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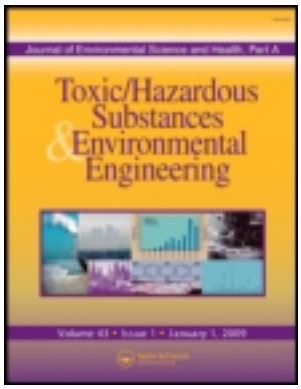

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Bladder cancer and arsenic through drinking water: A systematic review of epidemiologic evidence

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Bladder cancer and arsenic through drinking water: A systematic review of epidemiologic evidence

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Exposure to inorganic arsenic (As) through drinking water is a major international public health issue. We carried out a systematic review of the existing literature examining the association between the risk of bladder cancer in humans and exposure to arsenic through drinking water. We searched electronic databases for studies published from January 2000 up to April 2013. Eight ecological studies, six case-control studies, four cohort studies and two meta-analyses were identified. The vast majority of the studies were carried out in areas with high arsenic concentrations in drinking water such as southwestern and northeastern Taiwan, Pakistan, Bangladesh, Argentina (Cordoba Province), USA (southeastern Michigan, Florida, Idaho) and Chile. Most of the studies reported higher risks of bladder cancer incidence or mortality in areas with high arsenic concentrations in drinking water compared to the general population or a low arsenic exposed control group. The quality assessment showed that among the studies identified, arsenic exposure was assessed at the individual level only in half of them and only three assessed exposure using a biomarker. Further, five out of eight ecological studies presented results with adjustment for potential confounders except for age; all cohort and case-control studies presented results with adjustment for cigarette smoking status in the analysis. The majority of the studies with varying study designs carried out in different areas provided evidence of statistically siginificant increases in bladder cancer risk at high concentrations of arsenic (>50 μg L^{-1}). Assessing bladder cancer risk at lower exposure concentrations requires further investigation.

Keywords: Arsenic, bladder cancer, drinking water, mortality, morbidity.

Introduction

Inorganic arsenic (As) is a naturally occurring metallic element widely distributed in the earth's crust.[1] Arsenic occurs in drinking water through both natural and anthropogenic sources. It occurs naturally in rock, soil and sediment and these sources are particularly significant determinants of regional levels of arsenic in ground and surface water.[2] Arsenic is introduced into drinking-water sources primarily through the dissolution of naturally occurring minerals and ores.[3] Mining, smelting of non-ferrous metals and burning of fossil fuels are the major industrial processes that contribute to anthropogenic arsenic contamination of air, water and soil. Past use of arsenic-containing pesticides, herbicides, insecticides, defoliants, and soil biocides has led to agricultural land contamination.[2–4] The use of arsenic as a timber preservative and in livestock feed additives has also resulted in additional environmental contamination.[2–4] Arsenic has also been found in herbal medicine products[5,6] and in tobacco with an average concentration of about 1.5 μg per cigarette.[1]

The occurrence of arsenic in high concentrations in drinking water has been recognized, over the past 30 years, as a major public health concern in several areas worldwide.[7–9] Throughout the world, more than 100 million people are exposed through drinking water to arsenic at concentrations greater than 50 μg L^{-1},[10] levels considered to be harmful to human health. While exposure to such high concentrations is localized to specific regions[7] (Table 1), exposure to lower, but still potentially harmful, levels is even more widespread.[7,11] Argentina, Bangladesh, India, Pakistan, Mexico, Mongolia, Germany, Thailand, China, Chile, the United States, Canada, Hungary, Romania, Vietnam, Nepal, Myanmar and Cambodia are among the countries where arsenic exists in varying concentrations within groundwater.[7,12–14]

Setting regulations concerning arsenic concentrations in drinking water has been a controversial issue.[15] It has been

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Table 1. Regions of the world with naturally elevated levels of arsenic in groundwater.

Country/region	*Arsenic concentration ($\mu g\ L^{-1}$)*
Bangladesh	<0.5–2,500
India/West Bengal	<10–3,200
Viet Nam	
China/Taiwan	10–1,820
China/Xinjiang, Shanxi	40–750
Thailand	1–5,000
Mongolia/Inner Mongolia	<1–2,400
Argentina/Chaco-Pampean Plain	<1–7,550
Northern Chile/Antofagasta	100–1,000
Bolivia	
Mexico	8–620
Germany/Bavaria	<10–150
Hungary, Romania/Danube Basin	
Spain	<1–100
Greece	
Ghana	<1–175
Canada/Moira Lake, Ontario	50–3,000
Canada/British Columbia	0.5–580
USA/Arizona	<1,300
USA/California	<1–2,600
USA/Nevada	<2,600

Source: IARC.[7]

generally accepted that As concentrations $\geq$50 $\mu g\ L^{-1}$ in drinking water do not protect public health.[16] Even when the concentration in drinking water is reduced to 10 $\mu g\ L^{-1}$ according to the World Health Organization recommendation,[17] potential cancer risks remain.[18] World Health Organization Guidelines currently advise a concentration of 10 $\mu g\ L^{-1}$.[19] However, many developing countries still have their standards set at 50 $\mu g\ L^{-1}$. According to Council Directive 98/83/EC in the European Union (EU), the drinking water standard for arsenic is set at 10 $\mu g\ L^{-1}$.[20] In 2001, the government of USA reduced arsenic maximum contaminant level (MCL) from 50 to 10 $\mu g\ L^{-1}$. Table 2 shows elevated concentrations of arsenic in drinking water from arsenic endemic areas around the world and the respective current drinking water standards for arsenic in each country.[7,21]

Ingested arsenic exposures can occur due to industrial contamination, medicines or food. Worldwide, however, the most common mode of exposure is through consumption of groundwater containing naturally occurring arsenic. Acute effects caused by the ingestion of inorganic arsenic compounds are gastrointestinal damage, resulting in severe nausea, vomiting and diarrhea, muscular cramps and cardiac abnormalities. Shock can also develop rapidly as a result of dehydration.[7] Acute, high-dose exposure can lead to encephalopathy and peripheral neuropathy.[1] Chronic arsenic exposure through drinking water has been associated with Blackfoot disease, a severe form of peripheral vascular disease, hypertension,[22,23] cardiovascular disease, cerebrovascular disease,[24,25] diabetes

Table 2. Arsenic contaminations in groundwater and population at risk around the world.

