soft drinks and explained 14 % of the variance. Finally, the variation explained for the prudent pattern, loaded on fruit and starchy vegetables, and dairy foods, was 12 %. Factor scores corresponding to each pattern were defined for all subjects by means of the weighted least-squares method. These scores indicate the degree to which each subject's diet conforms to one of the identified patterns [20]. Based on the pooled distribution obtained previously from the control group (Pou et al. [13]), all participants were categorized into tertiles (low, medium and high) of each dietary pattern variable.

Other individual-level variables included were tobacco smoking (smoker for 30 years or more, yes/no), industrial exposure to chemical contaminants (occupational exposure during at least 2 years) and arsenic (As) exposure in drinking water (low, intermediate or high As exposure, according to county of residence) [21, 22]. Referred to industrial exposure classification, it was defined as a person occupationally exposed who works for at least 2 years in an industry, in direct contact with some chemical contaminants recognized by IARC as carcinogens [23] (i.e., industries of dyes, paints, textiles, plastics, rubber, leather, herbicides, automotive, chemical, coal). Rural–urban residence was considered as a second-level or clustering variable.

Thus, effects of all individual-level covariates were considered fixed and their estimates expressed as odds ratios (ORs) for interpretation, while rural–urban residence effect was proposed as random in order to consider the presence of a contextual aggregation estimated through a variance component. The Akaike information criterion (AIC) was used to select the suitable model.

Additionally, the intraclass correlation coefficient (ICC) and median odds ratio (MOR) [13, 24] were calculated to quantify the between-subject heterogeneity, given covariates and residual heterogeneity between cluster groups (in terms of odds ratios), respectively.

Finally, a probabilistic sensitivity analysis [25] was performed to quantify the systematic classification error inherent to retrospective studies. Using several simulated scenarios, differential misclassification was assumed by drawing the sensitivities and specificities from different trapezoidal distributions for cases and controls. Lower specificity was assigned in the cases group, taking into account the widely documented possibility of recall bias [26].

Stata 12.0 software (Statacorp LP. CollegeStation, TX, USA) was used for all analyses.

Results

A total of 123 subjects, 41 UTT cases and 82 controls, predominantly males (65 %), were considered, with a mean (SD) age of 66 (14.1) years. Table 1 shows the distribution of cases and controls. Cases reported a higher proportion of smokers and a family history of cancer. High school level, moderate physical activity and moderate alcohol intake (less than 30 g/day) were more frequent for controls. Cases had a higher proportion of subjects resident in urban areas (80.5 %) than controls (64.6 %).

Figure 1 presents the distribution of dietary patterns by tertiles. The control group has a higher proportion of subjects in the lower and higher tertiles of the Southern Cone and prudent patterns, respectively, compared with cases. As for the high-sugar drinks pattern, 41.5 % of controls were in the highest tertile, while a similar figure (48.8 %) was observed for cases, but for the lowest tertile.

Table 2 shows the estimated effects (OR, 95 % CI) of covariates from the multilevel modeling. Significant promoting effects were observed of Southern Cone and high-sugar drinks patterns, although an increasing risk at high levels of adherence to the pattern (tertile III versus I) was seen for the latter. The prudent pattern was not significantly associated with UTT, although the results suggest a slight protective effect. In addition, significant effects of smoking (OR 2.5) and of a high level of As exposure in drinking water (OR 2.75 in high versus low level of exposure) were also observed.

Geographical aggregation linked to urban or rural residence was noted through its variance component, which was statistically significant (Table 2). This means that the individual likelihood of occurrence of UTT was also dependent on a contextual condition (urbanization level). Moreover, 22 % of the variance of the outcome (ICC = 0.22) was attributable to this clustering. MOR around 2.5 indicated that for two persons with the same individual-level covariates but belonging to urban or rural residence groups, the risk of UTT increases, in median, 2.5 times. Probabilistic sensitivity analysis showed that the systematic and random error-adjusted median ORs (2.48) are higher than the conventional (1.81), and the ratio of 95 % simulation limits including systematic and random error is three times higher than the conventional (Table 2).

