

Paper Alert

Arsenic Induced Bladder Cancer

Edward M. Messing*

University of Rochester Medical Center, Rochester, NY, USA

Received 2 April 2020

Accepted 14 April 2020

Pre-press 8 May 2020

Published 11 June 2020

Bladder cancer (BC) is known to be a carcinogen induced malignancy with cigarette smoke, industrial chemicals and certain fungal exposures (e.g. *Aristolichia frangi*) being among the best appreciated carcinogens [1]. However, in several regions of the world, arsenic (As) exposure through drinking water (which of course also contaminates food), is a serious contributor to the development of BC [1]. Perhaps this has been best characterized in the southwestern region of Taiwan, where a vasculitis due to As ingestion from well water known as “black foot” disease, as well as urothelial cancer (UC) is prevalent [1, 2]. Other areas with As contamination and associated BC include regions of Bangladesh, Argentina and northern Chile [1, 3]. Indeed, many other locales including parts of North America and Scandinavia also have As contamination, but it is not to the extent of those mentioned [3]. The World Health Organization now recommends that As exposure be $<10\ \mu\text{g}/\text{l}$, although most studies and a large systematic review [3] concluded that only concentrations exceeding $50\ \mu\text{g}/\text{l}$ were convincingly associated with increased UC incidence, and in some reports, increased mortality.

It is with this background that a recent publication by Fernandez, et al., [4] sheds additional light on the impact of As exposure. Antofagasta is a city in northern Chile which experienced a drastic increase in As contamination with a change of sources of drinking water in the mid-1950s. Between 1957 and 1971 As contamination peaked, but with water treatment initiatives a fairly rapid decline occurred. As con-

centrations fell from $>850\ \mu\text{g}/\text{l}$ (for the 13+ years of peak exposure) to less than $50\ \mu\text{g}/\text{l}$ by 1990 and under $10\ \mu\text{g}/\text{l}$ by the early 2000’s [4].

The characteristics of new cases of bladder UC diagnosed between 2014–2016 at the state owned regional hospital in Antofagasta and two hospitals in Santiago, a low As region (one, a state owned hospital in southern Santiago with a population similar to that in Antofagasta, and the other, a private hospital in northern Santiago, with patients having a somewhat higher socioeconomic status), were included in the study. While central pathology review did not occur, specimens were handled similarly, and all subjects ($N=285$, 83 from Antofagasta and 202 from the two Santiago facilities), completed a similar questionnaire which included questions on demographics, socioeconomics, education, current and former tobacco smoking status, family history of BC and number of years living in Antofagasta during the period of peak exposure. Tumor characteristics, particularly grades and stages of BCs were then compared. Even though far fewer BC patients from Antofagasta had ever been cigarette smokers or were current smokers compared with those from the two Santiago cohorts, patients from the As exposed area had fewer low grade (12% vs 37% and 36% from the two Santiago hospitals, $p=0.001$), fewer stage Ta–T1 UCs (64% vs 79% and 81%) and more muscle invasive and more advanced (stage T2–T4) UCs (27.7% vs 19.3% and 18.5%, $p=0.002$).

On multivariable analysis only As exposure, not age, gender, family history, smoking history or socioeconomic status, correlated with high-grade histology ($p=0.001$), and on univariate analysis,

*Correspondence to: Edward M. Messing, MD, FACS, University of Rochester Medical Center, Rochester, NY, USA. Tel.: +1 585 275 3345; E-mail: Messing@urmc.rochester.edu.

As exposure again correlated with advanced tumor stage (T2–T4) ($p=0.036$). Owing to small numbers, As exposure did not correlate with stage on multivariable analysis ($p=0.28$). Because of potential differences in treatments between the facilities, overall and cause specific mortalities were not reported (or studied).

