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Clinical-Bladder cancer

Impact of arsenic exposure on clinicopathological characteristics of bladder cancer: A comparative study between patients from an arsenic-exposed region and nonexposed reference sites

Mario I. Fernández[a,d,*], Patricio Valdebenito[b], Iris Delgado[e], Jorge Segebre[f], Eduardo Chaparro[b], David Fuentealba[b], Martín Castillo[f], Cecilia Vial[d], Juan P. Barroso[a,c,f], Annemarie Ziegler[d], Alberto Bustamante[a,f]

[a] *Department of Urology, Clínica Alemana de Santiago, Vitacura, Santiago, Chile*
[b] *Department of Urology, Hospital Regional de Antofagasta, Antofagasta, Chile*
[c] *Department of Urology, Hospital Padre Hurtado, Santiago, Chile*
[d] *Center for Genetics and Genomics, Faculty of Medicine, Clínica Alemana Universidad del Desarrollo, Lo Barnechea, Santiago, Chile*
[e] *Center for Public Policies, Faculty of Medicine, Clínica Alemana Universidad del Desarrollo, Lo Barnechea, Santiago, Chile*
[f] *Faculty of Medicine, Clínica Alemana Universidad del Desarrollo, Lo Barnechea, Santiago, Chile*

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Abstract

Background: Beyond exposure to arsenic in drinking-water, there is few information about demographic and clinicopathological features of patients with bladder cancer living in arsenic-exposed regions. The aim of the study was to assess the impact of arsenic exposure on clinicopathological characteristics in patients with bladder cancer from a contaminated region compared to those of 2 reference areas.

Methods: Data of 285 patients with bladder cancer (83 with arsenic exposure from Antofagasta and 202 controls from 2 different sites in Santiago) were obtained through personal interviews and from review of medical records. Demographic, clinicopathological parameters, and information on relevant environmental risk factors were compared with parametric and nonparametric tests as needed. Multivariable analysis was performed to identify independent predictors for high grade and muscle-invasive disease (T2-4).

Results: We found no significant differences between groups regarding age at presentation (66.4 vs. 66.5 and 67.2 years; $P = 0.69$, for exposed vs. the 2 nonexposed groups, respectively) and female gender (28.9% vs. 29.8% and 26.2%; $P = 0.84$). Proportion of current smokers was significantly lower in the exposed population (10.7% vs. 38.6% and 26.9%; $P < 0.001$). There was a significantly higher proportion of locally advanced (10.8 vs. 1.8 and 0.7% T3/4; $P = 0.002$) and high-grade tumors (79.5% vs. 63.2% and 64.1%; $P = 0.001$) within arsenic-exposed patients. Arsenic exposure was the only significant predictor for the presence of high-grade tumors (adjusted OR: 5.10; 95%CI: 2.03−12.77) on multivariable analysis.

Conclusions: Our study revealed relevant clinical differences in bladder cancer patients with a history of arsenic exposure as compared to nonexposed cases. The more aggressive phenotype associated to arsenic-related bladder cancer should be considered when designing efficient screening strategies for this high-risk population.

Keywords: Neoplasm, Urinary bladder; Arsenic; Drinking water; Risk factor; Carcinogenesis

1. Introduction

Exposure to arsenic in drinking water is a well-known risk factor for bladder cancer (BC), leading to increased incidence and cancer-specific mortality rates [1]. Strongest evidence has been provided by studies of high exposure

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*Corresponding author. Tel.: +56-2-23279263.
E-mail address: mfernandeza@alemana.cl (M.I. Fernández).

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areas in Taiwan [2,3], Argentina [4], Bangladesh [5], the United States [6–8], and Chile [9,10], showing elevated estimates of relative risk. Therefore, confusion with other established risk factors, such as tobacco smoking, appears unlikely. The latter hypothesis referring to a minor role of tobacco smoking in the occurrence of arsenic-related BC is supported by a recent systematic review of several epidemiologic studies [11].

Inhabitants of Antofagasta (Northern Chile) were exposed to drastically increased levels of arsenic in drinking water between 1958 and 1970, which reached up to 850 μg/l. The installation of purification plants and the implementation of new technologies led to progressive reductions of concentrations, resulting in levels <10 μg/l after 2005 (Fig. 1).