Table 1 Case and control characteristics according to selected variables

Characteristics	Controls ($n = 82$) Subjects (%)	Cases ($n = 41$) Subjects (%)
Socioeconomic stratum[a]		
Low	41 (50.00)	19 (46.34)
Medium	27 (32.93)	16 (39.02)
High	14 (17.07)	6 (14.63)
Education level		
Illiterate or incomplete elementary	15 (18.29)	6 (14.63)
Elementary	39 (47.56)	24 (58.54)
Completed high school	12 (14.73)	3 (7.32)
Tertiary or degree	16 (19.51)	8 (19.51)
Occupational exposure[b]		
Without occupational exposure	71 (86.59)	35 (85.37)
With occupational exposure	11 (13.41)	6 (14.63)
Level of arsenic exposure in drinking water		
Low	40 (48.78)	19 (46.34)
Intermediate	34 (41.46)	18 (43.90)
High	8 (9.76)	4 (9.76)
Family history of cancer		
No present	55 (67.07)	21 (51.22)
Present	27 (32.93)	20 (48.78)
Rural–urban residence		
Rural	29 (35.37)*	8 (19.51)*
Urban[c]	53 (64.63)*	33 (80.49)*
Obesity		
No	67 (81.71)	33 (80.49)
Yes	15 (18.29)	8 (19.51)
Physical activity		
Moderate-active[d]	27 (32.93)	10 (24.39)
Sedentary	55 (67.07)	31 (75.61)
Smoking		
No smoker	50 (60.98)**	9 (21.95)**
Smoker	32 (39.02)**	32 (78.05)**
Alcohol intake[e]		
Moderate	69 (84.15)	32 (78.05)
High	13 (15.85)	9 (21.95)

Case–control study of urinary tract tumors in Córdoba, Argentina, 2006–2011

[a] Socioeconomic stratum categorized according to education level, occupation and medical insurance variables

[b] Industrial worker exposure to chemical compounds for at least 2 years (yes/no)

[c] Urban: subjects residing in a town with more than 10,000 inhabitants

[d] Moderate-active: who reported a regular physical activity (3 or more times/week) that represents a caloric expenditure higher than 5 and 3.5 Cal/min, for men and women, respectively

[e] Moderate: mean ethanol intake up to 30 g/day. High: mean ethanol intake higher than 30 g/day

* $p < 0.10$, ** $p < 0.001$ as significance levels

Discussion

The results show that the Southern Cone pattern (red meat, starchy vegetables and wine) and a medium adherence to the high-sugar drinks pattern were associated with increasing UTT risk, while a high adherence to the latter pattern was inversely associated. A slight protective tendency was observed for the prudent pattern, although this was not statistically significant. Importantly, UTT occurrence was coupled with place of residence.

The evidence regarding association between dietary factors and UTT still remains controversial [3]. Potential dietary carcinogens excreted in urine are involved in the cancer process, as is the role played by several nutrients in maintaining the integrity of the urothelium [3, 27]. In South America, the dietary pattern approach, as used in this work, was described by De Stefani et al. [14] in bladder cancer risk in Uruguay. For the Córdoba urban population, Andreatta et al. [15] described the dietary patterns linked to UTT using an exploratory analysis. The Southern Cone pattern was associated with UTT risk in our study, similarly to previous results [14, 15]. Meat consumption is unusually high in Argentina [6], and red wine and potatoes are, respectively, the main alcoholic beverage and starchy vegetable consumed in the population. Previous reports show a positive association between high consumption of red and processed meat and UTT occurrence [28], while alcohol does not seem to increase the risk [29, 30], contrary

