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Low-Level Exposure to Arsenic in Drinking Water and Risk of Lung and Bladder Cancer: A Systematic Review and Dose–Response Meta-Analysis

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Abstract

Background: Exposure to high levels of arsenic in drinking water has been associated with an increased risk of lung and bladder cancer, but the presence of an increased risk at low levels is questionable.

Methods: A systematic review and a dose–response meta-analysis were conducted on risk estimates of lung and bladder cancer for exposure to arsenic in drinking water up to 150 μg/L, using a 2-stage approach based on a random-effects model.

Results: Five studies of lung cancer were identified; the meta-relative risk (RR) for an increase of 10 μg/L arsenic level was 1.03 (95% confidence interval [CI]: 0.99-1.06; *P* heterogeneity = .05). The meta-analysis of bladder cancer included 8 studies; the meta-RR for an increase of 10 μg/L arsenic level was 1.02 (95% CI: 0.97-1.07, *P* heterogeneity = .01). Sensitivity analyses, including a 1-stage meta-regression, confirmed the main findings.

Conclusion: This systematic review and meta-analysis provided evidence of a lack of an increased risk of lung and bladder cancer for exposure to arsenic in drinking water up to 150 μg/L, the highest concentration studied.

Keywords

arsenic, bladder cancer, dose–response, drinking water, epidemiology, lung cancer

Introduction

High-level exposure to arsenic in drinking water has been known for many decades to occur in various regions of the world, including West Bengal (India), Bangladesh, China, Mongolia, Taiwan, Argentina, and Chile.[1] Exposure is mainly from natural source, although in some areas of Japan, Mexico, Thailand, and other countries, industrial activities have resulted in elevated arsenic levels in water.[2] The predominant form of arsenic found in drinking water is arsenate (As_V), although arsenite (As_{III}) can be present in reducing environments.

Exposure to high levels of arsenic in drinking water has been associated with increased cancer hazard. The International Agency for Research on Cancer (IARC), a specialized branch of the World Health Organization (WHO), has determined that exposure to inorganic arsenic in drinking water represents a cancer hazard for humans, with a strong evidence for lung and bladder cancer.[3] The IARC evaluation, however, does not include a risk assessment nor identifies potentially safe levels.

Several quantitative estimates of risk of cancer from exposure to arsenic in drinking water have been published, which in most cases were based on extrapolation from increased risks at higher exposure levels using a linear nonthreshold model of dose–response relationship.[4-6] Given the presence of an increased risk of cancer at high doses, linear nonthreshold models would result in a small increase in risk at low doses, even in the absence of empirical evidence for such an effect and

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even if such an effect does not exist. Only 1 meta-regression of available studies showed the data that were fit to a nonlinear relationship: This study provided evidence for a lack of effect at low doses.[7]

The objective of the present study was to perform a systematic review and dose–response meta-analysis of epidemiology studies of lung and bladder cancer, whose results included multiple categories of low-dose exposure to arsenic in drinking water. The definition of threshold for "low exposure" in the present study was set at 150 μg/L arsenic, a level that is 2 orders of magnitude higher than that recommended by WHO.[8]

Methods

A systematic review and a meta-analysis were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) and Meta-analysis of Observational Studies in Epidemiology guidelines.[9,10] A PRISMA checklist is included as Supplemental Appendix 1. The study protocol is available from the authors. Each step of the meta-analysis was performed independently by the 2 authors (P.B. and C.B.). Results of each step were compared between reviewers, and disagreements were resolved by consensus.

Selection of Studies

The PubMed, Scopus, and Embase databases were searched in November 2018 for studies providing results on risk of cancer of lung and urinary bladder among individuals exposed to arsenic in drinking water. We used search strings such as [(arsenic OR arsenate OR arsenite OR "arsenic acid" OR MMA OR DMA) AND bladder cancer] (similar strings were used for lung cancer; details on strings are reported in Supplemental Appendix 2): Such broad strings were chosen to increase sensitivity of the search. A total of 1955 articles on lung cancer and 1036 articles on bladder cancer were identified. The titles and abstracts of the articles were reviewed by the 2 authors, and a shortlist of articles was defined for each outcome for full-text review. List of references of articles selected for text review and recent reviews[3-7] were also searched for additional studies.