However, more than 2 decades after having controlled arsenic levels in drinking water in the early 70s, the consequences of this contamination remain a relevant issue to local health care systems due to the long latency of BC, as reflected by persistently high incidence and cancer-specific mortality rates at present time [12]. In fact, BC incidence in Antofagasta among men was more than 4 times higher than that of a comparable region within Chile for the period 2008 to 2010 (20.6 vs. 5.0/100,000 in Concepción). The latter incidence is similar to that estimated for the whole country (5.1/100,000). Meanwhile, the proportional difference was also significant among women for the same period (8.1 vs. 1.9/100,000) [13–15]. Furthermore, arsenic-related BC appears to have distinct tumoral features. To date, the only site reporting clinical data of patients with arsenic-related BC is Taiwan. A retrospective study comparing tumors of patients from 3 different areas within the island with variable amounts of arsenic exposure showed higher stage and grade tumors in those patients exposed to greater concentrations of arsenic in drinking-water (>350 μg/l) [16]. Accordingly, patients bearing such unfavorable tumor phenotypes showed a reduced cancer-specific survival. These findings were not explained by delayed diagnosis or poor access to medical care, and strongly suggested the existence of a higher malignant potential in arsenic-related BC. Recently, the same research team extended their analysis using a nationwide database, obtaining similar results [17]. However, cohorts analyzed were in nearby regions stratified by a census register, thus not necessarily reflecting the actual place of historical residency. Moreover, there was no comparison to a nonexposed control group, since arsenic contamination is present in drinking water throughout the entire island in amounts over the World Health Organization (WHO) recommendation (10 μg/l). Since, beyond arsenic exposure, little is known about further environmental and clinical factors related to BC in affected individuals living in these regions, the aim of our study was to assess and compare clinicopathological characteristics of these arsenic-exposed patients with those of 2 nonexposed groups from Santiago.

2. Material and methods

2.1. Patients and data

The study included data of 285 patients with urothelial BC, treated at 3 different referral centers in Chile between 2014 and 2016, including the Hospital Regional in Antofagasta (arsenic-exposed area) as well as Hospital Padre Hurtado and Clínica Alemana in Santiago (no arsenic contamination in drinking water). The study was approved by the involved institutional review boards and research committees (Comité Ético Científico, Facultad de Medicina, Clínica Alemana Universidad del Desarrollo 2011-20 and 2018-20; Hospital Regional de Antofagasta 2011-1571 and Comité Ético Científico, Servicio de Salud Metropolitano Sur Oriente 2018-2339) and conforms to the provisions of the Declaration of Helsinki of 1995. Information about demographics and environmental risk factors (age, sex, family history of BC, occupation history, tobacco smoking, amount of years living in the region with elevated arsenic levels in drinking water between 1958 and 1970) were obtained through personal interviews. Water consumption habits were not included in the questionnaire.

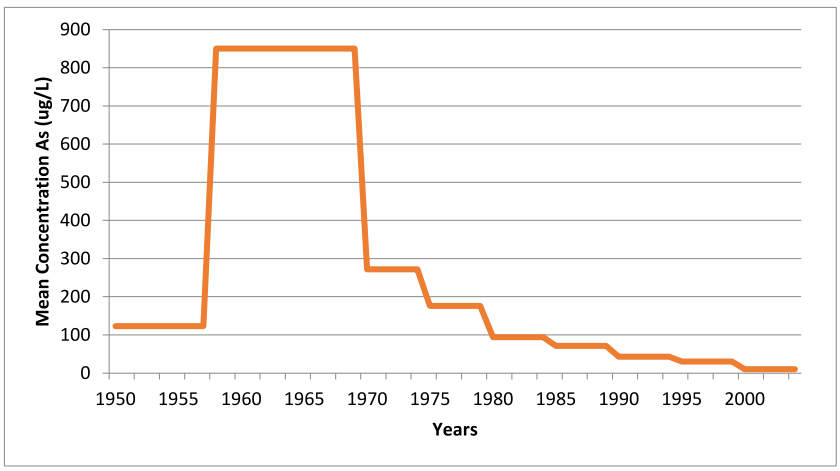

Fig. 1. Mean arsenic concentrations in the city of Antofagasta during the last decades.

Clinicopathological information (tumor stage and grade) was retrieved from medical records. Tumor grade and stage were classified according to the 2004 WHO Classification [18] and the 2009 TNM Staging System [19], respectively. All patients were staged with a Thorax-Abdomen-Pelvis computed tomography. Patients presenting with pure carcinoma in situ were excluded. Smoking status was assigned according to current or former activity.

