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Association between lung cancer risk and inorganic arsenic concentration in drinking water: a dose–response meta-analysis†

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High dose arsenic in drinking water (≥100 μg L^{-1}) is known to induce lung cancer, but lung cancer risks at low to moderate arsenic levels and its dose–response relationship remains inconclusive. We conducted a systematic review of cohort and case-control studies that quantitatively reported the association between arsenic concentrations in drinking water and lung cancer risks by searching the PubMed database till June 14, 2018. Pooled relative risks (RRs) of lung cancer associated with full range (10 μg L^{-1}–1000 μg L^{-1}) and low to moderate range (<100 μg L^{-1}) of water arsenic concentrations were calculated using random-effects models. A dose–response meta-analysis was performed to estimate the pooled associations between restricted cubic splines of log-transformed water arsenic and the lung cancer risks. Fifteen studies (9 case-control and 6 cohort studies) involving a total of 218 481 participants met the inclusion criteria. Meta-analysis identified significantly increased risks of lung cancer on exposure to both full range (RR = 1.21; 95% confidence interval [CI] = 1.05–1.37; heterogeneity I^2 = 54.3%) and low to moderate range (RR = 1.18; 95% CI = 1.00–1.35; I^2 = 56.3%) of arsenic-containing water. In the dose–response meta-analysis of eight case-control studies, we found no evidence of non-linearity, although statistical power was limited. The corresponding pooled RRs and their 95%CIs for exposure to 10 μg L^{-1}, 50 μg L^{-1}, and 100 μg L^{-1} water arsenic were 1.02 (1.00–1.03), 1.10 (1.04–1.15), and 1.20 (1.08–1.32), respectively. We provide evidence on the association between increased lung cancer risks and inorganic arsenic in drinking water across low, moderate and high levels. Minimizing arsenic levels in drinking water may be of public health importance.

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Introduction

Lung cancer is the most common cancer and the leading cause of cancer death in the world, as reported by the World Health Organization (WHO).[1] Cigarette smoking accounts for the majority of lung cancer cases, but about 25% of patients with lung cancer worldwide are lifelong non-smokers.[2] The role of other potential causes including environmental, occupational and genetic factors in the development and progression of lung cancer are of great concern to the public health.

Arsenic has been classified as a human pulmonary carcinogen by both the International Agency for Research on Cancer (IARC) and the US Environmental Protection Agency (EPA) based on consistent epidemiological evidence from studies conducted in Taiwan, Chile, and Bangladesh[3]. Drinking water is the most important source of arsenic, and it has been estimated that about 160 million people worldwide are exposed to naturally elevated levels of arsenic from ground water.[3] However, much of the evidence on the carcinogenicity of arsenic-inducing lung cancer is from South America and Asia, where drinking water contains high levels of arsenic and people there have different underlying characteristics compared with populations in other parts of the world. The maximum arsenic contaminant level in drinking water (10 μg L^{-1}) set by the United State Environmental Protection Agency (EPA) was also based on the linear extrapolation of cancer risks observed at higher concentrations.[4] However, it is unclear whether the dose–response relationship between arsenic and lung cancer is linear under low arsenic exposure and whether a safe threshold exists.[5]

The association between low-level arsenic in drinking water and lung cancer risks has been inconclusive amongst both individual epidemiological studies and systematic reviews. For example, a prospective cohort study conducted in Denmark

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found statistically non-significant elevated lung cancer risks among the 57 063 people exposed to low arsenic concentrations (mean = 1.2 μg L^{-1}) in drinking water.[6,7] In contrast, a large population-based study of 165 609 residents in Italy found increased mortality risk for lung cancer even at concentrations of arsenic in drinking water below 10 μg L^{-1}.[8] Similarly, two recent meta-regression analyses reported that low to moderate arsenic concentration (100 μg L^{-1}) in drinking water is unlikely to be associated with significantly elevated lung cancer risks,[9] but a meta-analysis reported significantly increased lung cancer risk at arsenic levels of 10 μg L^{-1}.[10,11]

Given that millions of people worldwide are chronically exposed to arsenic through drinking water,[6] there is a global need to examine the association between arsenic and lung cancer based on evidence from all sources, and to characterize the dose–response relationship between arsenic concentrations in drinking water and lung cancer.