Country/region	*Population at risk*	*Groundwater concentrations ($\mu g\ L^{-1}$)*	*Guidelines ($\mu g\ L^{-1}$)*
Argentina	2×10^6	100–1,000	50
Bangladesh	5×10^7	<1–4,700	50
Bolivia	2×10^4		50
Chile	4.37×10^5	900–1,040	50
China, Inner Mongolia	6×10^5	1–2,400	50
China, Xinjiang Province	1×10^5	1–8,000	50
Hungary	2.2×10^5	10–176	10
India, West Bengal	1×10^6	<10–3,900	50
Mexico	4×10^5	10–4,100	50
Nepal	Unknown	Up to 456	50
Peru	2.5×10^5	500	50
Romania	0.36×10^5	10–176	10
Taiwan	2×10^5	10–1,820	10
Thailand, Ronpibool	1×10^3	1–5,000	50
USA	Unknown	10–48,000	10
Vietnam	Millions	1–3,050	10
Canada			25
Australia			7
Laos			10
Brazil			50
Philippines and Indonesia			50
Sri Lanka and Zimbabwe			50
Bahrain, Egypt, Oman and Saudi Arabia			50
Jordan and Syria			10
Japan			10
European Union	Unknown		10

Source: Ng et al.,[21] IARC.[7]

mellitus, reproductive effects, respiratory disease and long-term neurological effects such as peripheral neuropathy.[1,4,7,18,26–29] Chronic exposure of humans to inorganic arsenic in the drinking water has been also associated with excess incidence of miscarriages, stillbirths, preterm births, as well as infants with low birth weights.[1] Long-term exposure to arsenic in drinking-water is causally related to increased risks of skin, lung, liver, prostate, urinary bladder and kidney cancer, as well as other skin changes such as hyperkeratosis and pigmentation changes.[4,7,18,26] Inorganic arsenic compounds in drinking water are classified by the International Agency for Research on Cancer (IARC) as a Group 1 carcinogen (carcinogenic to humans).[3,7,30]

Major epidemiological studies of cancer in respect to arsenic in drinking water include ecological studies and fewer case-control and cohort studies. Many systematic studies were conducted in various parts of the world (Taiwan, Japan, Argentina, Chile, Mexico, USA, Europe, Australia) regarding exposure to arsenic in drinking

water and increased risks of urinary bladder, kidney,[31–52] liver,[31–34,37,39–42,45,48–50,53] lung[31–34,37,39–42,45,46,48–50,53,54] and skin cancer.[7,31–34,36,37,39,40,45,55–66] Concerning bladder cancer specifically, in the past 13 years a series of epidemiological studies were conducted.[16,47,67–84]

Material and methods

Study search

We aimed to identify all studies assessing the association between exposure to arsenic through drinking water and bladder cancer. Using free text and key words (heavy metals, arsenic, drinking water, ingested water, potable water, water ingestion, cancer, mortality, cohort study, case-control study, ecological study), we searched the following search machines: PubMed (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=PubMed), the Cochrane Library (http://www.thecochranelibrary.com/view/0/index.html), and TOXLINE (http://toxnet.nlm.nih.gov/) through April 2013. In addition, we manually examined the reference lists from related original research and review articles or meta-analyses and documents (hand search). All studies that were published up to April 2013 were included as eligible for further evaluation.

Study selection

The following exclusion criteria were applied to the abstracts identified in the literature search: (1) no original data or new analysis (reviews, editorials); (2) studies not referring to the association between bladder cancer incidence and/or mortality and arsenic in drinking water; (3) studies not involving humans; (4) not in English language; (5) studies published before January 2000 and after April 2013 (6) studies that did not include measurements of arsenic in drinking water and (7) case series and case reports. We reviewed the full-text articles of all references selected using the same criteria. After the full-text review, references detailing observational studies (cohort, case-control studies), descriptive studies (ecological studies) and meta-analyses on the association between bladder cancer risk and arsenic exposure through drinking water were selected and examined so as to be included in this analysis. We included both negative and positive studies. If different reports from the same study were identified, the report with the most updated information was included. Furthermore, regarding duplicate publication, only one publication was included. Two reviewers evaluated the eligibility of every abstract or full-text article independently in a standardized manner. The study selection process is shown in Figure 1.

Data abstraction and quality assessment

In order to assess the study quality, the included studies were catergorized according to the quality criteria of Longnecker et al.[85] for observational studies (Table 3).

Results and discussion

Study selection

The search yielded 1,186 references (Fig. 1), of which 1,087 were excluded after abstract review as they did not address the association between arsenic in drinking water and cancer or they were case reports or case series or articles published before January 2000 and after April 2013, not in English language or with no full text available. Of the 99 articles obtained for full-text review, 74 pertained to arsenic exposure and cancer. We excluded 37 articles, as they were reviews, editorials and documents-reports. Five articles were also excluded as they only referred to arsenic exposure and another two because they didn't include measurements of arsenic in drinking water. An additional 32 studies were excluded because they referred to colon, prostate, kidney, liver, lung, skin, childhood cancer or cancer in general. One reference was excluded due to duplicate publication and 2 because they were survival studies. This left 18 original studies conducted in general populations and 2 meta-analyses (Fig. 1) that met our inclusion criteria.

