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Clinical-Bladder cancer

Arsenic exposure is associated with significant upper tract urothelial carcinoma health care needs and elevated mortality rates

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Abstract

Purpose: The aim of the study was to assess upper tract urothelial carcinoma (UTUC) health care needs and specific mortality rates in an arsenic-exposed region in Northern Chile and compare them to those of the rest of the country.

Material and methods: Arsenic levels of drinking water were correlated with UTUC hospital discharges and cancer-specific mortality rates. Mortality and hospital admission rate ratios were estimated using a Poisson regression model.

Results: There were 257 UTUC-specific deaths in Chile between 1990 and 2016; 81 (34%) of them occurred in Antofagasta, where only 3.5% of the population lives. The peak mortality rate observed in Antofagasta was 2.15/100,000 compared to 0.07/100,000 in the rest of the country. Mortality in the exposed region was significantly higher when compared to the rest of the country (MRR 17.6; 95%CI: 13.5−22.9). The same trend was observed for UTUC hospital discharges (RR 14.8; 95%CI: 11.5−19.1).

Conclusion: Even stronger than for bladder cancer, exposure to arsenic is related to a significant need for UTUC health care and high mortality rates, even 25 years after having controlled arsenic levels in drinking-water. Awareness of this ecologic factor in these affected regions is therefore mandatory. © 2020 Elsevier Inc. All rights reserved.

Keywords: Arsenic; Urologic neoplasms; Carcinoma, transitional cell; Mortality; Health services needs and demand

1. Introduction

The most common primary site for urothelial carcinoma (UC) is the urinary bladder. Nonetheless, around 5% of incident cases originate in the renal pelvis or ureter [1]. Although bladder cancer (BC) and upper tract urothelial cancer (UTUC) have a common histological origin and share several characteristics, they behave like different diseases. Probably, the most important clinical difference is that UTUC tends to have higher grade and stage at diagnosis, translating in worse survival. It has been suggested that wall thickness, which is dependent on anatomical location, may be a relevant factor accounting for these differences [2]. Furthermore, recent genetic studies have suggested that UTUC and BC exhibit significant differences in the prevalence of common genomic alterations, which could explain their distinct clinical behavior and play a role in the impact of different risk factors [3].

Arsenic is a metalloid that is considered carcinogenic to humans by the International Agency for Research on Cancer and over 140 million people have been exposed to arsenic worldwide [4]. Its exposure has been related to lung, bladder, kidney, skin, liver, and prostate cancer; as well as several other benign conditions such as skin lesions, nervous system disorders, respiratory diseases, anemia, cardiovascular diseases, myocardial infarction, and infant mortality [5−8]. Humans may be exposed to arsenic by intake (water and food) or inhalation. However, drinking water is the most relevant form of exposure for the general population [9].

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Association of arsenic in drinking water and UC has been reported in multiple ecological and case-control studies worldwide, especially in large areas of Bangladesh [10], China, India, and smaller areas of Argentina [6,11], Australia, Mexico, Taiwan [12−14], USA, Vietnam and Northern Chile [15−20]. Most of these epidemiological reports have focused on BC while only few studies have addressed the relation of arsenic exposure and UTUC. However, a clear association with higher UTUC mortality rates has not been reported so far [14,17,21]. The aim of our study was to asses UTUC mortality rates and healthcare needs in a specific, arsenic-exposed, region in Northern Chile, and to compare them with the same outcomes of the rest of the country.