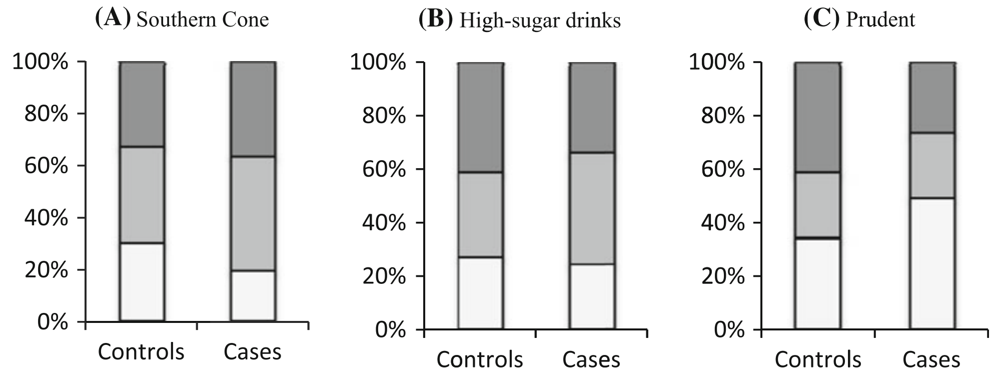

Fig. 1 Relative frequencies of scores from cases and controls, by tertiles of each dietary pattern. *Light*, *medium* and *dark gray* represent low, medium and high tertiles, respectively

to our results. Interestingly, in cooked carbohydrate-rich foods such as potatoes, acrylamide was reported as a carcinogen in animals and a probable human carcinogen [23, 31].

Table 2 Urinary tract tumor risk estimates obtained from multilevel logistic modeling on tertiles of the scored dietary patterns and other individual-level covariates, and their corresponding sensitivity analysis

	OR (95 % CI)	*p* values
Measures of association		
Dietary patterns (vs. tertile I)		
Southern Cone, tertile II	2.63 (1.99–3.47)	<0.001
Southern Cone, tertile III	1.75 (1.10–2.78)	0.017
High-sugar drinks, tertile II	2.55 (1.28–5.07)	0.008
High-sugar drinks, tertile III	0.72 (0.60–0.85)	<0.001
Prudent, tertile II	0.66 (0.25–1.70)	0.386
Prudent, tertile III	0.31 (0.08–1.23)	0.097
Smoker (vs. no smoker)	2.60 (1.99–3.39)	<0.001
Occupational exposure (yes vs. no)	1.07 (0.79–1.45)	0.669
Level of arsenic exposure in drinking water (vs. low exposure)		
Intermediate	1.08 (0.30–3.82)	0.909
High	2.75 (1.11–6.81)	0.028
Measures of variation or clustering		
Rural–urban residence, variance (SE)	0.93 (0.28)	
ICC[a]	0.22	
MOR[b]	2.509	

Sensitivity analysis	Percentiles			Ratio
	2.5	50	97.5	97.5/2.5
Conventional ORs	0.73	1.81	4.47	6.10
Systematic error ORs	1.27	2.30	11.62	9.16
Systematic and random error ORs	0.76	2.48	14.02	18.36

Case–control study of urinary tract tumors in Córdoba, Argentina, 2006–2011

OR odds ratio, *CI* confidence interval, *SE* standard error, *ICC* intra-class correlation, *MOR* median odds ratio

[a] ICC computed by latent variable method

[b] MOR quantifies cluster heterogeneity in terms of odds ratios

Regarding the high-sugar drinks pattern, this work revealed differential effects of an intermediate or high level of adherence to this pattern. Previously, matching our results, an increase in UTT risk was reported associated with a similar pattern, whereas less frequent use of sweet foods and beverages seemed to be protective [15]. Probably, a severe dysfunction of glucose metabolism is involved in the cancer process [32]. Even though not significant (Table 1), cases tended toward sedentarism and overweight, conditions that coexist with perturbations in the glucose metabolism [33]. Therefore, a high glycemic index from foods and beverages could play a role in promoting carcinogenesis [34]. Total fluid intake, however, has been reported as inversely associated with risk of UTT, since it seems to increase urination frequency, with a consequent decrease in the exposure of bladder epithelium to putative carcinogens excreted in urine [35].

In the present study, unlike those reported previously [15], no significant association with bladder cancer was observed for the prudent pattern. Increasing evidence suggests that fruit and cruciferous consumption reduces the risk of bladder cancer, which could be linked with several antioxidants present in these foods [3, 36]. However, the prudent pattern described here also included dairy foods, for which there is no conclusive evidence yet regarding UTT risk [3].

