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ORIGINAL PAPER

Bladder cancer mortality trends and patterns in Córdoba, Argentina (1986–2006)

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Abstract
Background Bladder cancer is common worldwide and the fourth most commonly diagnosed malignancy in men in Argentina.
Objective To describe bladder cancer mortality trends in Córdoba (1986–2006), considering the effect of age, period, and cohort, and to estimate the effect of arsenic exposure on bladder cancer, and its interaction with sex, while controlling by smoking habits and space and time variation of the rates.
Methods A joinpoint regression was performed to compute the estimated annual percentage changes (EAPC) of the age-standardized mortality rates (ASMR) in an adult population from Córdoba, Argentina. A Poisson model was fitted to estimate the effect of age, period, and cohort. The influence of gender, tobacco smoking (using lung cancer ASMR as surrogate), and arsenic in drinking water was examined using a hierarchical model.
Results A favorable trend (1986–2006) in bladder cancer ASMR in both sexes was found: EAPC of −2.54 in men and −1.69 in women. There was a decreasing trend in relative risk (RR) for cohorts born in 1931 or after. The multilevel model showed an increasing risk for each increase in lung cancer ASMR unit (RR = 1.001) and a biological interaction between sex and arsenic exposure. RR was higher among men exposed to increasing As-exposure categories (RR male low exposure 3.14, RR male intermediate exposure 4.03, RR male high exposure 4.71 versus female low exposure). A non-random space–time distribution of the rates was observed.
Conclusions There has been a decreasing trend in ASMR for bladder cancer in Córdoba. This study confirms that bladder cancer is associated with age, gender, smoking habit, and exposure to arsenic. Moreover, an effect measure modification between exposure to arsenic and sex was found.

Keywords Bladder cancer · Mortality · Arsenic exposure · Tobacco smoking · Cohort effect · Córdoba · Argentina

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Introduction

Bladder cancer is the tenth most common cancer worldwide and the eleventh leading cause of cancer-related death [1]. In Argentina, it was reported as the fourth and the fourteenth most commonly diagnosed malignancy in men and women, respectively, with age-standardized incidence rate per 100,000 people around 15.1 (men) and 2.6 (women) in the period 1998–2002 [2]. As reported by the WHO, the age-standardized mortality rate (ASMR) from bladder cancer in Argentinians over the age of 35 years was 12.32 and 2.08 for men and women, respectively, in 2005, showing decreasing trends in the last two decades [3].

Current research supports that gender and age [1, 4], smoking habits [1, 5, 6], and arsenic (As) exposure via drinking water [7–10] are established risk factors for bladder cancer. In fact, the evidence shows higher rates in men than in women (men are three to four times more likely to develop urothelial carcinoma of the bladder) [4] and increased risk with age [1, 4].

A causal relationship between tobacco use and urinary bladder cancer has been found. Estimated relative risk for current smokers of 2.80 (95% CI 2.01; 3.92) and 2.73 (95% CI 1.82; 4.10) among men and women, respectively, has been reported from a meta-analysis [5]. Moreover, the pathogenesis of bladder cancer is associated with the presence of carcinogens (such as tobacco smoke, dietary compounds, and other from industrial exposures), which are often excreted in the urine, thus exposing the bladder lining to these toxins [1].

Epidemiological findings indicate that As is a human bladder carcinogen [7–9, 11, 12], and evidence linking As in drinking water to this cancer has been classified as sufficient by the IARC [10]. Several epidemiological studies of arsenic-related diseases have been conducted in arsenic-exposed regions, including Argentina and particularly Córdoba [13–15], but they are correlation studies [13] and referred to a short time interval [14, 15].

In Argentina, several provinces have been affected by natural As water contamination [13, 16–18]. The best-characterized endemic area has been the eastern region of Córdoba [19, 20]. For the most part, high As concentrations are limited to well water, which is frequently used as a source of drinking water in rural areas as well as for agricultural and industrial activities [13]. The high As levels found in Córdoba's groundwater are due to the natural geological soil composition of the area [21, 22].