2. Material and methods

Using vital statistics records, deaths due to UTUC and BC were obtained, listing cases in the region of interest (Antofagasta) and the rest of Chile. These data are systematically collected on death certificates and processed by the National Institute of Statistics. The analysis included all deaths for the following codes of the International Classification of Diseases (ICD) ninth revision (ICD-9) between 1990 and 1996: 188 for malignant neoplasms of the bladder, 189.1 for malignant neoplasm of the renal pelvis, and 189.2 for malignant neoplasm of the ureter. Similarly, deaths between 1997 and 2016 under the following codes of the ICD-10 were included: C65 for malignant neoplasms of the renal pelvis, C66 for malignant neoplasms of the ureter, and C67 for malignant neoplasms of the bladder. Hospital discharges data were available from the Chilean Ministry of Health from 2001 to 2017 and codified according to the ICD-10 [22]. Population projections were obtained from the National Institute of Statistics according to national census data (1982, 1992, and 2002).

Cancer-specific, age-adjusted mortality rates were calculated for Antofagasta and the rest of Chile using the direct standardization method [23]. Mortality rate ratios (MRR) and trends in mortality rates were estimated using a Poisson regression model, with the response variable being the number of observed deaths in each age group for each year, comparing Antofagasta with the rest of the country [24]. MRR can be interpreted as the percentage of population-adjusted excess in Antofagasta when compared to the resto of the country. The 95% CIs for the MRR were calculated using an exact method. The same model was applied to hospital discharges data.

3. Results

There were 257 UTUC-specific deaths in Chile between 1990 and 2016; 81 (34%) of them occurred in Antofagasta, where only 3.5% of the Chilean population lives. The peak mortality rate in Antofagasta was 2.15/100,000 compared to 0.07/100,000 in the rest of the country. Observed deaths and rates for UTUC are summarized in Table 1. UTUC mortality rates were indeed significantly higher in Antofagasta than in the rest of Chile (Fig. 1), with an MRR of 17.6 (95%CI 13.5−22.9) for the period between 1990 and 2016. The trend was similar for BC, but with a lower MRR (5.5 [95%CI 5.2−5.9]). No significant time trend was observed throughout the analyzed period in Antofagasta or the rest of Chile. Interestingly, mean age at UTUC cancer-specific death was significantly lower in the exposed region (63.3 vs. 69.0 years; $P < 0.001$).

Hospital discharges for UTUC in Antofagasta were significantly higher when compared with those of the rest of Chile (Fig. 2 and Table 2), with a rate ratio of 14.8 (95%CI 11.5−19.1) between 2001 and 2017, with the highest hospital discharge rate in 2002 (2.13/100,000).

4. Discussion

Antofagasta is a desertic region located in Northern Chile (Fig. 3). Most of the population lives in urban areas (94%) and is not different from the rest of the country in terms of age and sex distribution. Around 14% declare themselves as native, however ethnicity is not specific to this administrative region since it is shared with adjacent regions of South America [25].

Table 1
Mortality due to UTUC (1990 to 2016)

Year	Chile (except Antofagasta)		Antofagasta	
	Deaths	Adjusted rate*	Deaths	Adjusted rate*
1990	4	0.03	4	1.46
1991	2	0.02	0	0.00
1992	5	0.04	3	1.15
1993	3	0.02	6	2.15
1994	9	0.07	2	0.60
1995	7	0.05	1	0.30
1996	4	0.03	1	0.40
1997	4	0.03	1	0.23
1998	8	0.06	3	0.75
1999	7	0.05	5	1.65
2000	4	0.02	4	1.14
2001	6	0.04	3	0.70
2002	5	0.03	2	0.57
2003	7	0.04	1	0.20
2004	3	0.02	3	0.79
2005	8	0.04	1	0.22
2006	10	0.05	2	0.40
2007	10	0.05	3	0.63
2008	6	0.03	3	0.63
2009	5	0.02	1	0.15
2010	0	0.00	7	1.51
2011	7	0.03	7	1.39
2012	9	0.04	2	0.43
2013	17	0.07	5	1.09
2014	11	0.05	3	0.67
2015	6	0.03	3	0.45
2016	9	0.04	5	0.71

* Rates per 100,000 habitants.