Inclusion criteria of studies for the meta-analysis were (1) cohort, case–control, or derived design; (2) at least 2 exposure categories (reference category and one "exposed" category) of level of arsenic in drinking water with mean/midpoint up to 150 μg/L; (3) measures of association (rate ratio, risk ratio, odds ratio; for simplicity referred to as relative risk [RR]) with the cancer of interest, including 95% confidence intervals (CIs), reported in the article, or sufficient data to calculate them; and (4) incidence or mortality from lung or bladder cancer as outcome.

Exclusion criteria included (1) cross-sectional, ecologic on noncomparative design; (2) less than 2 exposure categories with mean/midpoint up to 150 μg/L; (3) measures of arsenic exposure other than level of arsenic in drinking water; (4) no measures of association and CIs, or sufficient data to calculate them; (5) partial or total overlap with another report of the same study, with less extensive data (eg, early follow-up of a cohort for which a subsequent report with longer follow-up was available).

The flowcharts for the selection of the studies included in the meta-analyses are shown in Figure 1. The lists of studies that were examined for inclusion at each step of the selection process, including those that were excluded, are available from the authors.

Extraction of Data

The following information was extracted from each study retained in the meta-analysis: (1) study design; (2) study characteristics (country, geographic area, period of enrollment, and follow-up for cohorts; period of ascertainment of cases and controls for case–control studies); (3) study population (number of cohort members and of cases and controls; demographic characteristics); (4) exposure variables and categories with mean or midpoint up to 150 μg/L; (5) number of cases and person-years (cohort studies) or number cases and controls (case–control studies) in each exposure category; (6) RR and 95% CI, or sufficient data to calculate them; and (7) potential confounders included in the analysis.

The preferred exposure variable was average level of arsenic in drinking water (μg/L) over the whole lifetime; in some studies, results were not available for average lifetime exposure, and alternative variables were available such as arsenic levels at the current residence. Exposure categories with mean/midpoint above 150 μg/L were excluded. However, some of the categories selected for the analysis included individuals exposed to levels above 150 μg/L arsenic, although the mean/midpoint was not higher than that level. The most comprehensive results were used for each of the studies (eg, complete follow-up rather than a shorter follow-up period). When results were reported according to different lag periods, those closest to a 10-year period were selected. If only stratified results were available (eg, by smoking status), they were combined using a fixed-effects meta-analysis. In a few instances, RRs and CIs were not available from the published articles but were calculated based on data reported in the articles. Risk of bias in the studies selected for the analysis was not formally assessed.

Meta-Analysis

A 2-stage approach was used for the meta-analysis. First, a linear regression approach was taken within each study to derive an estimate of the dose–response relationship up to 150 μg/L arsenic in drinking water, expressed as RR for an increase of 10 μg/L. Then, a random-effects meta-analysis[11] was conducted to derive the combined RRs and CIs across all studies. The STATA programs *metan* and *glst* were used.[12,13] This approach is preferable to a meta-regression that combines all risk estimates from available studies, since it takes into account the covariance matrix of RRs from the same study. However, in order to compare with other meta-analyses of cancer risk from arsenic exposure in drinking water, we also