A recent publication revealed that bladder cancer incidence rates follow a non-random spatial pattern in Córdoba [23]. This means that some unknown or suspected factors linked to a geographical dimension (e.g., counties) could explain the observed occurrence pattern (spatially dependent, non-random) in cancer distribution. The results of that study, as well as the soil characteristics of Córdoba (with a highly variable As concentration in groundwater, ranging from counties where As is not present to counties with a mean value of 1.01 mg/l or more), provide an ideal scenario in which to examine the association between As exposure and bladder cancer. However, it is important to note that the As contamination of water is not a localized problem. Indeed, chronic exposure to As, via drinking water, has been reported as a major health concern in several areas of the world, other than Argentina [11, 24, 25].

The objective of this work was to describe bladder cancer mortality trends in Córdoba (1986–2006), considering the effect of age, period, and cohort and to estimate the effect of arsenic exposure on bladder cancer. Additionally, the effect of measure modification of sex on arsenic exposure was estimated while controlling by smoking habits and space and time variation of the rates.

Materials and methods

Population study

Córdoba is a province of Argentina, located at the center of the country, with an estimated population size of around 3,254,279 inhabitants in 2005 and a territorial extension of 165,000 km^2.

Cancer mortality data on the adult population (aged 35 years or older) in the 26 counties of Córdoba province, from 1986 to 2006, were obtained from the Department of Statistics database, Ministry of Health of Córdoba, Argentina. In Argentina, death is certified by a physician and less than 1% is deaths from unknown causes. We estimated the resident population by linear interpolation of official census data obtained from the INDEC (National Institute of Statistics and Census) records.

Bladder (ICD-10 67) and lung (ICD-10 33-34) mortality rates for each county, expressed per 100,000 persons at risk per year by sex, were then age-standardized according to the world standard population based on 5-year age-groups.

Exposure data

Due to the absence of direct information on smoking history by area, we used lung cancer ASMR as a surrogate for tobacco smoking over the same period of time (1986–2006), following the same conceptual framework presented by other authors [26, 27].

Categories of As concentrations in drinking water in Córdoba were obtained from Hopenhayn-Rich et al. [15]. We assigned each county to a low (0–0.04 mg/l), intermediary (0.04–0.32 mg/l) or high (0.32–1.8 mg/l) arsenic exposure category. As Hopenhayn-Rich's study was restricted to rural areas, Córdoba and the Río Cuarto counties lacked an exposure category. So, we assigned Córdoba to a low As exposure category as drinking water in the city comes from surface water and Río Cuarto to the intermediate As exposure category, in accordance with Francisca and Carro-Perez [13].

Despite the fact that one survey measuring As groundwater contamination was conducted more than 50 years ago [19], As levels showed a high degree of consistency with a more recent survey [20]. Moreover, if the lag time between As exposure and bladder cancer is 20 or more years [14], the study period 1986–2006 should reflect exposure dating back to 1970 or before. So, As exposure was considered as a sustained, unchanging exposure over time.

Statistical analysis

An exploratory analysis of the bladder cancer ASMR trends for Córdoba province as a whole was performed using joinpoint regression. Joinpoint analysis is used to identify the calendar years in which changes in trends occur, as a statistical algorithm finds the optimal number and location of places where the trend changes. The estimated annual percentage change (EAPC) is then calculated by fitting a regression line to the natural logarithm of the rates or of the number of cases, using the calendar year as a regression variable [28].