Study characteristics

Ecological studies. Eight out of the 20 studies included in this analysis were ecological studies (Table 4). Of these, four were conducted in high arsenic areas of USA,[67,68,70,78] two in Taiwan,[16,84] one in Chile [71] and one in Argentina.[69] All studies included both male and female participants. Arsenic exposure was assessed either using grouped or ecologic measurements of drinking water concentrations (tap or artesian well). All studies except three, compared age standardized bladder mortality rates across geographic regions or through time. Han et al.[70] calculated age-adjusted incidence rate for cancers of the urinary bladder, kidney and renal pelvis, liver and bile duct, lung and bronchus, non-Hodgkin's lymphoma (NHL), and all malignant cancers. Nieder et al.[68] calculated bladder cancer Odds Ratio (OR) (95% Confidence Interval [CI]) based on distance from the well water arsenic exposure.[68] At last, Pou et al.[69] calculated bladder cancer age-standardized mortality rates concerning low, intermediate and high level of arsenic exposure (Table 4).

Cohort and case–control studies. Ten of the studies included in this analysis were cohort or case-control studies (Table 4). Of the six case-control studies, 3 were conducted in USA,[72,74,82] one in Argentina,[73] one in Finland [83] and one in Pakistan.[75] Of the four cohort studies, two were conducted in Taiwan,[47,76] one in Denmark [77] and one in Bangladesh.[79] All case-control studies had more than 100 cancer cases.[72–75,82] Four case-control studies assessed bladder cancer incidence among both males and females.[72–74,82] The study of Wadhwa et al.[75] compared As concentrations in whole blood and scalp hair samples

Table 3. Quality criteria[a] (meta-analyses excluded).

A. All studies:	*Lamm et al.*[67]	*Nieder et al.*[68]	*Yang et al.*[84]	*Pou et al.*[69]	*Morales et al.*[16]	*Yueh-Ying Han et al.*[70]	*Marshall et al.*[71]	*Meliker et al.*[78]	*Steinmaus et al.*[72]	*Bates et al.*[73]	*Meliker et al.*[74]	*Wadhwa et al.*[75]	*Karagas et al.*[82]	*Michaud et al.*[83]	*Chen et al.*[76]	*Chiou et al.*[47]	*Baastrup et al.*[77]	*Chen et al.*[79]
1. Exposure assessment at an individual level	No	Yes	No	No	No	No	No	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
2. Biomarker based exposure assessment	No	No	No	No	No	No	No	No	No	No	No	Yes	Yes	Yes	No	No	No	No
3. Results based on objective tests (histological confirmation) in >90% of the study subjects	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4. Internal comparisons within study participants	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
5. Control for other confounding risk factors (plus age)	No	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
B. Cohort studies:																		
1. Loss to follow-up independent of exposure	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Yes	Yes	Yes	Yes
2. Intensity of the disease search independent of exposure status	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Yes	Yes	Yes	Yes
C. Case–control studies:																		
1. Data collected in a similar way for all participants	NA	NA	NA	NA	NA	NA	NA	NA	Yes	Yes	No	Yes	No	Yes	NA	NA	NA	NA
2. The same exclusion criteria used to all participants	NA	NA	NA	NA	NA	NA	NA	NA	Yes	Yes	Yes	Yes	Yes	Yes	NA	NA	NA	NA
3. The same time period over which cases- controls were interviewed	NA	NA	NA	NA	NA	NA	NA	NA	Yes	Yes	Yes	Yes	Yes	Yes	NA	NA	NA	NA
4. Blinded interviewer with regard to the case status of the interviewed person	NA	NA	NA	NA	NA	NA	NA	NA	Yes	Yes	–	–	Yes	Yes	NA	NA	NA	NA
5. The response rate among controls at least 70%	NA	NA	NA	NA	NA	NA	NA	NA	Yes	Yes	No	Yes	Yes	Yes	NA	NA	NA	NA
6. All cases interviewed within 6 months of diagnosis	NA	NA	NA	NA	NA	NA	NA	NA	No	No	–	No	–	No	NA	NA	NA	NA
7. Study based on incident cases of disease	NA	NA	NA	NA	NA	NA	NA	NA	Yes	Yes	No	Yes	Yes	Yes	NA	NA	NA	NA
8. Controls who developed the disease became cases	NA	NA	NA	NA	NA	NA	NA	NA	No	No	No	No	No	No	NA	NA	NA	NA

[a]Adapted from Longnecker et al.[85]
NA: not applicable.

Table 4. Summary of epidemiological studies of arsenic in drinking water and risk for bladder cancer (meta-analyses excluded).