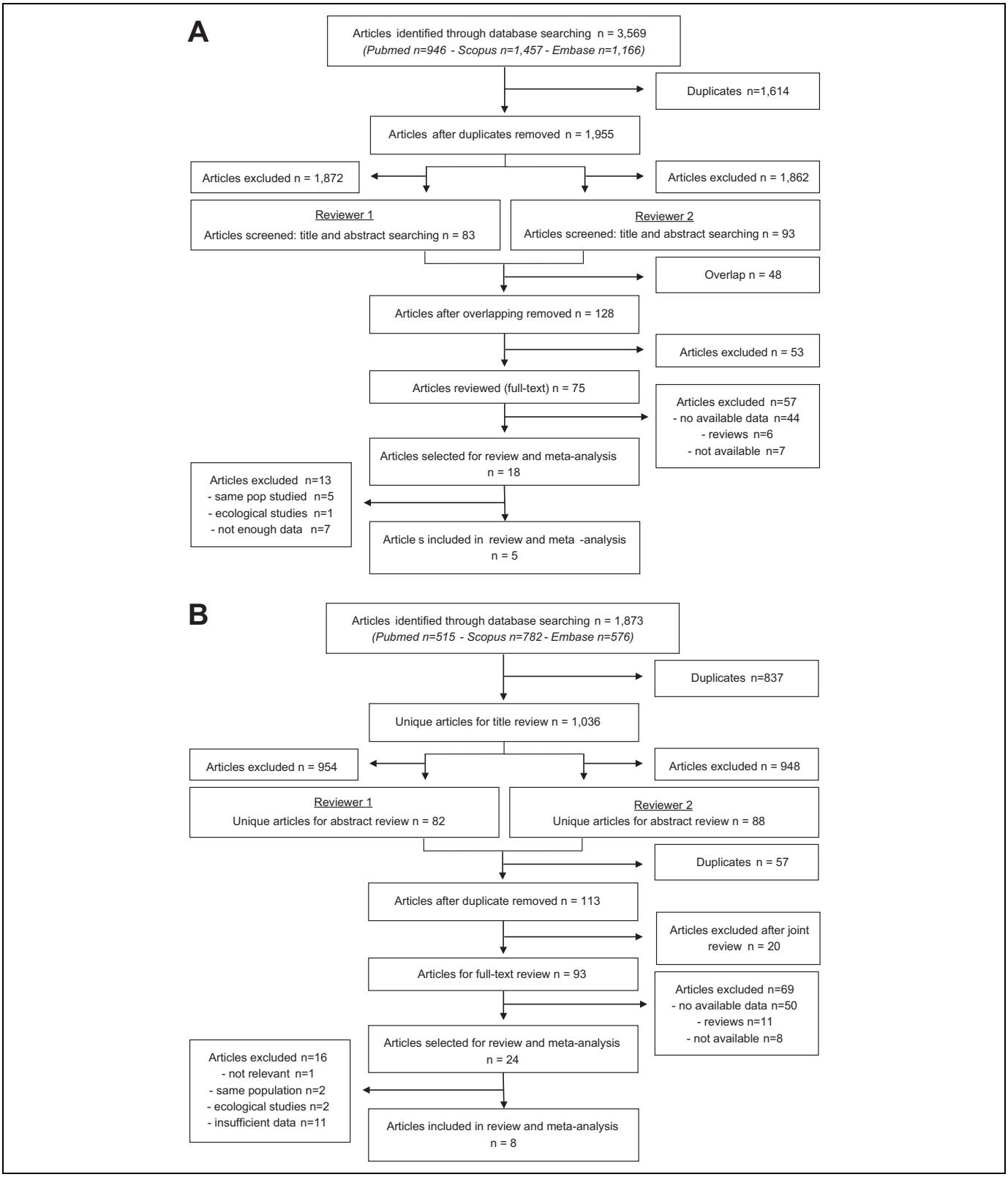

Figure 1. Flowchart for the identification of articles for the meta-analyses: (A) lung cancer; (B) bladder cancer.

Table 1. Studies of Lung Cancer Included in the Meta-Analysis.[a]