2.2. Arsenic exposure in Northern Chile

Climatologic conditions in Northern Chile, especially in the city of Antofagasta, which is located 675 miles north of Santiago (Fig. 2), are extremely arid. Accordingly, water is scarce and only few large sources of drinking water have been functional during the last decades. Consequently, arsenic concentrations have been accurately measured and recorded since the 1950s. This is highly relevant, since drinking water in most other foreign regions with high arsenic exposures is obtained from wells. The existence of high variabilities in concentrations from well to well is thus a significant source of bias, making assessment of impact of arsenic on human health challenging in these settings.

According to well documented information, arsenic concentrations in drinking-water in Antofagasta experimented an abrupt increase from 120 to 650−900 μg/l after the incorporation of the Toconce and Holajar rivers as the main water sources in 1958 (Fig. 1). Consequently, almost the entire population in Antofagasta was exposed to arsenic levels up to 17 times over the WHO recommendations until 1970, when the first water treatment plant began to operate. During the next decades, implementation of additional plants led to continuous reductions of arsenic concentrations in drinking water, reaching levels below 10 μg/l during the last years (Fig. 1).

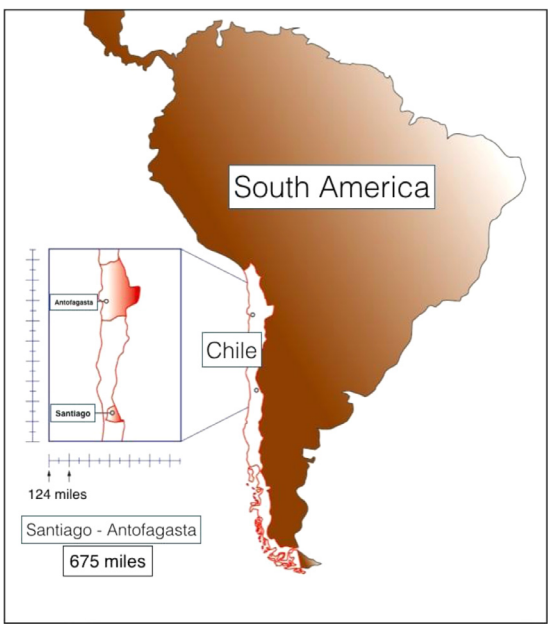

Fig. 2. Location of Antofagasta.

2.3. Demographic and socioeconomic characteristics of the 3-study sites

The state-owned Hospital Regional de Antofagasta is a regional referral center for all major health problems occurring in Northern Chile, with an assigned population of approximately 405,000. The cohort treated for BC at this center was defined as the arsenic-exposed group, while the control group consisted of 2 different cohorts of patients treated in Santiago, with no exposure to arsenic during lifetime (according to explicit question about eventual residence in Antofagasta). This was to account for potential biases related to the existence of different demographic indicators according to the type of healthcare system (public or private) for patients treated in Santiago [20] (Table 1). In terms of demographic and socioeconomic situation, the population in Antofagasta is similar to that assigned to the Hospital Padre Hurtado, a state-owned hospital in Southern Santiago, namely low and middle socioeconomic status. In contrast, Clínica Alemana is a private hospital in a wealthy neighborhood in Northeastern Santiago, serving approximately 285,000 inhabitants of this area with comparatively better socioeconomic and health indicators. Detailed information on demographic and socioeconomic parameters of the 3 studied populations is listed in Table 1.

2.4. Statistical analyses

Statistics analyses were performed using SPSS 22.0 for Windows (SPSS Inc., Chicago, IL). Contingency tables were constructed, and data were compared by chi-square test. The ANOVA test was used to compare means between groups. All statistics tests were 2-tailed and $P < 0.05$ was considered statistically significant. Univariate logistic regression analysis was performed to test association of demographic, socioeconomic, and clinical variables with the presence of high grade in any T Stage (reference group low-grade tumors), muscle-invasive disease (T2-4; reference group Ta-T1) and locally advanced disease (T3-4; reference group Ta-T1-T2). Statistically significant, biologically important variables and potential confounders were then entered in a logistic regression model to identify independent predictors of the different outcomes. The results of the multivariable analysis are reported as adjusted odds ratios with a 95% CI.