Regarding environmental factors linked to UTT, smoking [5], occupational exposure to carcinogens [3, 4] and As exposure in drinking water [3, 37] are recognized as associated with bladder cancer. The observed promoter effect of smoking is also consistent with our previous study in Córdoba [22]. However, we must highlight that in the present study, tobacco smoking was measured from years of smoking, but it was not considered an indicator of smoking intensity, as number of cigarettes smoked. We recognize that this represents a major constraint, knowing that smoking is a major cause of bladder cancer. On the other hand, our study did not show the expected effect of occupational exposure, maybe due to the lag time from exposure to the onset of disease. There are studies on geographical As exposure areas, including Argentina, describing an association with bladder cancer [21, 37, 38], and these agree with ours. Gender was also seen to affect mortality rates from arsenic exposure in the Córdoba population [22].

As regards risk estimation, the present work considered the variance between responses from the contextual aggregation of urban–rural residence. The results showed a dependence of the outcome (occurrence of UTT) linked to this clustering. This is consistent with the previous studies on the geographical distribution of cancer patterns in Córdoba that found a non-random space distribution of incidence or bladder cancer mortality rates, suggesting a direct association between the incidence of cancer and socioeconomic urbanization rates [2, 16, 22]. The link between diet, urbanization level and non-transmissible chronic diseases has also been previously described from the nutritional transition approach [39].

Some limitations concerning case–control studies need to be considered. Case–control studies were commonly affected by recall bias caused by "rumination" in cases regarding the possible causes of their disease. On the other hand, it is known that in general, the low specificity is associated with a higher degree of bias when the exposure prevalence is low [40], but the Argentinean population showed a high exposure prevalence given the dietary patterns found in the present and in other recent studies [13, 15]; hence, the possibility of misclassification is low. Further, it should be noted that the reproducibility of our 5-year FFQ has been accurately tested for epidemiological cancer studies [18]. The sensitivity analysis performed showed no major evidences of influence of classification bias.

Another aspect is the small size of our study. Epidemiological and statistical literature provides asymptotic formulas for the computation of case–control sample sizes required for odds ratios, unadjusted or adjusted for a confounder [41], but all these recommendations take into account only fixed effects of covariates, including the intercept. While the size of our study is small, we believe that the limited number of parameters imposed in the model (one for each pattern) and the constraint on the sources of variability (a variance component to quantify the intraclass correlation) adequately compensate this fact.

Despite its limitations, the present work has several strengths. Although principal component factor analysis (PCFA) is the main statistical method proposed today to derive dietary patterns in cancer epidemiology research [11], we have found only one study applying PCFA to dietary pattern effects for UTT, so our results add evidence to this subject. Moreover, our work goes further into the dietary effects for Córdoba population [15], incorporating now both rural and urban areas, and proposing a methodological strategy that overcomes the classical analysis to risk estimates. A multilevel modeling approach has been recognized as an efficient tool in social epidemiology, which conveys essential information to quantify the importance of the context of residence for understanding disparities in health [24, 42]. Although multilevel regression analysis makes it possible to obtain unbiased standard errors for regression parameters [42], in the specific case of binary outcome (as in UTT occurrence), it is not easy to compute and interpret measures of variation and clustering. So, following Merlo et al. [24], our work is an attempt to calculate and interpret these measures in the study of contextual determinants of a binary response.

In conclusion, the present work adds evidence for the effect of particular dietary patterns on the occurrence of urinary tract tumors, coupled with the association with urban–rural contexts. In order to reduce UTT risk, this research suggests moderating intake of red meat, potatoes, wine and sweet drinks and promoting the intake of fruits, vegetables and dairy products, focusing on populations residing in urban areas. However, further studies are needed to assess the public health impact of contextual phenomena such as the urbanization process.

Finally, we emphasize that the recognition of environmental factors associated with UTT occurrence (typical dietary patterns added to urban context) may guide clinical practice to detect patients with increased risk for disease development, which has clinical significance related to the prevention and early diagnosis of the pathology.

Acknowledgments We would like to thank the National Science and Technology Agency (ANCyT), the Science and Technical Secretary of the University of Córdoba (SECyT-UNC) for financial support (grants PICT 2008-1814, PICT-O 2005-36035 FONCyT and 05/H207 SECyT) and the National Scientific and Technical Research Council (CONICET) for SAP and CN fellowships. Special thanks to Córdoba Cancer Registry (Córdoba, Argentina) and the physicians who participated in this study.

Conflict of interest The authors declare that they have no conflicts of interest.

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