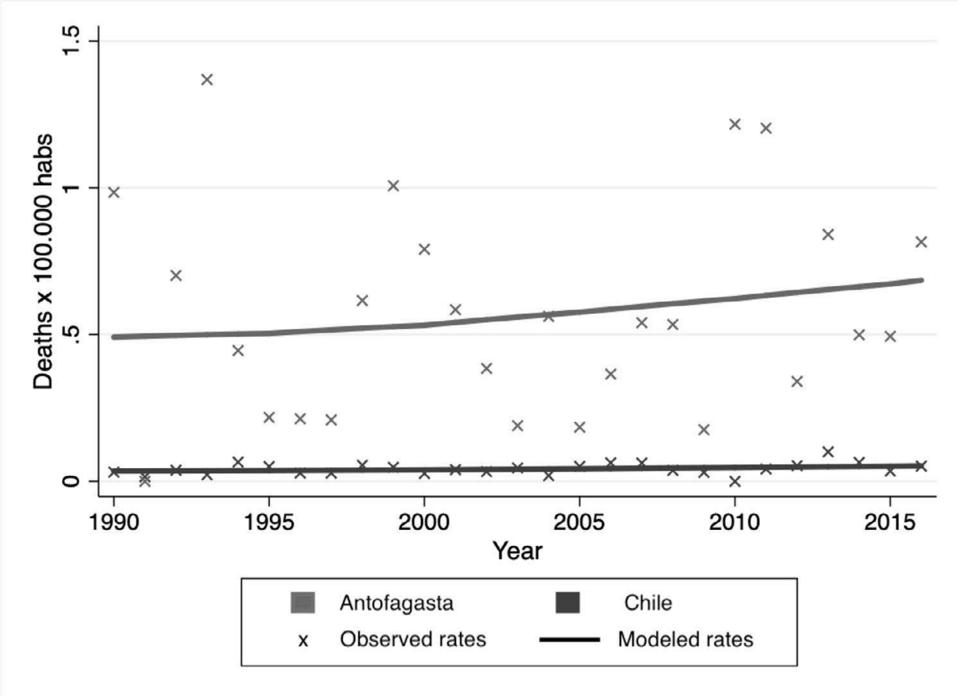

Fig. 1. Modelled and observed mortality rates due to UTUC in Antofagasta and the rest of Chile (1990 to 2016).

With one of the most arid climates worldwide and very limited sources of water supply, Antofagasta is one of the most well-known arsenic-exposed regions. Arsenic concentration in drinking water has been well documented in this region, since it has been thoroughly measured and recorded since the 1950s. After the incorporation of the Toconce and Holajar rivers as drinking water sources in 1958, mean arsenic concentrations rose from 90 to up to 870 μg/l, exposing the whole population to arsenic levels up to 17 times the WHO recommendation. It was not until 1971, when the first water treatment plants were installed, that arsenic concentrations began to drop [19]. Further installation of treatment plants and the implementation of new technologies led to progressive decreases in arsenic