3. Results

All patients from Antofagasta ($n = 83$; 29.1%) had well-defined periods of arsenic exposure during their lives within the period of 1958 to 1970, while 202 controls from Santiago had no history of exposure to arsenic. Of the latter, 57 (20.0%) were recruited from Hospital Padre Hurtado and

Table 1
Demographic and socioeconomic characteristics of the 3-study sites

	Hospital regional, Antofagasta (exposed)	Hospital Padre Hurtado, Santiago (nonexposed)	Clínica Alemana, Santiago (nonexposed)	Chile
Healthcare system	Public	Public	Private	–
District	Antofagasta	San Ramón	Vitacura	–
Demographic indicators				
Assigned population	405,000	395,000	285,000[a]	–
Male population (%)	52.1	49.5	43.5	49.5
≥60 years (%)	11.6	15.0	18.9	14.1
Socioeconomic indicators				
Monthly income per household [median (IQR); US$]	1,208 (674–1,969)	923 (538–1,418)	4,465 (1,538–8,118)	888 (482–1,544)
Education (mean; years)	11.8	9.1	16.2	10.8
Health indicators				
Life expectancy at birth (male)	72.1	73.3	81.5	75.2
Life expectancy at birth (female)	79.1	81.2	84.6	82.2

Source: Encuesta Caracterización Socioeconómica Nacional, 2015.
[a] Private hospitals like Clínica Alemana do not have assigned populations. This population is an estimate according to monthly income per household (highest quintile, which is required to afford medical attention in this center) in the 3 closest city districts (Vitacura, Lo Barnechea, and Las Condes)

145 (50.9%) from Clínica Alemana. There were no significant differences between the 3 groups regarding age at presentation (66.4 vs. 66.5 and 67.2 years; $P = 0.69$, for exposed vs. 2 nonexposed groups, respectively) and female gender (28.9% vs. 29.8 and 26.2%; $P = 0.85$) (Table 2). Tobacco smoking prevalence was significantly higher in individuals from Santiago, especially for current smokers (10.7% in Antofagasta vs. 38.6 and 26.9% in Santiago; $P < 0.001$). A significantly higher proportion of locally advanced (10.8 vs. 1.8 and 0.7% T3/4 tumors; $P = 0.002$) and high-grade tumors (79.5% vs. 63.2 and 64.1%; $P = 0.001$) was observed in arsenic-exposed patients (Table 2).

Table 2
Demographic, environmental, and clinical characteristics of BC cases

Variable	Hospital Antofagasta (exposed) *n* (%)	Hospital Padre Hurtado (nonexposed) *n* (%)	Clínica Alemana (nonexposed) n (%)	*P* value
Total	83	57	145	
Age, mean (SD)	66.4 (9.9)	66.5 (10.6)	67.2 (13.6)	0.69
Gender				
Male	69 (71.1)	40 (70.2)	107 (73.8)	0.84
Female	24 (28.9)	17 (29.8)	38 (26.2)	
Family history of BC				
No	70 (84.3)	51 (89.5)	142 (97.9)	**<0.001**
Yes	12 (14.5)	4 (7.0)	3 (2.1)	
Unknown	1 (1.2)	2 (3.5)	0	
Smoking status				
Never smoker	34 (41.0)	13 (22.8)	20 (13.8)	**<0.001**
Former smoker	40 (48.3)	20 (35.1)	74 (51.0)	
Current smoker	9 (10.7)	22 (38.6)	39 (26.9)	
Unknown	0	2 (3.5)	12 (8.3)	
T Stage				
Ta–T1	53 (63.9)	45 (78.9)	118 (81.4)	**0.002**
T2	14 (16.9)	10 (17.5)	25 (17.2)	
T3–T4	9 (10.8)	1 (1.8)	1 (0.7)	
Unknown	7 (8.4)	1 (1.8)	1 (0.7)	
Tumoral grade				
Low	10 (12.0)	21 (36.8)	52 (35.9)	**0.001**
High	66 (79.5)	36 (63.2)	93 (64.1)	
Unknown	7 (8.4)	0	0	

Bold values mean statistically significant

On univariate analysis, a low or middle socioeconomic status (OR 1.84, 95%CI [1.09−3.11]) and arsenic exposure (OR 3.74, 95%CI [1.81−7.71]) were statistically significant risk factors for the presence of high-grade tumor in the pathological specimen. On multivariable analysis, only arsenic exposure (adjusted OR: 5.10; 95%CI: 2.03−12.77) remained statistically significant (Table 3a). Meanwhile, there was no significant association with the presence of muscle-invasive disease (T2-T4) on multivariable analysis (Table 3b). The latter was not performed on locally advanced disease (T3-T4) because of the low number of events ($N = 11$).