In order to estimate the effects of age at death (expressed as rates/100,000 person-years), period, and cohort of birth (depicted as logs of relative risk in figures) on bladder cancer mortality rates for the study period, we performed an APC analysis. We considered 11 5-year age-groups (from 35–39 to 85 or over) and four calendar periods (1986–1990, 1991–1995, 1996–2000 or 2001–2006). Cohorts of birth were identified by the central year of birth, from 1901 to 1966, yielding 13 ten-year cohorts each overlapping by 5 years. The analysis was performed by assuming that the number of deaths is distributed as a Poisson variable, as suggested by several authors [29–32], and that mainly cohort effects drive the change in age-specific rates; then, we fitted a sequential Poisson model [33]. First, we fitted an age–cohort model and subsequently we fitted a period-only model, using the log-fitted values from the previous age-cohort model as the offset. So, age was defined as the major timescale, cohort of birth as the secondary timescale (the major secular trend), and period of death as the residual timescale, conditional on the estimated age and cohort effects. The central cohort (midpoint year 1941) was chosen as reference cohort because several dams were built to supply water to Córdoba between 1930 and 1940 (fully operationally since 1940).

In a second step, we investigated the influence of sex, smoking, and As exposure on bladder cancer mortality in Córdoba by using generalized linear latent and mixed models (GLLAMM) [34], which account for time and space variations in the patterns of rates. Due to the clustered structure of our dataset (longitudinal information related to bladder mortality, nested in counties), we used a two-level random-intercept Poisson regression model, considering the calendar year of death i as level 1 and the geographical area j (county) as level 2. So, the bladder cancer ASMR (y_{ij}) was related to three explanatory variables: sex (x_1), smoking habit (x_{2ij}), and As exposure in drinking water (x_{3j}). Smoking was assessed with a surrogate variable, the lung cancer ASMR (varying over time and county). Each county was also classified into three categories of As exposure: low, intermediate, or high. Finally, an interaction term between sex and As exposure was considered in the model. Several models were fitted to the data, but the one including the interaction between sex and As exposure was chosen. It was not the most parsimonious but it offered biological plausibility. The interaction between smoking and sex, and smoking and As exposure was not assessed because it was used as a smoking surrogate.

The log-likelihood ratio test (LLR) was performed to test the contribution of each variable or term to the model [35].

The Joinpoint Regression Program v.3.2.0 (National Cancer Institute, US, 2008) was used to perform joinpoint analysis, and Stata 11.0 (Statacorp LP. College Station, TX: USA, 1990) for data management and all other statistical analyses.

Results

This study included 2,772 certified deaths from bladder cancer between 1986 and 2006 in Córdoba, Argentina, among people aged over 35 years. In 1986 (population size around 1,020,821 inhabitants), a total of 98 men (ASMR 18.9) and 19 women (ASMR 2.6) died of bladder cancer, whereas in 2006 (1,351,987 inhabitants), these figures were 101 (ASMR 12.3) and 35 (ASMR 3.0), respectively. Overall, a decreasing trend was observed for both sexes throughout the study period (Table 1 and Fig. 1), with men showing the strongest change in the last calendar segment (EAPC = −3.6 in 1993–2006 period).

APC analysis results are illustrated in Fig. 2 where age at death is expressed as rate, while period of death and cohort of birth effects are expressed as log of relative risk (RR). Bladder cancer mortality rates tended to increase with age, from 0.88 (95% CI 0.3; 2.4) to 91.1 (95% CI: 71.6; 115.9) for men, and 0.36 (95% CI: 0.08; 1.72) to 31.6 (95% CI: 20.7; 48.2) for women. This increase was greater and faster in men. No period effect was observed although there were fluctuations from 1986–1990 to 2001–2006 for each sex. Finally, the cohort effect exhibited a similar pattern for men and women, characterized by a decreased risk of death, particularly in post-1931 generations. The increased RR for the male cohort of birth from 1901 to

Table 1 Bladder cancer mortality rates: Joinpoint regression analysis by sex. Córdoba (Argentina), 1986–2006

	ASMR#		EAPC† (95% CI)	p-values	Joinpoint analysis					
					Trend 1			Trend 2		
	1986	2006	1986–2006		Years	EAPC† (95% CI)	p-values	Years	EAPC† (95% CI)	p-values
Males	18.9	12.3	−2.54 (−3.5; −1.6)	<0.0001	1986–1993	−0.1 (−4.6; 4.7)	0.979	1993–2006	−3.6 (−5.6; −1.7)	0.001
Females	2.6	3.0	−1.69 (−3.2; −0.2)	0.028	1986–1996	0.3 (−4.0; 4.7)	0.893	1996–2006	−3.8 (−7.9; 0.5)	0.081