References	Study Area	Study Period[b]	Study Design	Exposure Level, μg/L	Cases	Non-Cases[c]	Relative Risk	95% Confidence Interval	Adjustment Factors
Ferreccio et al[17]	Chile (3 Northern regions)	1993-1996	Case–control	0-9.9[d]	11	92	1.00	–	Age, sex, SES, smoking, employed in copper smelting
				10-29	3	62	0.30	0.1-1.2	
				30-59	4	19	1.80	0.5-6.9	
				60-89	22	51	4.10	1.8-9.6	
				90-199	13	36	2.70	1.0-7.1	
Mostafa et al[18]	Bangladesh (Dhaka)	2003-2006	Case–control[e]	*0-10[d]*	*354*	*186*	*1.00*	-	Age, smoking status and level
				11-50	*1303*	*576*	*1.13*	*0.91-1.40*	
				51-100	*208*	*84*	*1.28*	*0.92-1.77*	
Chen et al[19]	Taiwan (Tungshan, Chuangwei, Chiaohsi, Wuchieh)	1991-2006	Cohort	0-9[d]	48	26 567	1.00	–	Age, sex, education, smoking status, alcohol consumption
				10-49.9	51	24 222	1.10	0.74-1.63	
				50-99.9	20	10 329	0.99	0.59-1.68	
Steinmaus et al[20]	Chile (2 Northern regions)	2007-2010	Case–control	0-25.9[d]	61	202	1.00	–	Age, sex, race, SES, smoking, employed in mining, BMI
				26-79	61	189	0.98	0.62-1.53	
				80-197	85	142	1.70	1.05-2.75	
Dauphine et al[21]	United States (Nevada, California)	2002-2005	Case–control	0-10[d]	141	241	1.00	–	Age, sex, education, smoking history, occupational exposures
				11-84	37	82	0.75	0.45-1.25	
				85-125	18	36	0.84	0.41-1.72	

Abbreviations: SES, socio-economic status; BMI, body mass index.
[a]Results in italics were derived from results reported in the original articles.
[b]Period of enrollment in case–control studies, period of follow-up in cohort studies.
[c]Controls in case–control studies, cohort members in cohort studies.
[d]Reference category.
[e]Controls were patients with benign lung lesions.

calculated and reported the results of a 1-stage meta-regression for which the program *metareg* in STATA was used.[12] Inter-study heterogeneity was assessed using the I^2 statistics,[14]; publication bias was assessed using a visual inspection of the funnel plot,[15] as well as the test proposed by Egger and colleagues,[16] for which the STATA programs *metafunnel* and *metabias* were used.[12]

Two sets of sensitivity analyses were conducted: (1) one study at a time was excluded from the meta-analysis to assess its influence on the overall risk estimate; (2) studies whose results were calculated by the authors were excluded and the meta-analyses were repeated only on results reported in the original articles. When results from more than 2 studies were available, meta-analyses were stratified by smoking status.

Results

Lung Cancer

A total of 5 studies were retained in the meta-analysis of lung cancer risk and low-level exposure to arsenic in drinking water (Figure 1A).[17-21] Two studies overlapping with the cohort study from Taiwan were excluded.[20,22,23] Selected characteristics of the studies are listed in Table 1: 4 studies were of case–control design (2 from Chile, 1 from Bangladesh, and 1 from the United States) and 1 was a cohort study (from Taiwan). A detailed description of the studies is included in Supplemental Appendix 3.

The results selected for the meta-analyses are also listed in Table 1, while the results of the study-specific regression (RR for an increase of 10 μg/L) are listed in Figure 2. The random-effects meta-analysis resulted in an RR of 1.03 (95% CI: 0.99-1.06; Figure 2). The meta-analysis of case–control studies also resulted in a meta-RR of 1.03 (95% CI: 0.99-1.07). The exclusion of 1 study at a time did not reveal a strong influence of individual studies, as the range of the meta-RRs was 1.02 to 1.04. In particular, the exclusion of the only study with results calculated by us based on data reported in the original articles[18] resulted in a meta-RR of 1.03 (95% CI: 0.98-1.07). The small number of studies hindered the assessment of publication bias, but there was no suggestion that this source of bias played a role (Egger test, $P = .91$). The (1-stage) meta-regression resulted in a meta-RR of 1.05 (95% CI: 0.98-1.12) for an increase of 10 μg/L. Results stratified by smoking status were reported only in 2 studies[17,18]: No meta-analysis was performed.

Bladder Cancer

A total of 8 studies were included in the meta-analysis of the risk of bladder cancer (Figure 1B).[20,24-30] Three studies were from the United States, and one each from Argentina, Bangladesh, Chile, Finland, and Taiwan (Table 2).