Study	*Type of study*	*Location*	*Exposure level*	*Results*	*Main finding according to authors*
				SMR (95% CI)	
Lamm et al.[67]	mortality, ecologic	USA	3.0–60.0 μg L^{-1}	0.95 (0.89, 1.01) to 0.73 (0.41, 1.27)	no trend
Yang et al.[84]	mortality, ecologic	Taiwan	gradually declining from 1971 to 2000	male: 215–1025 female: 763–2424	substantially higher in females
Pou et al.[69]	mortality, ecologic	Argentina	0–1.800 μg L^{-1}	male: 0.88 (0.3, 2.4) to 91.1 (71.6, 115.9) female: 0.36 (0.08, 1.72) to 31.6 (20.7, 48.2)	substantially higher in males
Morales et al.[16]	mortality, ecologic	Taiwan	0 – 600+ μg L^{-1}	1.002–766.00	no trend
Marshall et al.[71]	mortality, ecologic	Chile	gradually declining from 1955 to 1994 (566.00–43.00 μg L^{-1})	male: 0.53 (0.16, 1.79) to 6.10 (3.97, 9.39) female: 1.07 (0.31, 3.71) to 13.8 (7.74, 24.5)	Bladder cancer mortality rate ratios started to elevate approximately 10 years after high arsenic exposure began and continued to increase with a peak in 1986 – 1997.
Meliker et al.[78]	mortality, ecologic	USA	population-weighted mean arsenic concentration of 11.00 μg L^{-1}	male: 0.94 (0.82, 1.08) female: 0.98 (0.80, 1.19)	no trend
Chen et al.[79]	mortality, cohort	Bangladesh	<50.00 – >599.00 μg L^{-1}	(lifetime mortality risk) male: 5.43 female: 0.28	A doubling of lifetime mortality risk from bladder cancer is observed.
				OR (95% CI) or RR (95% CI) or (S)IRR (95% CI)	
Nieder et al.[68]	incidence, ecologic	USA	regarding proximity to arsenic contaminated well (<3 – >5 mi)	Late stage bladder cancer: 3–5 miles: 1.4 (1.1, 1.8) <3 miles: 2.0 (1.7, 2.5)	An elevated likelihood of being close to known contaminated wells with arsenic had advanced bladder cancer clusters.
Yueh-Ying Han et al.[70]	incidence, ecologic	USA	<2.00 – >10.00 μg L^{-1}	male: 35.2 (32.7, 37.8) to 39.3 (37.2, 41.4) female: 7.2 (6.2, 8.3) to 9.2 (8.4, 10.1)	Female bladder cancer incidence rates were higher when intermediate arsenic counties were compared to low ones.
Steinmaus et al.[72]	incidence, case-control	USA	<10.00 – >80.00 μg/day (highest 1-year average)	ever smokers: 0.54 (0.16, 1.80) to 3.67 (1.43, 9.42) never smokers: 0.31(0.06, 1.66) to 1.51 (0.33, 6.99)	Those who consume water with arsenic at concentrations near 200 μg/day and smoke may be at elevated risk of bladder cancer when compared with smokers exposed to lower concentrations.
Bates et al.[73]	incidence, case-control	Argentina	– >200.00 μg L^{-1}	excluding proxy wells: 0.28 (0.10, 1.40) to 1.11 (0.30, 3.70) including proxy wells: 0.60 (0.20, 1.70) to 1.02 (0.50, 2.30)	no trend
Meliker et al.[74]	incidence, case-control	USA	<1.00 – >10.00 μg L^{-1}	overall: 1.10 (0.65, 1.86) ever smokers: 0.94 (0.50, 1.78)	no trend
Karagas et al.[82]	incidence, case-control	USA	0.009 – 2.484 mcg/g (toenail As concentration)	ever smokers: 0.50 (0.13, 1.88) to 2.17 (0.92, 5.11) never smokers: 0.49 (0.12, 2.05) to 1.18 (0.53, 2.66)	When smokers with >0.330 mcg/g were compared to smokers with <0.06, an increased OR = 2.17 (0.92–5.11) was observed.
Michaud et al.[83]	incidence, case-control	Finland	<0.105 – >0.399 μg/g (toenail As concentration)	0.93 (0.56, 1.54) to 1.38 (0.68, 2.80)	no trend
Wadhwa et al.[75]	incidence, case-control	Pakistan	3–15-fold >10.00 μg L^{-1}	blood (μg L^{-1}), x ±SD Exp: 6.82±3.36 Non-exp: 2.68±1.04 scalp hair (μg L^{-1}), x ±SD Exp: 4.98±2.36 Non-exp: 2.08±0.74	The arsenic levels in blood and hair scalp samples were clearly increased in exposed bladder cancer patients compared to non-exposed.
Chen et al.[76]	incidence, cohort	Taiwan	<10.00 – ≥300.00 μg L^{-1}	1.85 (0.45, 7.61) to 10.8 (2.90, 40.3)	At high arsenic concentrations >100 μg L^{-1}, long-term exposure was found to be associated with increased risk of urothelial carcinoma.
Chiou et al.[47]	incidence, cohort	Taiwan	≤10.00 – >100.00 μg L^{-1}	1.96 (0.94, 3.61)	A dose-response relation between cumulative arsenic exposure and incidence rates for bladder cancer was found.
Baastrup et al.[77]	incidence, cohort	Denmark	0.05–25.3 μg L^{-1} Mean = 1.2 μg L^{-1}	1.01 (0.93, 1.11)	no trend