ASMR: age-standardized (35 years old or more) mortality rates

† EAPC (95% CI): estimated annual percent change (95% confidence interval)

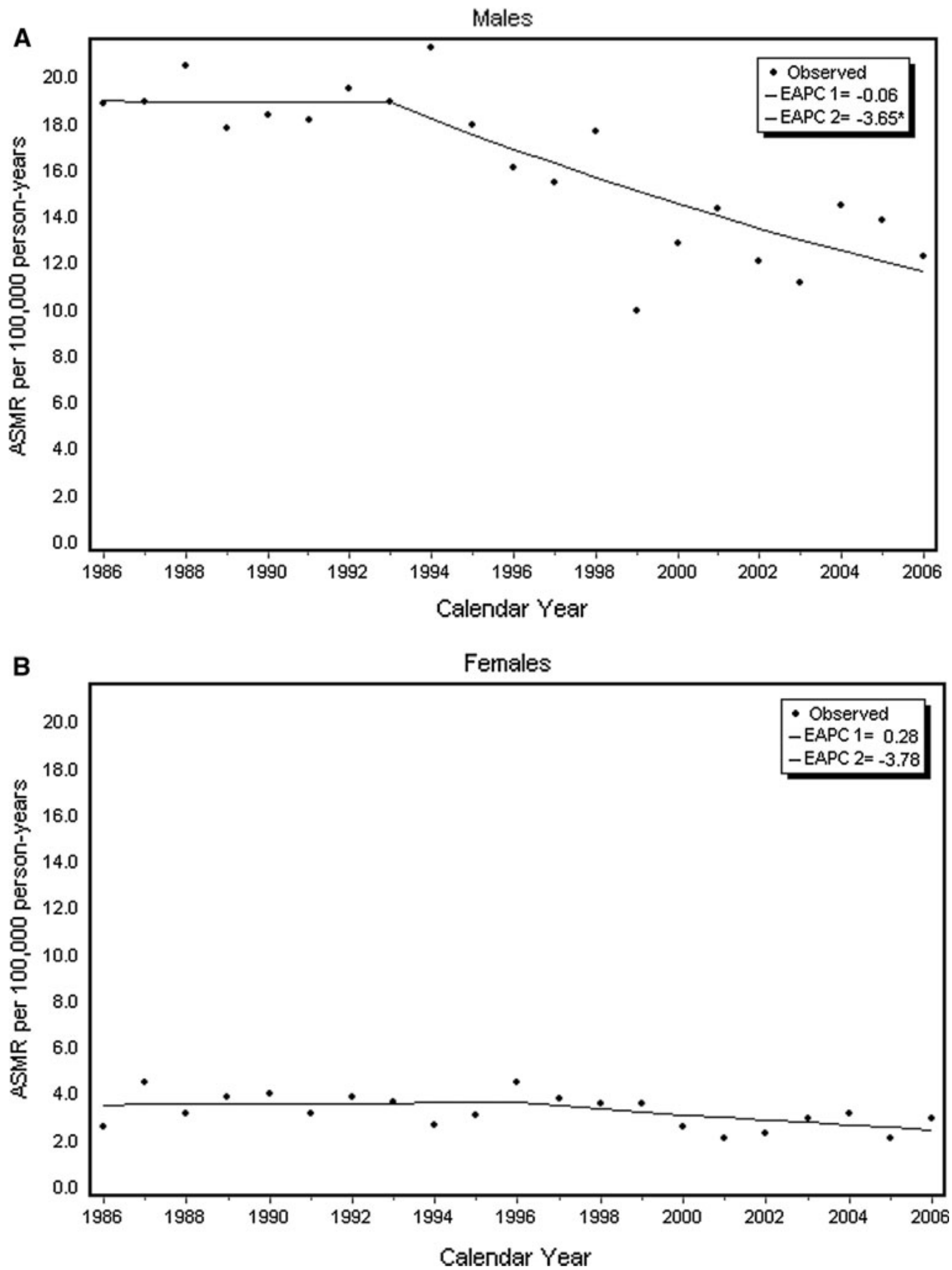

Fig. 1 Trends in age-standardized (world population, truncated at 35 years or over) cancer mortality rates (ASMR) for bladder cancer in Córdoba province: Joinpoint analysis (1986–2006) for men **a** and women **b**. Observed rates, *circles*. Estimated trend, *line*. Estimated annual percentage change (EAPC) statistically significant from zero, *asterisk*