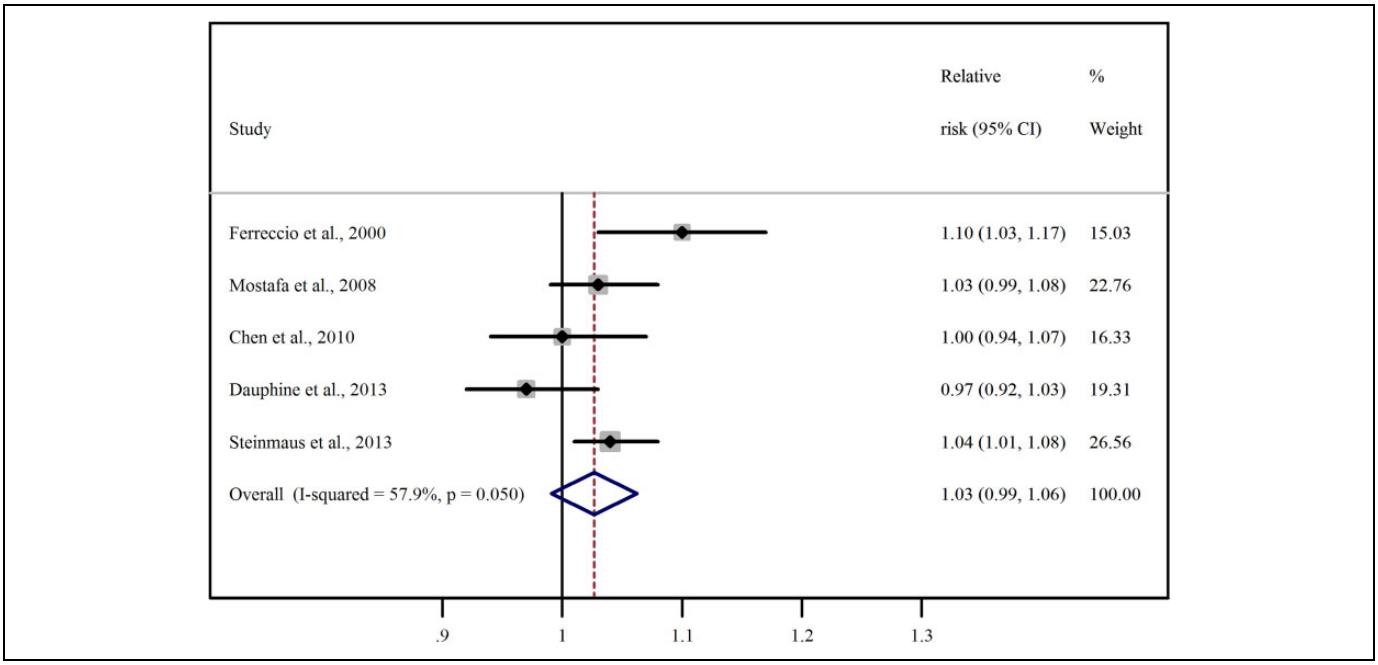

Figure 2. Forest plot of meta-analysis of results on risk of lung cancer for an increase in 10 μg/L arsenic (range: 0-150 μg/L).

Table 2. Studies of Bladder Cancer Included in the Meta-Analysis.