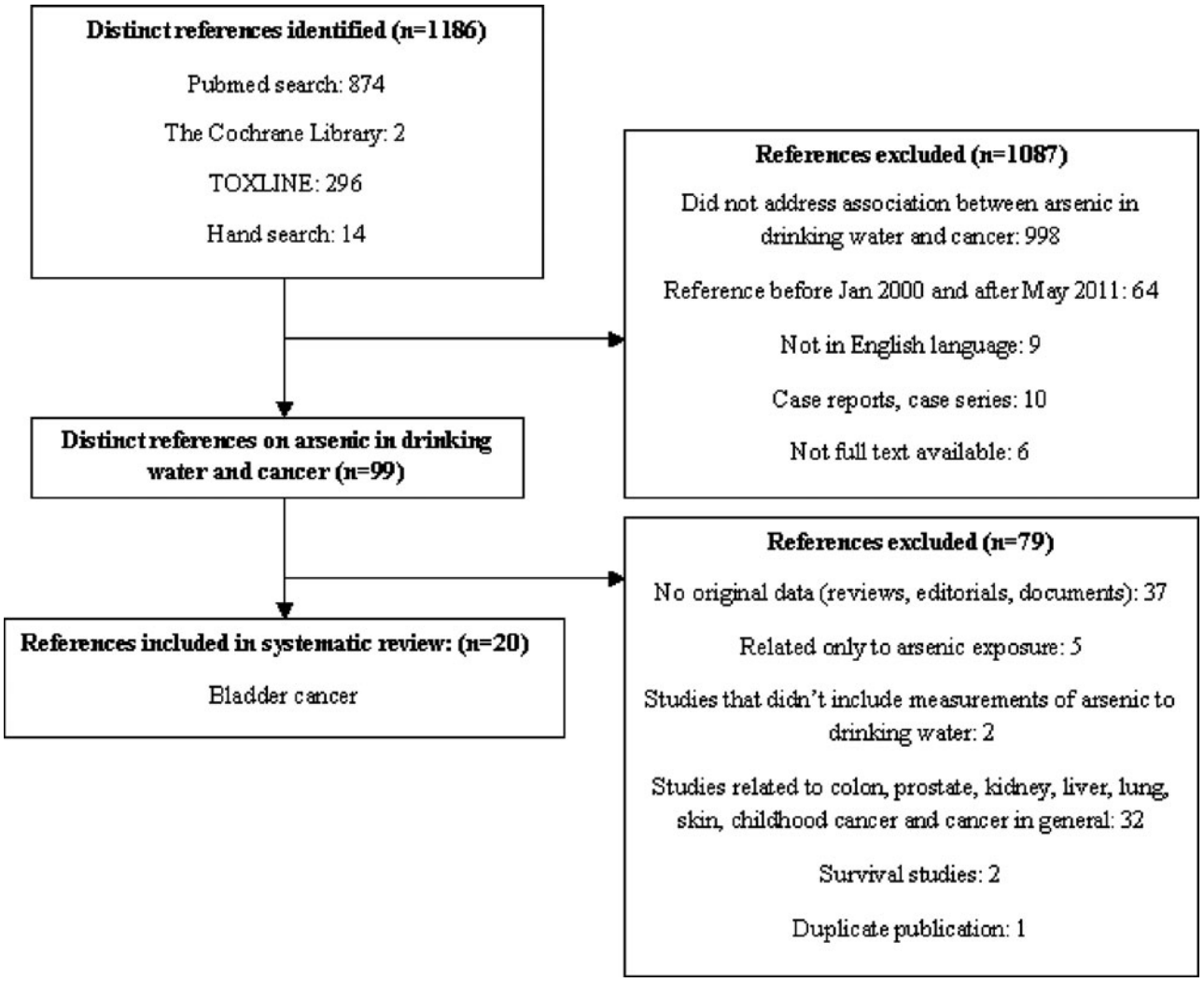

Fig. 1. Flow diagram of study selection process.

of exposed male patients with cancer and controls vs. non-exposed male patients with cancer and controls. The study of Michaud et al.[83] carried out in Finland estimated bladder cancer risk based on toenail arsenic level among male smokers.[83] All case-control studies used community-based controls. Three out of four cohort studies[47,76,77] assessed urinary cancer (including bladder cancer) incidence, except for Chen and Ahsan,[79] which measured lifetime mortality risk from liver, bladder and lung cancer. Of all the studies identified, only three assessed As exposure using a biomarker, such as blood, scalp hair or toenails.[75,82,83]

Documentation of arsenic exposure through drinking water was based on geographic or other ecologic or grouped water measurements in most of the studies. The study conducted in Michigan calculated arsenic exposure by collecting water samples from sources used for drinking (including coffee) and cooking, as well as untreated well water in current residences of participants and by using a geostatistical model for predicting arsenic concentrations at past residences on private well water.[74] Steinmaus et al.[72] determined arsenic exposure for each subject by linking each residence within the study area to a water arsenic measurement for that residence. In this way, an arsenic concentration could be assigned to each year of a subject's life within the study area. In the study of Bates et al.[73] water samples were collected from each subject's current residence and as many of his or her residential sources within the previous 40 years as practicable, particularly from wells.

Historical records of arsenic content were also obtained for community water supplies. Regarding the case-control studies, in the investigation conducted in Pakistan, cases (exposed) resided in villages of south western part of Pakistan using surface and underground water, which have had chronically high levels of As. The controls (non-exposed) lived in big cities and drank municipal treated water with low levels of As (<10 μg L^{-1}) and smoked branded cigarette containing low levels of As, as well.[75] Of the cohort studies, the Chen et al.[76] study carried out in northeastern Taiwan estimated arsenic concentrations using water samples collected in the 85.1% households.

Similarly, in the second study conducted in northeastern Taiwan well water samples were also collected from 85.1% of households during the home interview.[47] On the other hand, arsenic concentrations in Danish drinking water were taken from a database that developed from the Geological Survey of Denmark and Greenland.[77,86] Finally, the Chen and Ahsan [79] study in Bangladesh used water samples from 5,966 contiguous hand-pumped tube wells tested for arsenic in 2000, in a well-defined geographic area of Araihazar, Bangladesh.