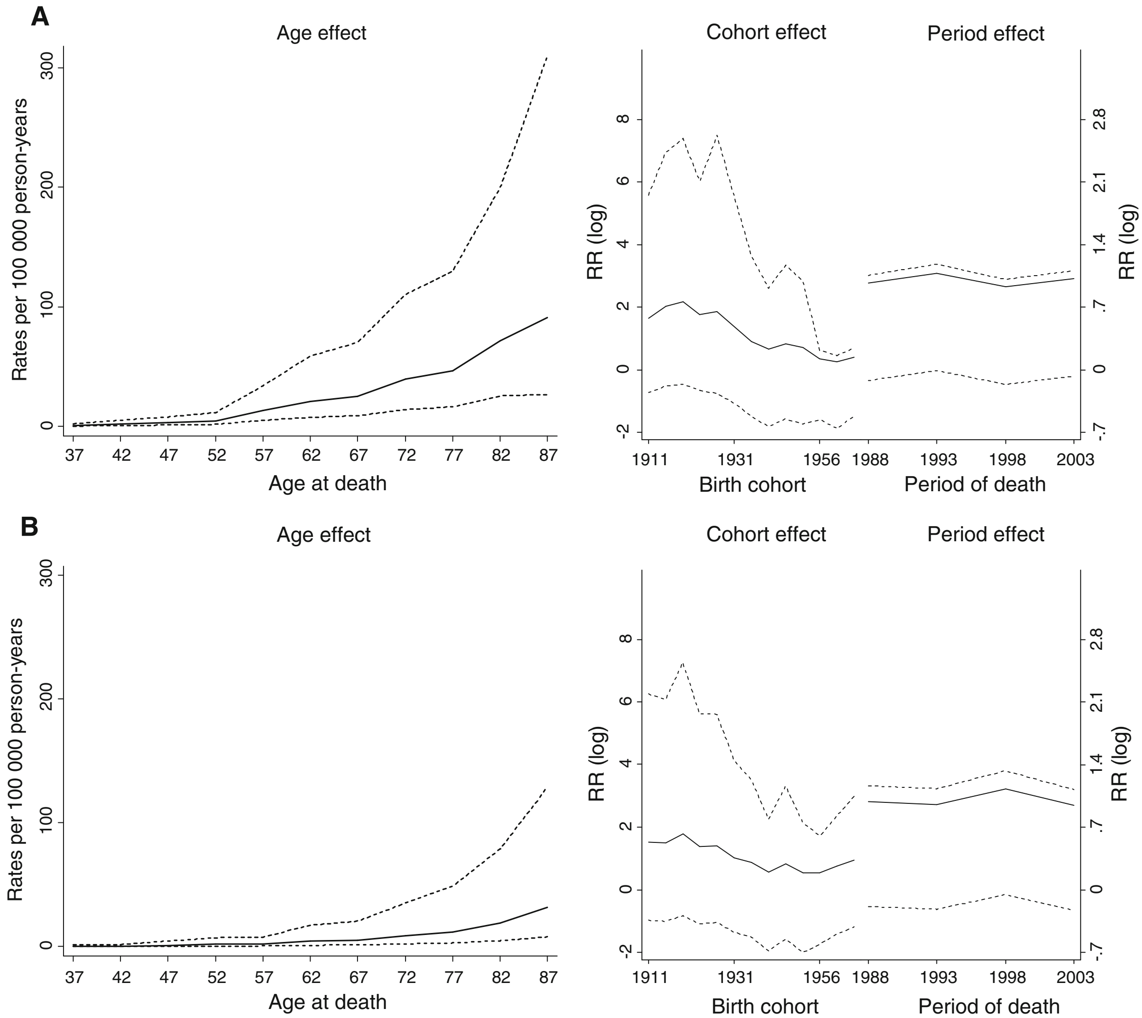

Fig. 2 Bladder cancer mortality: age–period–cohort modeling for men **a** and women **b** for Córdoba (Argentina) 1986–2006. *Solid line*: effect estimate; *dashed line*: 95% CI. RR (log): log of relative risk

1926 ranged from 1.38 (95% CI: 1.16; 1.64) to 2.17 (95% CI: 1.73; 2.72).

Table 2 shows the results of multilevel analysis. The chosen model showed an increasing risk for each increase in lung cancer ASMR unit (RR = 1.001) and a biological interaction between sex and arsenic exposure. RR was higher among men exposed to increasing As-exposure categories (RR male low exposure 3.14, RR male intermediate exposure 4.03, RR male high exposure 4.71 versus female low exposure). As smoking was assessed by means of a surrogate variable, effect modification estimates related to smoking would therefore be unreliable. The multilevel structure was able to quantify otherwise unobserved heterogeneity attributable to the geographical and temporal variability in data distribution, namely space and time distributions. In fact, there was a non-random space–time distribution of bladder cancer ASMR, according to the estimated variances of random effects of the clustering variables (calendar year of death and county) (Table 2).

Discussion

A favorable trend in bladder cancer ASMR was found from 1986 to 2006 in both sexes in Córdoba (Argentina). Overall, this trend was more evident among men and stronger from 1993 until 2006. Mortality rates increased with age, and more strongly and rapidly in men. No period effect was found, either among men or women. There were increased RRs for cohorts born from 1901 to 1936 and decreased RRs thereafter.

Risk of death was associated with smoking habit and As exposure, with a biological interaction among women and high As exposure and among men and As exposure. There was also a non-random space–time distribution of bladder cancer ASMR.