In this review, we comprehensively and systematically collected evidence on the association between lung cancer risks and arsenic in drinking water with full range and low to moderate (<100 μg L^{-1}) range of concentrations. We also built a dose–response relationship between arsenic concentrations in drinking water and lung cancer risks.

Methods

Search strategy and data abstraction

We searched for relevant studies in the PubMed database using the medical subject heading terms 'arsenic' and 'lung neoplasms' and their relevant keywords to obtain studies published in English. References of all relevant studies were also screened to identify additional potential data sources. These searches were not restricted by publication year and were last updated on 14 June 2018.

Studies were included if they met the following criteria: (1) they were original cohort or case-control studies; (2) the main exposure was arsenic in drinking water, represented by concentrations of biomarkers, cumulative, highest or average arsenic concentrations in drinking water; (3) lung cancer was included in observational endpoints; and (4) measures of association with corresponding confidence intervals were reported or data provided in the articles were sufficient to compute these parameters. If more than one study investigated the same population, we included the study with the largest sample size.

The following study-level data were extracted onto a standardized spreadsheet: first author, publication year, study design, study country, sample size, number of lung cancer cases, determination of arsenic in drinking water, exposure metrics, arsenic concentration at different levels, outcome metrics, measures of association and their confidence levels, adjusted factors. Study countries were grouped by continents.

Quality of included studies was assessed using the Newcastle-Ottawa Assessment Scale.[12] Newcastle-Ottawa systems assess the risk of bias from three broad categories: participant selection (4 criteria), comparability (2 criteria), and assessment of outcome/exposure. Studies fulfilling five or more criteria were classified as low risk of bias.[13]

Statistical methods

The relative risks (RR) of lung cancer among people exposed to all levels of arsenic in drinking water were pooled using random-effects model for meta-analysis. Since the absolute risk of lung cancer is low, incidence rate ratios, hazard ratios from cohort studies and odds ratios from case-control studies are expected to generate similar estimates of RR. In order to ensure comprehensiveness and maximize statistical power, we pooled all measures of association together.[14] Q test and I^2 statistics were used to evaluate heterogeneity across studies. A p value for Q test of less than 0.1 indicates significant heterogeneity. I^2 values of near or less than 25%, near 50% and near or higher than 75% represent low, moderate and high heterogeneity, respectively.[15] Publication bias was examined using the Egger test, with p value less than 0.05 indicating significant publication bias.[16] We performed subgroup analyses stratified by study design, geographic location, exposure metric, measure of association, type of analysis (adjusted *vs.* unadjusted), and determination of lung cancer cases to investigate possible sources of heterogeneity. To investigate the potential lung cancer risk at low-level arsenic exposure, we pooled RRs at arsenic concentrations less than 100 μg L^{-1}. A sensitivity analysis was performed to detect outliers that may have a significant influence on pooled effect size by removing one study in each turn and then recalculating the new overall estimate risk of the remaining studies.

In addition, we performed a dose–response meta-analysis using the method of Greenland and Long Necker.[17] This analysis was restricted to studies with the same study designs and measures of association and studies that examined the lung cancer risks under three or more arsenic exposure levels. Midpoint arsenic concentrations were calculated and assigned to corresponding RRs. The highest exposure level with an open upper boundary was considered to share the same range with its adjacent level, while the lower boundary of the lowest level with an open-end was set to zero. Urine and toenail arsenic concentrations were converted to their equivalent drinking water arsenic concentrations (1 μg g^{-1} urine concentrations or 0.05 μg g^{-1} toenail concentration = 1 μg L^{-1} drinking water concentration).[6,18] A two-stage hierarchical regression model was performed by modeling arsenic concentrations using restricted cubic splines with 3 knots at fixed percentiles (10%, 50%, and 90%). The methods of generalized least squares and multivariate maximum likelihood were used to estimate the linear dose–response relationship, and a p value for nonlinearity was calculated. Data analyses were conducted using Stata version 14.1 (Stata Corp, College Station, TX, USA).