4. Discussion

In the present study, which extends on our previous report [12] showing high cancer-specific mortality rates in arsenic-related BC, we were able to identify relevant differences in demographic and clinicopathological characteristics of BC patients in this arsenic-exposed region as compared with 2 reference, nonexposed sites within the country. Arsenic exposure in BC patients was also associated with a significantly lower tobacco smoking prevalence, especially at the time of diagnosis, despite a similar prevalence when considering general population (30.5% in Antofagasta and 35.0% in Santiago in 2016) [21]. Interestingly, arsenic exposure was an independent predictor of the occurrence of high-grade tumors and was also significantly associated to locally advanced disease.

Our finding of more aggressive types of BC in cases related to arsenic are similar to previous reports from Taiwan, although differences in healthcare, registration, and reproducibility of tumor grading have to be considered. Chen et al. compared patients from 3 geographical areas with different levels of arsenic in drinking water. A significantly higher proportion of high-grade tumors was observed in patients exposed to arsenic levels >350 μl/l, especially in endemic blackfoot disease areas [16]. A further study by the same group based on analysis of a nationwide database confirmed these findings. Interestingly, the proportion of high-grade tumors in cases exposed to >350 μl/l was similar to our exposed cohort (80.9 and 79.5%, respectively). This aggressive phenotype differs from data derived from large, BC population-based studies, reporting only up to 51% of high-grade carcinoma according to WHO 2004 Classification criteria [22,23].

Several studies have looked at different features potentially involved in carcinogenesis of arsenic-related BC. Ingested inorganic arsenic is metabolized through methylation by a detoxification pathway. Arsenic methylation capability can be assessed according to levels of arsenic metabolites in urine, including arsenite, arsenate, monomethylarsonic acid and dimethylarsinic acid, which are reliable markers for cumulative arsenic exposure [24]. Recent studies have shown that polymorphisms of related metabolic enzymes (*CYP1A1*, *SULT1A1*, *EPHX1*, *GSTT1*, and *GSTM1*) affect BC incidence. Hence, Chung *et al*. reported a significant association of a *GSTM1* wild/null polymorphism

Table 3a
Univariate and multivariable logistic regression analysis for presence of high tumoral grade in pathological specimen

		Univariate analysis			Multivariable logistic regression		
Variable	N	OR	95% CI	*P* value	OR	95% CI	*P* value
Age	278	1.02	0.99−1.04	0.21	1.02	0.99−1.05	0.13
Female gender	278	1.24	0.68−2.24	0.48	1.21	0.64−2.29	0.56
Family history of BC	277	2.49	0.76−8.19	0.13	1.78	0.54−5.91	0.34
Ever smoker	264	0.99	0.53−1.82	0.96	1.54	0.74−3.18	0.25
Current smoker	264	0.83	0.46−1.51	0.55	1.12	0.57−2.20	0.74
Low or middle socioeconomic status	278	1.84	1.09−3.11	**0.023**	0.97	0.49−1.91	0.92
Arsenic exposure	278	3.74	1.81−7.71	**<0.001**	5.10	2.03−12.77	**0.001**

Table 3b
Univariate and multivariable logistic regression analysis for presence of muscle-invasive disease in pathological specimen

		Univariate analysis			Multivariable logistic regression		
Variable	*N*	OR	95% CI	*P* value	OR	95% CI	*P* value
Age	276	0.99	0.97−1.02	0.63	0.99	0.97−1.02	0.64
Female gender	276	1.22	0.65−2.30	0.53	1.42	0.72−2.81	0.31
Family history of BC	275	1.05	0.41−2.71	0.92	0.83	0.31−2.26	0.72
Ever smoker	262	1.28	0.63−2.59	0.50	0.91	0.43−1.92	0.80
Current smoker	262	0.41	0.18−0.91	**0.03**	0.56	0.22−1.43	0.23
Low or middle socioeconomic status	276	1.58	0.89−2.80	0.12	1.21	0.52−2.87	0.66
Arsenic exposure	278	1.91	1.04−3.50	**0.036**	1.85	0.67−3.95	0.28