Bladder cancer is an important cause of death worldwide and in Argentina. Known risk factors for this cancer include age, male sex, smoking habit, and exposure to arsenic. Evidence for Argentina, and in particular Córdoba,

Table 2 Multilevel modeling of bladder cancer ASMR in Córdoba (Argentina) 1986–2006: effects of ASMR for lung cancer, sex, and arsenic exposure and space–time variations

Effects of covariables (Fixed effects)	RR (95% CI)†	*p*-values
ASMR lung cancer (smoking surrogate)	1.001 (1.0008; 1.002)	<0.001
Interaction sex * arsenic exposure		
Female, low exposure	1.000	
Female, intermediate exposure	0.938 (0.835; 1.054)	0.284
Female, high exposure	1.220 (1.038; 1.435)	0.016
Male, low exposure	3.143 (2.891; 3.416)	<0.001
Male, intermediate exposure	4.030 (3.581; 4.536)	<0.001
Male, high exposure	4.712 (4.089; 5.431)	<0.001
Clustering variables (random effects)	**Variances (standard deviation) of random effects**	
Calendar year of death (level 1)	0.960 (0.036)	
County (level 2)	0.385 (0.024)	

† RR: relative risk (95% confidence interval)

concerning As exposure and bladder cancer has showed increased mortality risk with increased As exposure via drinking water [14, 15, 36].

Although suggestive, these data are not sufficient to describe both the risk and the exposure by itself. As outlined below, our work confirms already-known risk factors and adds valuable information about age and cohort effects and, especially, about the link between As exposure and bladder cancer mortality (for example, the effect change of gender on As exposure, and the effect of smoking habit considering moreover geographical and temporal variations).

The estimated downward trend in bladder cancer mortality over the last decades has been previously reported for Argentina [3, 37, 38] and other countries of the European Union [39], as well as South and North America [38].