Results

Literature search

We initially identified 860 records from PubMed. Among these, 103 potentially eligible records were chosen for abstract

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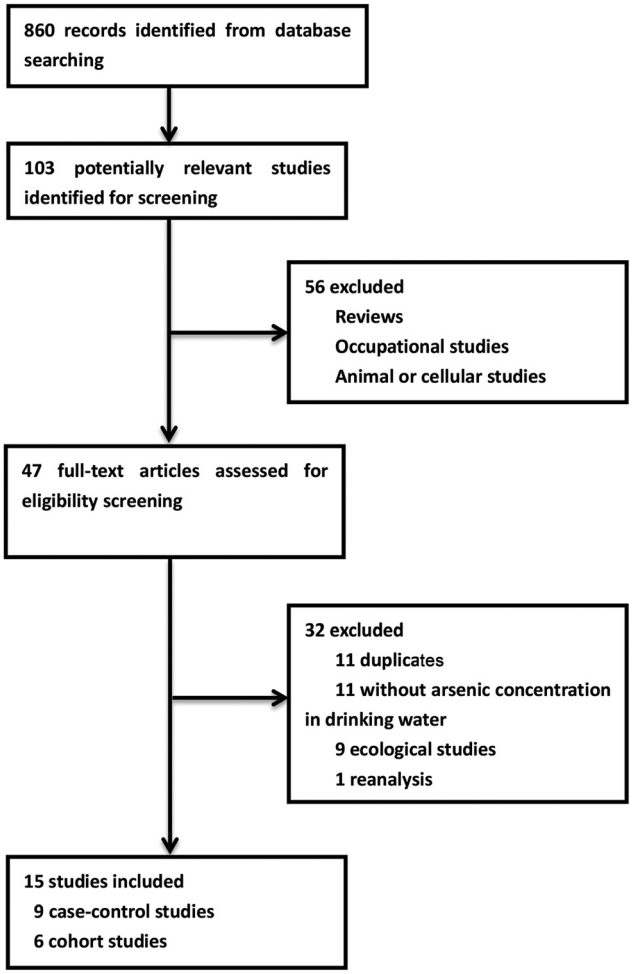

Fig. 1 Flow diagram of the study selection process.

screening and 56 studies were excluded because they were reviews, occupational studies, animal studies, or cellular studies. After full-text screening the remaining 47 articles, 15 studies[8,9,12,19–30] involving a total of 218 481 participants met the inclusion criteria (Fig. 1).

Study characteristics

Table 1 shows the characteristics for each of the included studies. The publication year of the 15 included studies ranged from 1995 to 2015, including 6 from South America (five studies in Chile[11,20,23,29,30] and one study in Argentina[25]), 4 from Asia (2 studies in Taiwan,[19,24] one study in Bangladesh,[22] and one study in Japan[20]), 3 from the US,[23,26,28] and 2 from European countries (Denmark[8] and Italy[9]). These consist of nine case-control studies[12,21–23,25–27,29,30] and six cohort studies.[8,9,19,20,24,28] The nine case-control studies were incidence studies with adjusted odds ratios as the measure of the association. Three of the six included cohort studies were incidence studies with adjusted incidence rate ratio as the measure of association.[8,19,24] The other three cohort studies were mortality studies,[9,20,28] with two of them using hazard ratio[9,28] and the third study using standardized mortality ratio[20] as the measure of association. Six[8,9,20,24,28,30] of the 15 studies ascertained lung cancers from national/local cancer registry and nine from hospitals. Two studies estimated arsenic exposure *via* biomarkers (toenail[23] and urine,[28] respectively), 1 estimated cumulative arsenic exposure from drinking water per year,[19] 8 used recorded average arsenic concentrations,[8,9,12,21,22,27,29,30] 1 used medium arsenic concentrations,[24] and 3 used the highest known arsenic concentrations among all measured drinking water as the exposure metric.[20,25,26] Twelve of the 14 studies provided results adjusted for potential confounding factors,[8,9,12,19,21–26,28–30] while eleven of them provided results adjusted for smoking.[12,19,21,22,24,26,28–30]