with an increased BC risk, in addition to an apparent gene −environment interaction with arsenic exposure and also with cigarette smoking [25]. Further, polymorphisms in the gene coding arsenic (+3) methyltransferase (*AS3MT*) were recently associated with the profile of arsenic metabolites in urine and with risk of BC and lung cancer in an exposed cohort from Northern Chile [26]. A relationship between tobacco and arsenic as environmental risk factors had previously been suggested by the same group based on a large case-control study from the same geographical area, reporting BC odds ratios of up to 23 (95%CI 8.2−66) among smokers exposed to arsenic [27]. Therefore, tobacco smoking, the best known risk factor for BC that accounts for up to 52% of cases [28], may share common mechanisms with arsenic induced carcinogenesis through the involvement of the same enzymes needed to catalyze the metabolism of cigarette smoke. Although the exact mechanisms of this synergism are unknown to date, it appeared that arsenic exposure was more relevant for disease risk in the mentioned report by Ferreccio et al. [27]. This is in line with the lower smoking prevalence within cases in Antofagasta observed in the present study. Moreover, smoking history has not been shown to be an independent prognostic factor for survival in patients with arsenic-related BC [16]. Additional variants in genes related to DNA repair, 1 carbon metabolism, and metal transport, have been associated with BC risk in arsenic exposed populations in isolated studies, and thus await further validation [29−31].

Similar to our findings with arsenic-related BC, several studies have shown that duration and quantity of another environmental risk factor, namely tobacco smoking, are associated with the presence of a higher tumor stage and grade in patients with newly diagnosed BC. A recent hospital-based, multicentric study on 1,544 patients reported that current smokers had larger tumors (mean difference: 0.48cm, 95%CI: 0.04−0.91), a higher T stage (mean difference: 0.25, 95%CI: 0.08−0.41), and a borderline significantly higher grade than never smokers (mean difference: 0.15, 95%CI: 0−0.30) [32]. On the other hand, a meta-analysis including 24 studies showed a higher risk for local recurrence in nonmuscle invasive BC (HR 1.27, 95%CI: 1.09−1.46) and for cancer-specific mortality in muscle invasive BC (HR 1.23, 95%CI: 1.02−1.44) for current smokers. In summary, the continuous effect of carcinogens may lead to cumulative molecular damage promoting disease progression. However, a detailed review of molecular pathways of BC is beyond the scope of this article and further studies should assess this phenomenon.

Mining is an important occupation in Antofagasta and individuals involved in this activity might be exposed to arsenic exposure by inhalation. However, the main form of human exposure to arsenic is oral intake (drinking-water and food). Indeed, a previous study showed that in Antofagasta, contribution of drinking-water to total intake of arsenic sums up to 82%, compared to only 17% for food and 1.5% for air [33]. We considered therefore that inhalation is not relevant as a source of arsenic-exposure. In fact, occupation was not relevant when compared to controls in our own case-control study in Antofagasta (data not shown). Therefore, it was not included as a variable in the analysis of the present project.

Our study bears some potential limitations. Hence, arsenic-exposure and smoking information were collected retrospectively. However, they were assessed in similar manners for all groups, therefore reducing the chance of differential misclassification. Meanwhile, water consumption habits were not included in the questionnaire and dose- and time-effect exposures to arsenic were therefore not assessed. In addition, since this was a hospital-based study, selection bias cannot be ruled out. To counter this, we included 2 different populations from Santiago as controls, accounting for potential differences in terms of socioeconomic conditions, which may be relevant for access and awareness to medical attention. However, differences in diagnostic delays may be possible. Concerning clinicopathological characteristics, no central pathology review was performed. Finally, survival outcomes were not included in the analysis because of potential differences between and within hospitals regarding disease management. This is due to the absence of uniform clinical guidelines and because of economic and structural issues.

5. Conclusions

Patients with arsenic-related BC presented relevant clinical differences in terms of tumor features as compared to patients without exposure. The more aggressive phenotype associated to arsenic-related BC should be considered when designing efficient screening strategies for this high-risk population.

Conflict of interest

All authors have seen and approved the manuscript being submitted and have no conflict of interest to declare.

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