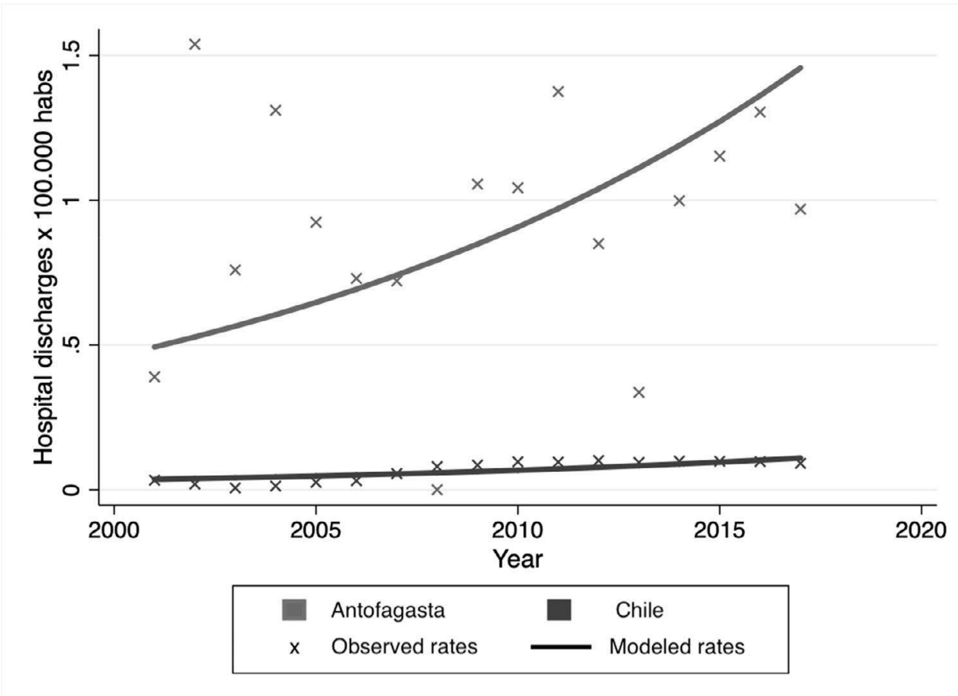

Fig. 2. Modelled and observed hospital discharge rates due to UTUC in Antofagasta and the rest of Chile (2001 to 2017).

Table 2
Hospital discharges due to UTUC (2000 to 2017).

Year	Chile (except Antofagasta)		Antofagasta	
	Discharges	Adjusted rate*	Discharges	Adjusted rate*
2001	12	0.08	2	0.52
2002	11	0.07	8	2.13
2003	13	0.08	4	0.92
2004	10	0.06	7	1.89
2005	11	0.06	5	1.15
2006	11	0.06	4	1.19
2007	12	0.07	4	0.99
2008	5	0.02	0	0.00
2009	12	0.06	6	1.20
2010	10	0.05	6	1.19
2011	12	0.06	8	1.63
2012	11	0.05	5	0.93
2013	11	0.05	2	0.30
2014	12	0.06	6	1.19
2015	12	0.06	7	1.02
2016	12	0.06	8	1.13
2017	11	0.05	6	0.84

* Rates per 100,000 habitants.

Fig. 3. Map of Chile. Adapted from NordNordWest (2018) Chile administrative divisions. Retrieved January 12, 2020 (https://commons.wikimedia.org/wiki/File:Chile,_administrative_divisions_-_en_-_colored_2018.svg).

concentrations, which reached levels of <10 μg/l in recent years (Fig. 4). Therefore, everyone living in Antofagasta during this period was exposed to very well-known arsenic concentrations from a single source, creating a very special scenario. This is in contrast with most of the other affected regions worldwide, where sources of drinking water are artisan or private wells. Obtaining reliable arsenic concentrations from them is a difficult task as a consequence of the high variability in concentrations among wells which, in addition, are usually present in a large number. Moreover, arsenic concentration in drinking water was much higher in Antofagasta than in most of these other regions (mean concentration 570 μ/l vs. 50−178 μ/l) [4].

Our results support previous reports suggesting significantly high UTUC cancer-specific mortality rates in arsenic exposed regions [14,17,21]. Furthermore, we found that the effect of exposure to arsenic in drinking water is greater for UTUC than BC, with an MRR over 3 times higher. This difference on the magnitude of increase in mortality can be explained at an epidemiological and biological level. Firstly, although incidence is increased by arsenic exposure in both diseases, UTUC is less common and usually more aggressive due to higher stage at diagnosis and therefore more lethal. In contrast, BC is more common and frequently diagnosed at earlier stages, leading to better chances of survival. From a biological perspective, several genetic and molecular expression differences in the carcinogenic process have been previously identified. The latter might drive a more aggressive course of the disease [26]. Similarly, there might be even differences in arsenic metabolism between UTUC and BC. However, evidence is limited to a single exposed population [27].