Mortality rates were similar to those estimated by the IARC, for Argentinian adults aged 35 or older in the period 1986–2000 [3, 5] but higher than those reported by other authors at local [40] and national level [37, 38, 40, 41]. These differences could be attributed to the fact that our estimates are truncated rates, whereas the national ones are not.

Even though several epidemiological studies have explored cancer data from Córdoba [41–45], only three recently published papers [43–45] describe temporal changes in rates, considering the influence of age, period, and cohort of birth on cancer mortality, and none of them are referred to bladder cancer.

APC models showed two effects of time on bladder cancer mortality rates: age and cohort of birth effects. This is consistent with the nature of the disease under study. In fact, for most human cancers, there is often an interval of several decades between the first exposure to a carcinogen and the clinical appearance of the disease, [46] usually in the elderly. The period effect tends to be more prominent for diseases for which the cumulative effects of previous exposure are relatively unimportant, while in chronic diseases such as cancer, cumulative effects are usually important, and thus cohort effects tend to affect rates in a strong way [47].

With this assumption in mind and understanding that the cohort effect usually result from environmental and social changes [29], it may be supposed that our successive cohorts, from the older cohorts to younger ones, experienced a decreasing exposure to some etiological agents.

In this context, it is interesting to note that improvements in the water supply system, such as the construction of several dams, have been made since the 1930s in Córdoba province. Official statistics about access to the public drinking water supply system (50 and 90.7% of housing in 1960 and 2001, respectively) [48] reflect the favorable impact of public health interventions carried out in this field. Therefore, it is reasonable to assume that the reduction in arsenic exposure due to changes in the drinking water supply (from well water to surface water) has led to a decrease in mortality rates from bladder cancer among successive cohorts of birth. In fact, a decreased risk of death was observed particularly in post-1931 generations. Our findings are consistent with another epidemiological study [25], which concluded that this kind of finding strengthens the likelihood of a significant association between arsenic exposure and bladder cancer, based on the reversibility criterion.

Owing to the fact that the effects of cohort of birth and age at death effects were the most important temporal dimension affecting bladder cancer mortality rates, we subsequently tried to disentangle these effects by introducing a hierarchical model in order to account for some potential risk factors reported in the literature such as the gender, [4] smoking habit [1, 5, 6], and As exposure [11, 14, 49] while controlling for space and time distribution of the rates.

Consistently higher rates in men than in women have been reported in the literature [4] and, as expected, our study confirms this concept. The disparity among genders is hypothesized to be the result of a differential exposure to carcinogens (i.e., tobacco and chemicals) as well as genetic, anatomical, hormonal, societal, and environmental factors [4], including dietary habits [42, 50]. The exposure to aromatic amines, for example, may have played a role in the decreasing pattern observed for successive generations of men, although its effect remains unclear [39]. In addition, previous studies suggested that sex differences may exist in certain aspects of bladder cancer therapy (but not cystectomy), like variations in the use of radiotherapy and different lethal rates [51]. In effect, due to differing survival between populations, and over time, these data must be interpreted with caution. However, it has been recognized that mortality statistics for bladder cancer are almost certainly more comparable than statistics on the incidence, which is particularly hard to interpret because of changing classifications, variations in counting multiple cancers in the same individual and, most importantly, the variable inclusion of non-invasive cancers in different datasets [52].

In this sense, it is important to consider some confounding factors such as the quality of cancer mortality statistics, changes in the cause of death due to misclassification or improvements in health care facilities (including diagnostic techniques and treatment). It may be hypothesized that the overall and between sexes differences found in Córdoba could be attributed to changes in health care technology. However, the quality of the registers and classification protocols are thought to have remained substantially unchanged, even if there are no available studies supporting this hypothesis. It is important to note that no screening program for bladder cancer is included in the public health policies, either in Córdoba or in Argentina. Nevertheless, general health care has progressed since the industrialization process gathered momentum in Córdoba, from the beginning of the 1950s onwards. This complex process induced a significant migration of rural people to Córdoba city and its surroundings, with concomitant changes in lifestyles and better access to health care [53].