Three of the cohort studies and all the case-control studies were based on incident bladder cancer cases.[47,72–77,82,83] Only Chen and Ahsan [79] estimated excess lifetime risks of death from bladder cancer using an exposure distribution, death probabilities and cancer mortality rates from Bangladesh and dose-specific relative risk estimates from Taiwan.[79] In all case-control studies, there was histopathological confirmation of the cancer diagnoses for the cases.[72–75,82,83] In all cohort and case-control studies there was at least adjustment for age. There were other adjustment factors such as gender in eight studies,[47,72–74,76,79,82,83] smoking in seven studies,[47,72–74,76,77,82] race in two studies,[72,74] education in five studies,[72–74,76,77] income in one study,[72] alcohol consumption in two studies [76,77] and occupational exposure in three studies.[72,74,77]

Meta-analyses

The Chu and Crawford-Brown [80] meta-analysis estimated the dose-response relationship between excess probability of bladder cancer and arsenic intake by water ingestion combining seven epidemiologic studies of populations from several regions such as Taiwan, the United States, Argentina, Chile and Finland (case-control and cohort studies)[43,44,46,47,72,73,87] exposed to low- and high-level of arsenic through drinking water.

The Mink et al.[81] meta-analysis was based on eight epidemiologic studies of populations from several regions such as the United States, Argentina, Finland and northeastern Taiwan (case-control and cohort studies) exposed to low levels of arsenic (<100–200 μg L^{-1}) through drinking water [43,44,47,49,72,73,82,83] and evaluated the association between the risk of bladder cancer and low-level exposures to arsenic through drinking water.

Quality assessment

When we rated the included studies using quality criteria, the overall quality of evidence was considered to be high (Table 3). Half of the studies assessed arsenic exposure individually.[47,68,72–74,76,77,79,82,83] Five out of eight ecological studies used adjustments for other potential confounders except for age.[68–71,84] All cohort and case-control studies were adjusted for cigarette smoking status. Of all the studies identified, only three assessed exposure using a biomarker.[75,82,83]

Associations between arsenic and bladder cancer

Ecological studies

The Lamm et al.[67] study stratified analysis and regression analyses (both unweighted and weighted by county population and using both mean and median arsenic concentrations) of the county-specific white male bladder cancer mortality data (1950–1979) and county-specific groundwater arsenic concentration data (obtained for 133 U.S. counties known to be exclusively dependent on groundwater for their public drinking water supply) found no arsenic-related increase in bladder cancer mortality over the exposure range of 3 to 60 μg L^{-1}.

In the study conducted in Florida by Nieder et al.[68] advanced bladder cancer clusters had an increased likelihood of being near known arsenic contaminated wells. Regarding late stage bladder cancer, the OR was 1.4 (95% CI: 1.1, 1.8) for those living >3–5 miles from a drinking water well and 2.0 (95% CI: 1.7, 2.5) for those living <3 miles from a well known to be contaminated with arsenic.

Yang et al.[84] conducted a standardized mortality ratio analysis for bladder cancer calculated for the Blackfoot disease endemic area in Taiwan for the years 1971–2000 in order to examine the hypothesis that bladder cancer mortality decreased after installing a tap-water supply system, which eliminated arsenic exposure through artesian well water. During the period preceding tap-water installation, the Standardized Mortality Ratio (SMR) for bladder cancer was markedly elevated for both men and women and substantially higher in females (male: 215–1025, female: 763–2424). The results of the study showed that mortality from bladder cancer decreased gradually after installing tap-water supply system that eliminated arsenic exposure from artesian well water. This particular study strengthens the possibility that the observed association between arsenic exposure and bladder cancer is causal.[84]

Consistent with the findings from a previous study conducted in Córdoba (Argentina), where bladder cancer SMRs were consistently higher in counties with documented arsenic exposure (Hopenhayn-Rich et al.[38]), Pou et al.[69] found that bladder cancer mortality rates tended to increase with age, in a more strong and rapid way in men, from 0.88 (95% CI 0.3, 2.4) to 91.1 (95% CI: 71.6, 115.9) for men, and from 0.36 (95% CI: 0.08, 1.72) to 31.6 (95% CI: 20.7, 48.2) for women, in both genders for the 5-year age groups from 37–42 to 82–87. The association between bladder cancer, gender and exposure to arsenic was confirmed. Relative Risk (RR) was higher among men who were exposed to increasing As exposure categories. RR for male at low exposure (0–40 μg L^{-1}) was calculated equal to 3.14, for male at intermediate exposure (40–320 μg L^{-1}) 4.03 and for male at high exposure (320–1800 μg L^{-1}) 4.71 versus female at low exposure. Given the magnitude of the RRs and the precision of the estimates, the association between exposure to arsenic through drinking water and

bladder cancer mortality increase is unlikely to be due to confounding factors.

In the study conducted in Idaho by Yueh-Ying Han et al.[70] female incidence rates for bladder cancer were higher in the intermediate arsenic counties compared to the low ones. The results did not show a dose-response effect between arsenic levels in ground water and cancer incidence. What is more, multivariate regression analysis found that bladder cancer incidence was not associated with ground water arsenic levels after adjusting for race, gender, population density, smoking and body mass index (BMI). Counties with a higher prevalence of current smoking had a higher bladder cancer incidence ($P = 0.024$). Female bladder cancer incidence rates were higher when intermediate arsenic counties were compared to low ones.

Investigating bladder as well as lung cancer mortality for the period 1950–2000, Marshall et al.[71] compared Chile's region II with region V. In region V drinking water was free of arsenic while in region II during the period 1958–1970 the arsenic drinking water concentrations averaged 870 μg L^{-1}. After water treatment plants installation in the 1970s arsenic concentrations in drinking water began to decline. Elevated rate ratios in region II became apparent about 10 years after arsenic exposure increased, with a peak in the years around 1990, and continued to be remarkably increased up to the year 2000. The peak bladder cancer RRs were calculated equal to 6.10 (95% CI: 3.97, 9.39) for men and 13.8 (95% CI: 7.74, 24.5) for women. The patterns of latency shown in this mortality study provide further evidence for relationship of causality between arsenic in the water and increased rates of bladder cancer since increased rates of this type of cancer temporally followed the increase in arsenic exposure in a plausible manner.