Mortality due to BC in Antofagasta increased dramatically in the 1970s, nearly 10 years after beginning of exposure [18]. However, at present day, and more than 25 years after exposure ceased due to implementation of water treatment plants, UTUC and BC mortality rates are still significantly high. Similar to other UC risk factors, arsenic has a long latency pattern with long-term impact over health care and mortality. This scenario of a population at high risk for a long period of time is the ideal setting for the implementation of early detection and surveillance strategies. In fact, the threefold difference for UTUC hospital discharge rates between Antofagasta and the rest of the country is an example of the impact on arsenic exposure has had on UTUC healthcare. Since healthcare systems in Antofagasta are the same as in the rest of the country, the existence of bias regarding decreased treatment opportunities leading toward increased mortality or lower recognition of the disease is unlikely for the studied period. Moreover,

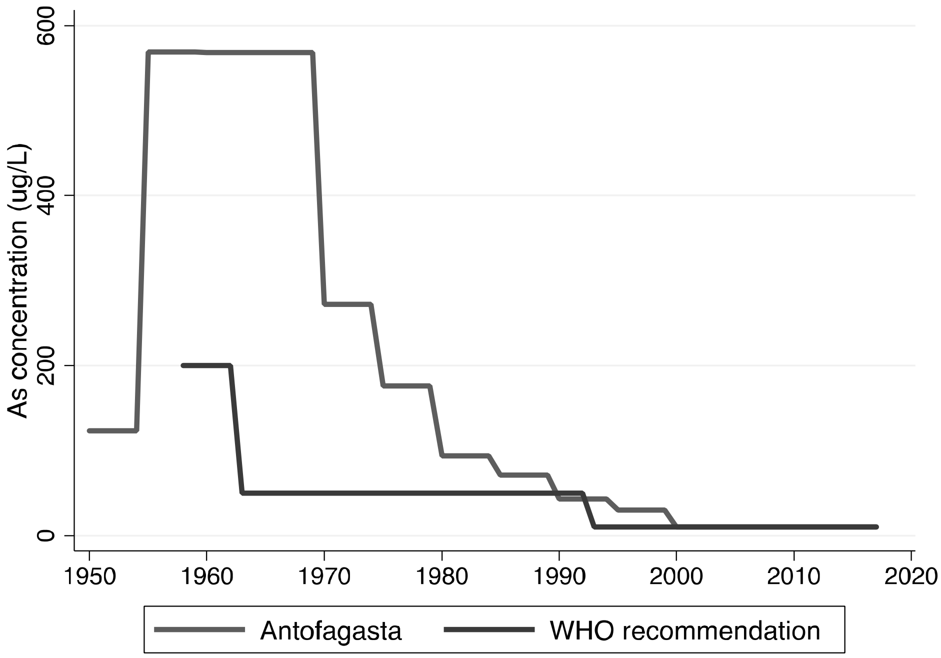

Fig. 4. Mean Arsenic concentration in drinking water in Antofagasta and WHO recommendation (1950 to 2017). Adapted from Fernández et al. The Journal of Urology (2012) 187: 856-861.

not until recently, specific actions have been taken to make physicians aware of this problem and improve access to treatment. Although exposure ceased decades ago, it is still uncertain if effects will disappear. Moreover, it is also not clear which individuals bear a higher risk of occurrence. A birth-cohort analysis would be useful to address this issue. However, since UTUC and BC are more common after the seventh decade of life, we might need to wait several years to answer this question.

Most publications assessing arsenic-related diseases have included renal cell carcinoma (RCC) and UTUC in the same category. In fact, only a single study has evaluated these cancers separately in relation to arsenic exposure. In this case control-study conducted in Antofagasta by Ferreccio et al. [17], UTUC and RCC incidence from a 3 year period (2007−2010) were considered. A causal, dose-dependent relation between arsenic and UTUC incidence was observed. Our findings support that this relation might also be true for UTUC mortality.