Current scientific evidence considers tobacco as a carcinogenic in human, with a causal relationship also to urinary bladder cancer [6]. The spatial distribution (i.e., geographical variations) of bladder cancer has been reported to be related to the prevalence of known risk factors, especially exposure to tobacco, responsible for almost one-third of bladder cancer deaths [52]. Unfortunately, a detailed ascertainment of smoking habits is frequently lacking in developing countries [27]. Thus, it is difficult to study their influence over time, in order to explain disease patterns.

The First National Survey of Risk Factors reported a smoking prevalence in adults (18–64 years old) of 33.4 and 34.5% in 2004 for Argentina and Córdoba, respectively, with higher rates in men than women [54]. Furthermore, this source indicated that there has probably been an increased consumption of tobacco among Argentinian women in the last years, which is consistent with regional epidemiological evidence that smoking is becoming more prevalent in women in Latin America [55].

The effect of smoking on bladder cancer was found to be strong in our study, in agreement with a recently published meta-analysis [5]. This is particularly important in the context of this work as it has been shown that lung cancer incidence rates follow a random spatial distribution in Córdoba [23].

As mentioned earlier, there is agreement about the relationship between As exposure and bladder cancer. Our findings are consistent with a previous study conducted in Córdoba, where bladder cancer standardized mortality ratios were consistently higher in counties with documented arsenic exposure [14], as well as in another study conducted in Chile [49]. Effect modifications of arsenic exposure by other risk factors, such as smoking [56], have also been suggested in the literature. However, to our knowledge, there is no enough about the effect modification of gender on As exposure, which is a finding that our study added to the current literature.

A population-based case–control study in Córdoba province found that the association between smoking and bladder cancer occurrence was limited to smokers who also used well water for over 50 years before interview [36]. In fact, it has been suggested that there is a lag time of 30 years or more from exposure to the onset of disease [12, 57]. In view of our results, it is possible to argue that the lag time between As exposure and bladder cancer is long because the mortality from bladder cancer continued to be high around the 2000s, even though major decreases in arsenic exposure had occurred more than 50 years earlier, when improvements of the drinking water supply system were introduced. Nevertheless, it is also plausible that smoking is still the reason why bladder cancer mortality is high today. Unfortunately, it is difficult to draw some conclusion related to smoking due to lack of longitudinal studies of prevalence and the fact that public health interventions have been recently implemented in Córdoba province (Law No. 9113 for the prevention and control of tobacco use, 2003).

As expected, bladder cancer mortality rates exhibited a non-random space and time variation. This geographical correlation of the bladder cancer distribution is in agreement with a previous study about the geolocation of the cancer incidence in Córdoba [23]. Different spatial patterns in chronic diseases, including cancer, have been associated with some sociodemographic characteristics such as socioeconomic status [58] and urbanization level [23].

A weakness of this study is not only the short interval of time considered but also the use of a surrogate to measure smoking habit. This use has been reported as valid by other authors [26, 27] but should be interpreted with caution. Using lung cancer mortality rates as a marker for an accumulating smoking hazard may result in an overestimation of risk where there has been a sharp decline in smoking, and an underestimation of risk in places where smoking has increased [27]. However, since 80% of lung cancers are attributable to cigarette smoking [59] and the reported association between cigarette smoking and lung cancer, the use of that surrogate is justified in absence of a better index.

On the other hand, the base of the study, which is the population-time that generated the cases, is sizeable, so estimates should be valid other than precise as evidenced by CI.

In conclusion, the results of this study show a biological plausibility, are consistent with other studies, and provide an interesting point of view to analyze the role of As exposure and other related variables on the causal pathway of bladder carcinogenesis, providing evidence for the formulation of etiological hypothesis and the identification of potentially susceptible populations. Given the magnitude of the RRs and the precision of the estimates, the differences are unlikely to be due to confounding factors. All this suggests a need for greater efforts to reduce arsenic exposure in drinking water and to discourage the smoking habit.

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