In the study carried out by Meliker et al.[78] the relationship between moderate drinking water arsenic levels (mean arsenic concentration: 11 μg L^{-1}) and selected disease outcomes concerning several types of cancer (including bladder cancer), diseases of the respiratory and circulatory system, diabetes mellitus, liver and kidney diseases was evaluated by conducting a SMR analysis in six counties in southeastern Michigan for the period 1979–1997. For the whole of the six counties the mean and median arsenic concentrations (population-weighted) were 11.00 μg L^{-1} and 7.58 μg L^{-1}, respectively. Concerning bladder cancer, Meliker et al.[78] did not find an elevated bladder cancer SMR (0.94 [95% CI 0.82, 1.08] for males and 0.98 [95% CI 0.80, 1.19] for female). In Taiwan, Morales et al.[16] found no increase in bladder cancer mortality examining arsenic exposure levels below 400 μg L^{-1}.

Cohort studies

In an effort to explain the relationship between urinary cancer and ingested arsenic in lower concentrations and to evaluate the influence of duration, latency and recency of these exposures, Chen et al.[76] conducted a cohort study of 8,086 residents in the area of northeastern Taiwan for 12 years. On the whole, they observed 45 urinary cancers, including 23 bladder cancers. An increasing risk of urinary cancer was found in relation to increasing arsenic concentration ($P < 0.001$). The age- and sex-adjusted RR (95% CI) was calculated equal to 7.73 (2.69, 22.3) when exposure to ≥300 μg L^{-1} was compared with <10 μg L^{-1}. For those exposed to high concentrations (>100 μg L^{-1}), the relative risks were greater than 5-fold, while the risk was increased but not significant for low concentrations (<100 μg L^{-1}). What is more, comparing to subjects at low arsenic exposure (<10 μg L^{-1}) at enrollment, the subjects that drank water from wells with higher concentrations (≥10 μg L^{-1}) since their birth (RR = 3.69; 95% CI: 1.31, 10.4) or still drank at enrollment (RR = 3.50; 95% CI: 1.33, 9.22), or drank for more than 50 years (RR = 4.12; 95% CI: 1.48, 11.5) had a significantly increased urinary cancer risk.

Similarly, Chiou et al.[47] found a significantly increased incidence of urinary cancers (including 10 bladder cancer cases) for those drinking As-contaminated water >100 μg L^{-1} (with half of those residents having exposures over 300 μg L^{-1}) when compared with the general population in Taiwan (Standardized Incidence Ratio-SIR = 2.05; 95% CI: 1.22, 3.24). The SIR for bladder cancer was 1.96 (95% CI: 0.94, 3.61).

With the objective of determining if an increased risk for bladder cancer is associated with exposure arsenic through drinking water with low As concentrations (range: 0.05–25.3 μg L^{-1}) in Denmark, Baastrup et al.[77] carried out a prospective cohort study of 57,053 persons (214 cases) in the areas of Copenhagen and Aarhus. No significant association between exposure to arsenic at low levels and risk for bladder cancer was found after adjustment for smoking status, smoking duration, smoking intensity, education and occupation. Specifically, the incidence RR for bladder cancer was 1.0 (95% CI: 0.93, 1.11) for a time-weighted average exposure of 1.2 μg L^{-1}, and 1.0 (95% CI: 0.98, 1.04) for a cumulative exposure of 5 mg during the total observation period (1970–2003).

At last, in order to estimate excess lifetime risks of death from liver, bladder and lung cancer an exposure distribution, death probabilities and cancer mortality rates from Bangladesh and dose-specific relative risk estimates from Taiwan were used by Chen et al.[79] The study resulted in an at least doubling of lifetime mortality risk from liver, bladder and lung cancers (229.6 vs 103.5 per 100,000 population) in Bangladesh owing to arsenic in drinking water (range: <50 μg L^{-1} – ≥599 μg L^{-1}). Lifetime excess mortality risks (per 100,000 population) from bladder cancer in Bangladesh was calculated equal to 5.43 and 0.28 for male and female respectively.

Case-control studies

In the case-control study of Steinmaus et al.[72] in seven counties of western United States (181 cases diagnosed

during the period 1994 to 2000 and 328 age and gender matched controls) no increased risks were observed for arsenic intake greater than 80 μg/day (OR = 0.94, 95% CI: 0.56, 1.57). However, when the analysis was focused on exposures going back 40 or more years ago, an OR of 3.67 (95% CI: 1.43, 9.42) was found for arsenic intake greater than 80 μg/day (median intake: 177 μg/day) in smokers. They concluded that the results provided some evidence that smokers who ingest water with arsenic at concentrations close to 200 μg/day may be at increased risk of bladder cancer.

In Bates et al.[73] study in two Córdoba counties of Argentina during 1996–2000 (114 case-control pairs, matched on age, sex and county) no evidence of associations between bladder cancer incidence and exposure estimates based on arsenic concentrations in drinking water were identified. However, when well-water consumption per se was used as the exposure measure, time-window analyses provided the evidence that use of well water for more than 50 years before interview was associated with an increased bladder cancer risk. This conclusion was limited to ever smokers (OR = 2.5, 95% CI: 1.1, 5.5 for 51–70 years before interview), without being able to exclude the possibility of this result occurring due to chance.

In the study carried out by Wadhwa et al.[75] in Pakistan, they compared As in whole blood and scalp hair samples from exposed male patients with lung or bladder cancer and referents versus non-exposed lung or bladder male patients with cancer and referents. Concentrations of arsenic in biological samples were clearly elevated in exposed male (lung and bladder) cancer patients consuming drinking water with high arsenic concentration when compared to cancer patients consuming municipal treated water of low level of As and the exposed and unexposed referents, as well.