References	Study Area	Study Period[a]	Study Design	Exposure Level, μg/L	Cases	Non-Cases[b]	Relative Risk	95% CI	Adjustment Factors
Kurttio et al[24]	Finland	-	Case–control	0-0.09[c]	26	112	1.00	–	Age, sex, smoking
				0.1-0.5	18	51	0.81	0.41-1.63	
				0.5-4.5	17	51	1.51	0.67-3.38	
Steinmaus et al[25]	United States (Nevada, California)	1994-2000	Case-control	0-4.5[c,d]	121	211	1.00	–	Age, sex, occupation, smoking history, income, education, race
				4.6-36.4[d]	35	74	0.74	0.45-1.21	
Bates et al[26]	Argentina (Cordoba)	1996-2000	Case–control	0-50[c]	70	62	1.00	–	Year of birth, county, sex, smoking, education, consumption of mate
				51-100	13	18	0.88	0.30-2.30	
				101-200	22	19	1.02	0.50-2.30	
Meliker et al[27]	United States (Michigan)	2000-2004	Case–control	0-0.9[c]	187	264	1.00	–	Age, race, sex, smoking, education, family history of bladder cancer, high-risk occupation
				1-10	182	180	0.84	0.63–1.12	
				10-37.4	38	37	1.10	0.65-1.86	
Chen et al[28]	Taiwan (Tungshan, Chuangwei, Chiaohsi, Wuchieh)	1991-2006	Cohort	0-9[c]	5	26 609	1.00	–	Age, sex, education, smoking status, alcohol consumption
				10-49.9	8	24 247	1.70	0.56-5.19	
				50-99.9	5	10 359	2.49	0.72-8.59	
Steinmaus et al[20]	Chile (2 Northern regions)	2007-2010	Case–control	0-25.9[c]	33	202	1.00	–	Age, sex, smoking, mining, race, BMI, SES
				26-79	33	189	0.92	0.52–1.61	
				80-197	71	142	2.62	1.53-4.50	
Mostafa and Cherry[29]	Bangladesh (Dhaka)	2008-2011	Case–control[e]	0-10.0[c]	238	206	1.00	–	Age, sex, smoking
				10.1-50.0	319	190	1.52	1.08-2.14	
				50.1-100.0	204	145	1.07	0.73-1.57	
				100.1-200.0	278	244	0.99	0.69-1.41	

(continued)

Table 2. (continued)

References	Study Area	Study Period[a]	Study Design	Exposure Level, μg/L	Cases	Non-Cases[b]	Relative Risk	95% CI	Adjustment Factors
Baris et al[30,31]	United States (Maine, New Hampshire, Vermont)	2001-2004	Case–control	0-0.5[c]	303	325	1.00	–	Age, sex, ethnicity, state of residence, smoking status, high-risk occupation, trihalomethanes
				0.51-1.0	226	318	0.77	0.60-0.98	
				1.1-2.1	281	323	0.97	0.76–1.24	
				2.2-7.0	225	259	0.98	0.74-1.28	
				7.1-10.4	18	30	0.64	0.33-1.23	
				>10.4[f]	26	32	1.10	0.61-2.00	

[a]Period of enrolment in case–control studies, period of follow-up in cohort studies.
[b]Controls in case–control studies, cohort members in cohort studies.
[c]Reference category.
[d]Derived from results on arsenic exposure per day assuming average daily water intake = 2.2 L.
[e]Including cases of cancer of the ureter and the urethra; controls were subjects with benign bladder lesions.
[f]Upper limit set at 30 μg/L.