Although confounding factors are an important limitation in ecological studies and causality cannot be claimed, the described scenario has special conditions that restrain their importance and favor their evaluation, by the reduction of inherent biases of these types of studies. Firstly, as described previously, the whole population was exposed to arsenic. Here, it has to be considered that internal migration rates in Chile and especially in Antofagasta are extremely low and remained stable during the studied period [28]. Secondly, the time lapse of exposure was very clear and the chance that further risk factors would have risen or fallen at the same time that arsenic did is unlikely. Thirdly, the magnitude of MMR is high and hardly explained by other known risk factors. Lastly, there is strong evidence from previous studies and national surveys, that tobacco smoking has not been a confounding factor in this region [16,18,29,30]. In Taiwan, reports have linked Chinese herbs nephropathies to UC, which, similar to Balkan endemic nephropathies, are related to ingestion of aristolochic acid [31]. This exposure is not a plausible cause for UC in Antofagasta, because the harsh arid conditions do not allow any crops nor wildlife to grow in the region. Therefore, every vegetable is brought from elsewhere within the country. Furthermore, there are no reports of aristolochic acid exposure in Chile.

Mortality data were obtained from the vital statistics register kept by the Chilean Ministry of Health and the National Institute of Statistics. These databases are easily available and suitable to assess long-term outcomes in populations, although they are not generated for research or quality assessment purposes. Chilean mortality data for the period included in this study have been considered of high quality by the World Health Organization standards, considering its completeness, usability, and continuity on reporting [32]. Moreover, a particular strength is that the methodology used in mortality registries has been uniform throughout the country for the last 50 years [33]. Therefore, quality of demographic data in Chile is good, allowing accurate population estimates.

Some relevant issues regarding mortality coding have to be addressed. From 1990 to 1996, the ICD-9 was used, in which category “189 malignant neoplasms of the kidney” included renal pelvis (189.1) and ureter neoplasms (189.2) as subcategories. Thus, publications assessing arsenic related kidney cancer mortality in that period considered in the same group dissimilar diseases like RCC and UTUC, reporting rate ratios for "kidney cancer" mortality between 1.1 and 58.0, depending on the amount of arsenic exposure [34]. By 1997 ICD-10 became the standard, recognizing RCC and UTUC as different entities, assigning to each one a different category code. This improvement in coding diminished misclassification and inaccurate reporting. As noted, when analyzing the 1990−1996 period, we might have introduced a selection bias by using subcategories of the coding which are more specific and therefore more sensible to misclassification [35]. In order to asses this bias, we analyzed separately UTUC data coded by ICD-9 (1990−1996) and ICD-10 (1997−2016), obtaining MRRs of 19.1 (IC 95% 10.6−34.2) and 17.3 (IC 95% 12.9−23.2), respectively. The similarity of these ratios suggests that ICD-9 subcategory codes for UTUC are accurate. Moreover, the higher MRR in the 1990 to 1996 period when compared to the following years is in accordance with a decaying effect of arsenic after exposure ceased.

Upper tract UC is an uncommon type of cancer. As a consequence, a small absolute number of specific deaths occurred during the studied period. Although this generates important variability when looking at yearly rates, the selected statistical approach was useful to asses this heterogeneity and find a significant difference between the exposed region and the rest of the country.

We acknowledge that it would have been helpful to provide incidence data for a better understanding of UTUC epidemiology. Regretfully, cancer registries were implemented recently in Chile and there are no previous data about cancer incidence. Specifically, Antofagasta's cancer registry was only started in 2003, and no specific information about UTUC has been released since.

5. Conclusions

Even stronger than for BC, exposure to arsenic is clearly related to a significant need for UTUC health care and high mortality rates, even 25 years after having controlled arsenic levels in drinking water. Affected populations should be aware of the significant impact of this ecologic factor.

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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