In the case-control study conducted by Meliker et al.[74] in southeastern Michigan, the objective was to evaluate the relationship between bladder cancer and arsenic concentration between 10 and 100 μg L^{-1} in drinking water for the period 2000–2004. Low-level time-weighted average (TWA) arsenic concentration in drinking water and arsenic intake were not associated with bladder cancer when cases were compared with a control group exposed to arsenic concentration <1 μg L^{-1} (OR = 1.10; 95% CI: 0.65, 1.86). Even among ever-smokers, bladder cancer risks for those exposed to arsenic level greater than 10 μg L^{-1} were not elevated when compared to the control group exposed to arsenic concentration <1 μg L^{-1} (OR = 0.94; 95% CI: 0.50, 1.78).

Similarly, in order to examine the effects of low to moderate levels of arsenic exposure through water ingestion on bladder cancer incidence in New Hampshire (USA), Karagas et al.[82] conducted a case-control study for the period July 1994–June 1998. In this area, As levels in private wells are typically above 10 μg L^{-1}. Arsenic exposure was assessed at the individual level using toenail clippings as a biomarker. An elevated odds ratio for bladder cancer was found (OR: 2.17, 95% CI: 0.92, 5.11) when smokers with greater than 0.330 μg g^{-1} nail As were compared to smokers with less than 0.06 μg g^{-1} in their toenail. No association between toenail As concentration and bladder cancer risk was observed among never smokers.

In order to evaluate the relation between low exposure to inorganic arsenic through drinking water (<100 μg L^{-1}) at the individual level and bladder cancer risk, Michaud et al.[83] used arsenic toenail concentrations as a biomarker in the context of a nested case-control study. The study included 280 bladder cancer cases and 293 controls that were all male smokers aged 50–69 and participants in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study, a cohort study carried out in Finland for 14 years. ORs were calculated using logistic regression analyses. No association between bladder cancer risk and inorganic arsenic concentration was noted when men with the highest arsenic concentrations in their toenail were compared with those with the lowest: 1.13 (95% CI: 0.70, 1.81) for the highest quintile versus 1.14 (95% CI: 0.52, 2.51) for the lowest quintile.

Meta-analyses

Assuming a linear dose-response association at all levels of arsenic exposure, Chu and Crawford-Brown[80] used fixed-effect and random-effect models in order to estimate the averaged coefficient of the linear-logistic regression model for the relationship between the excess probability of bladder cancer and the amount of arsenic intake. A homogeneity test was carried out, as well. Taking into account the maximum contaminant level (MCL) of 10 μg L^{-1} the associated bladder cancer risk was estimated (at this MCL) equal to 2.29×10^{-5}. Chu et al.[80] meta-analysis produced an aggregated dose-response model whose best estimate of the slope factor was calculated equal to 3.0×10^{-5} (with unit of probability per μg/kg/day), with the upper bound of 1.27×10^{-4}.

Using stratified analyses on smoking status Mink et al.[81] evaluated the association between arsenic exposure in drinking water at low concentrations and risk of bladder cancer calculating summary relative risk estimates. They also examined heterogeneity; study design and sample size across studies and improved the precision of estimates. They concluded that arsenic exposure at low concentrations (<100–200 μg L^{-1}) alone did not seem to be an important independent risk factor for bladder cancer.

Conclusions

Based on a complete review of the international epidemiologic evidence on the topic and following a systematic review protocol, the present report found fairly consistent evidence of an increased risk of bladder cancer incidence and mortality in association with high concentrations of arsenic in drinking water (>50 μg L^{-1}). Considerable uncertainty remains about the bladder cancer risks at

Table 5. Overall results from the original studies with arsenic measurements in drinking water (μg L^{-1}).

Arsenic concentration level in drinking water (μg L^{-1})	*Number of studies with* positive *result*	*Number of studies with* negative *result*
Mortality	SMR or Lifetime mortality risk >1	SMR or Lifetime mortality risk <1
≤10	1	3
11–50	2	2
51–100	3	2
101–250	2	2
251–500	2	1
>500	2	1
Lamm et al.,[67] Pou et al.,[69] Morales et al.,[16] Meliker et al.[78] and Chen et al.[79]		
Incidence	RR or OR>1	RR or OR<1
≤10		4
11–50	1	3
51–100	2	1
101–250	1	1
251–500	1	1
>500		
Yueh-Ying Han et al.,[70] Bates et al.,[73] Meliker et al.,[74] Chen et al.,[76] Chiou et al.[47] and Baastrup et al.[77]		

lower concentrations of arsenic (<50 μg L^{-1}) in drinking water, which requires further investigation.

It was notable that among the case-control studies we evaluated, an increased bladder cancer risk with As in drinking water was only observed among smokers. In Table 5, overall findings from the original studies that contain arsenic measurements in drinking water (μg L^{-1}) are shown providing the number of studies with positive or negative results categorized by the level of exposure to arsenic through drinking water. It is clear that at exposure levels above 50 μg L^{-1}, more studies found positive results (concerning both bladder cancer mortality and incidence) than negative ones. Although there were some methodologic limitations in the included studies, the fairly consistent observations of statistically significant associations from the majority of studies, at higher levels of exposure across varying study designs carried out in different areas, provide support for a causal association between ingesting drinking water with concentrations of arsenic >50 μg L^{-1} and bladder cancer risk. Bladder cancer risk at lower exposure concentrations requires further investigation taking into account smoking as well as other probable confounding factors such as occupational exposure, age, gender, and race.

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