This study lends support to the concept that As exposure leads not only to a higher BC incidence but also more aggressive disease, as Chen et al reported in the exposed Taiwanese patients [2]. Indeed, the difference in high-grade disease was even greater in this Chilean study, perhaps because the controls in the Taiwanese study came from the remainder of the island [2], and still had exposure to elevated levels of As (up to 350 $\mu\text{g/l}$) [4].

There are limitations to this study including the authors not stating explicitly that all BC patients treated at the hospitals were included in the study, or whether all had been approached to take part and a similar proportion in each population agreed to. After all if a higher percentage of cases in the As exposed population had aggressive disease, this conclusion requires that we know how many cases were not included and why. Additionally, smoking and As exposure histories were obtained by questionnaire, and historical fluid consumption habits were not ascertained at all. However the three Chilean populations were relatively stable, and all cohorts completed the same questionnaire. Furthermore, the study did not use an objective personal measure of As exposure (e.g. As levels in hair or toenail clippings) [3], although it's not clear such measurements at the time of BC diagnosis would accurately reflect an exposure occurring several decades before (since even in Antofagasta, by 1990 water levels of As had been reduced markedly and continued to drop because of water treatment initiatives) [4].

Also, none of the known As metabolizing pathways which involve multiple methylations and other modifications, or polymorphisms of the enzymes involved in As detoxification were evaluated [3, 4]. Moreover, the authors did not report on some of the other medical problems that chronic As exposure can lead to, including severe vascular (peripheral, cardiac-and cerebral-vascular) diseases, diabetes, respiratory diseases, peripheral neuropathies, and a

variety of other malignancies (e.g. skin, lung, liver, kidney) (reviewed in Christoforidou) [3].

However, that the mean ages in the three Chilean groups were 66–67 years [4] and peak As exposure in the Antofagasta population ended 45 years before BC was diagnosed, indicates that As-induced urothelial carcinogenesis is an extremely complex process with a very long latency. Whether As is serving as an initiating agent, or a complete carcinogen is uncertain, but understanding what chemicals (including As itself at much lower concentrations) and other factors promote As-initiated bladder tumorigenesis, and modifying these exposures, would be critical in preventing development of BC in As exposed populations. Additionally, given the higher grade and stage of UC that exposed individuals have at diagnosis, some sort of early detection effort such as hematuria screening in As exposed individuals should be considered [5, 6].

CONFLICT OF INTEREST

The author has no conflict of interest to report.

REFERENCES

- [1] Messing EM. Urothelial Tumors of the Bladder in: Walsh PC, Vaughan Jr ED, Retik AB, Wein AJ, eds. Campbell's Urology. Ninth Edition. Philadelphia, PA. WB Saunders Co. 2007, 2407-2447.
- [2] Chen CH, Chiou HY, Hsueh YM, et al. Clinicopathological characteristics and survival outcome of arsenic related bladder cancer in Taiwan. *J Urol* 2009;181:547-53.
- [3] Christoforidou EP, Riza E, Kales SN, et al. Bladder cancer and arsenic through drinking water: A systematic review of epidemiologic evidence. *J Environ Science and Health, Part A* 2013;48:1764-75.
- [4] Fernandez MI, Valdebenito P, Delgado I, et al. Impact of arsenic exposure on clinicopathological characteristics of bladder cancer: A comparative study between patients from an arsenic-exposed region and nonexposed reference sites. *Urologic Oncology* 2020;38:40.e1-40.e7.
- [5] Messing EM, Young TB, Hunt VB, Gilchrist KW, Newton MA, Bram LL, Hisgen WJ, Greenberg EB, Kuglitsch ME, Wegenke JD. Comparison of bladder cancer outcome in men undergoing hematuria homescreening versus those with standard clinical presentations. *Urology* 1995;45:387-97.
- [6] Messing EMM, Madeb R, Young T, Gilchrist KW, Bram L, Greenberg EB, Wegenke JD, Stephenson L, Gee J, Feng C. Long-term Outcome of Hematuria Home Screening for Bladder Cancer in Men. *Cancer* 2006;107:2173-9.