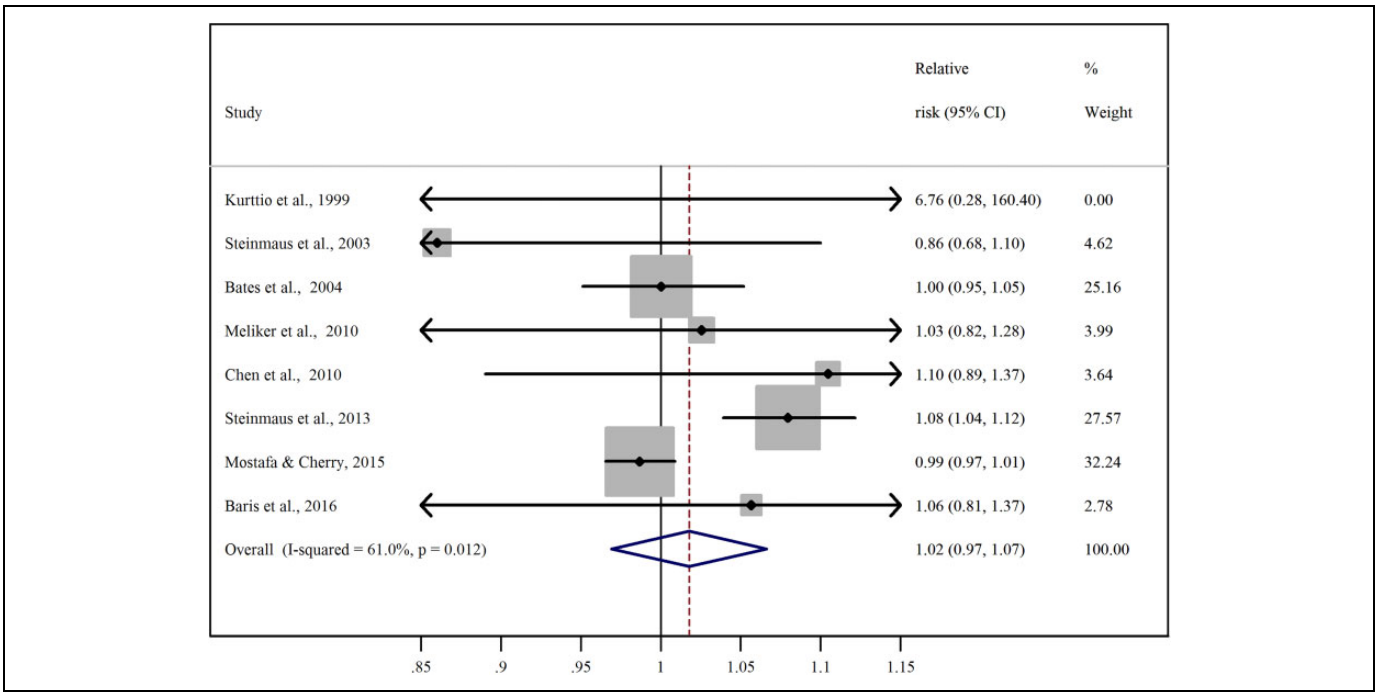

Figure 3. Forest plot of meta-analysis of results on risk of bladder cancer for an increase in 10 μg/L arsenic (range: 0-150 μg/L).

A detailed description of the studies is included in Supplemental Appendix 3.

The results selected for the meta-analyses are listed in Table 2 and those of the study-specific meta-regressions are listed in Figure 3. The meta-analysis resulted in a summary RR of 1.02 (95% CI: 0.97-1.07; Figure 3). The exclusion of 1 study at a time (including the only cohort study)[28] resulted in summary RRs ranging from 0.99 to 1.03. In particular, the exclusion of the study from Bangladesh[29] resulted in a meta-RR of 1.03 (95% CI: 0.98-1.09). The *P* value of the test for publication bias was 0.51. The (1-stage) meta-regression resulted in a meta-RR of 1.03 (95% CI: 0.98-1.10) for an increase of 10 μg/L. Results stratified by smoking status were reported in 4 studies[25-27,29]: The meta-analysis of results among non-smokers resulted in an RR of 0.99 (95% CI: 0.93-1.06) for an increase of 10 μg/L; the corresponding RR among smokers was 1.03 (95% CI: 0.99-1.07). The 2 results were not significantly different ($P = .32$).

Discussion

This systematic review and meta-analysis of risk of lung and bladder cancer from exposure to arsenic in drinking water at levels up to 150 μg/L provided strong evidence of a lack of an increased risk of these 2 neoplasms in this exposure range. The results of the 2 analytical approaches (2-step meta-analysis, the preferred approach, and 1-stage meta-regression) were consistent, and multiple sensitivity analyses confirmed the robustness of the results. The heterogeneity between study results was small, no single study had a strong influence on the overall

results, and there was no evidence of publication bias. The results on bladder cancer risk were consistent with those of 2 previous reviews and meta-analyses of low-dose exposure circumstances.[32,33]

These results for lung cancer are also consistent with the conclusions of the risk assessment study based on a nonlinear dose–response relationship, which also provided evidence for a lack of an association at low doses for this neoplasm.[7] Conversely, the increased risk of lung and bladder cancer at low exposure levels found in linear, nonthreshold dose–response analyses across the whole range of exposure[6] likely resulted from the extrapolation of results observed at high levels of exposure, irrespective of the empirical low-exposure data.

Strengths of the present study include the vast underlying review of the literature, which is unlikely to have resulted in the exclusion of any relevant study, and the relatively large database: The available studies of lung cancer include a total of 2440 cases included in the categories of exposure up to 150 μg/L and those of bladder cancer, 2996 cases. Strict criteria were adopted for the selection of studies, aimed at maximizing the comparability of studies in order to combine their results in a meta-analytic approach. This choice has resulted in the exclusion of potentially relevant studies (eg, studies with partial overlap or with results based on cumulative rather than average exposure). In particular, several studies predominantly conducted in populations with low to moderate arsenic level reported results on cancer risk based on measurements of arsenic in urine or toenails.[34-36] These approaches integrate multiple sources of arsenic exposure and—to some extent—take into account individual variability in absorption, metabolism, and excretion of the agent. Such studies are important to characterize the carcinogenic risk from low-level exposure to arsenic and integrate the evidence provided by the drinking water–based studies included in the present meta-analysis. However, limitations of these biomarker-based studies include the facts that they reflect only recent exposure (1-2 days for urine), are influenced by dietary intake of arsenic organic forms, and do not take into account hydration state or urine concentration.

The authors of several of the studies included in the meta-analysis reported multiple sets of results, for example, with different potential confounders included in the regression models or according to different time-related aspects of exposure, such as latency, lag, or time windows. In order to increase the comparability of data across studies, results were selected in which tobacco smoking, a strong risk factor for both lung and bladder cancer, was adjusted for, resulting in shortest time lag. In most instances, however, these different analytical approaches provided similar results, and it is unlikely that our choice had a major influence on the results of the meta-analysis.

The validity of a meta-analysis depends on that of the underlying studies, and potential limitations and sources of bias of studies of health effects of exposure to arsenic in drinking water have been reviewed.[6] The most important issues are likely to be low response rate of cases and controls, recall bias, misclassification of arsenic exposure, and residual confounding. Participation in a case–control study might be associated with arsenic exposure in drinking water; for example, residents in rural areas using wells might be less likely to be included in the analysis than individuals served with municipal water supplies. A high response rate in both cases and controls reduced the opportunity of this form of bias. While all studies relied on some form of measurement of arsenic level in drinking water, they varied in the approaches used to collect information on residence of study participants, potentially resulting in misclassification, especially when information on residence relies on proxy interviews[20,21,25] and on exposure levels collected at ecological level.[18] Lifetime average water exposure concentrations are difficult to assess because of the large variability between towns in the study areas and over time: for example, studies from Northern Chile reported 15-fold differences in arsenic concentration in drinking water within a 50-km distance.[17] As a result, the highest exposure categories in this analysis may have included individuals who had some exposure to higher arsenic water concentrations, resulting in overestimate of the dose–response relationship. Since several studies adjusted for tobacco smoking using broad categories, residual confounding remains a possibility, especially in the analysis of lung cancer risk. Use of smokeless tobacco products is prevalent among the populations included in several of the studies from Asia and is a suspected risk factor for bladder cancer[37]; none of these studies, however, adjusted for this potential risk factor.

In the presence of a nonlinear dose–response relationship with a threshold, such as the one identified here for arsenic exposure, it might not be appropriate to fit a linear, nonthreshold model across the whole exposure range. Such nonthreshold model, in fact, would overestimate the risk at low dose and underestimate it at high dose. It is understandable that authors of individual studies might downplay the significance of low-level results as anomalies due to low statistical power: Hence, the value of this meta-analysis shows the consistency across studies and provides summary results that are precise and robust. The only meta-regression that allowed for nonlinearity of the dose–response[7] provided evidence on lung cancer risk consistent with our study, which was based on a larger set of studies.

The lack of an association between low-level exposure to arsenic and risk of lung and bladder cancer is consistent with the experimental evidence on the mode of action of the agent. Arsenic does not directly react with DNA and does not have a genotoxic mode of action.[38,39]

In conclusion, this meta-analysis provides strong evidence of lack of an increased risk of lung and bladder cancer in categories of exposure with mean/midpoint up to 150 μg/L arsenic in drinking water. The presence of a risk at higher exposure levels was not investigated. This study demonstrated the feasibility and importance of directly estimating the risk of cancer at low-level arsenic exposure, rather than relying on interpretation of results primarily derived from high-level exposure.

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Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: PB was involved as expert for the plaintiff in litigation involving arsenic carcinogenicity.

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Supplemental Material

Supplemental material for this article is available online.

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