As for methodological quality (Tables 2 and 3), six[12,21,23,26,29,30] of the nine (62%) case-control studies and five[8,9,19,24,28] of the six (83%) cohort studies were based on low risk of bias.

Full concentration ranges of arsenic exposure

Table 4 shows the RRs of lung cancer observed among people exposed to different arsenic concentrations. The pooled RR indicated that exposure to arsenic in drinking water over the full concentration range (10 μg L^{-1}–1000 μg L^{-1}) was significantly associated with increased risk of lung cancer (RR, 1.21; 95% confidence interval [CI], 1.05–1.37; Fig. 2). Sensitivity analysis did not detect an outlier among these studies. Heterogeneity among studies was substantial in these meta-analyses (I^2 = 53.4%), which warranted further examination *via* subgroup analysis.

In subgroup analysis (Table 5), heterogeneity disappeared in studies conducted in North America and studies that used cumulative exposure or biomarkers as the exposure metric. The significant association between arsenic in drinking water and increased lung cancer risks remained in studies conducted in South America (RR, 1.50; 95%CI, 1.20–1.88) and Europe (RR, 1.39; 95%CI, 0.88–1.39). Moreover, this statistically significant association was stronger in adjusted studies (RR, 1.21; 95%CI, 1.05–1.37) than in unadjusted studies (RR, 1.25; 95%CI, 0.40–2.09).

Low to moderate arsenic concentrations exposure

Of the thirteen included studies that exclusively examined the potential lung cancer risks at low to moderate arsenic concentrations (<100 μg L^{-1}) in drinking water, four studies[9,23,28,29] provided supportive evidence. One case-control study (92 cases and 288 population-based controls) conducted in Chile reported that after adjustment for age, sex, and smoking, there was a significant trend of increased lung cancer risks among both old and young residents exposed to 6.5 μg L^{-1} to 58.6 μg L^{-1} mean arsenic water concentrations.[29] Similar results were obtained from an Italian cohort of 165 609 residents, in which mean arsenic exposure of 19.3 μg L^{-1} and average exposure duration of 39.5 years was significantly associated with increased risks of lung cancer in both sexes (hazard ratio [HR] = 2.61 males; HR = 2.09 females).[9] In an American study

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Table 1 Characteristics of included 15 studies by study design

Author and year	Population	Continent	N (follow-up)	Exposure metric	Exposure levels	Outcome	Outcome ascertainment	Measure of association	Adjustment
Case-control study									
Steinmaus *et al.*, 2014[29]	Northern Chile, early-life (<15 years) exposure	South America	Case: 370/ control: 289	Average exposure (μg L^{-1})	≤110, 111–800, >800	Incidence	Hospital	OR	Age, sex, smoking, mining work, occupational carcinogen exposure, socio economic status, and obesity
Ferreccio *et al.*, 2000[21]	Northern Chile	South America	Case: 152/ control: 419	Average exposure (μg L^{-1})	0–10, 10–29, 30–49, 50–199, 200–400	Incidence	Hospital	OR	Age, sex, socioeconomic status, smoking, and working in a copper smelter
Mostafa *et al.*, 2008[22]	Bangladesh	Asia	Case: 3223/ control: 1588	Average exposure (μg L^{-1})	≤10, 11–50, 51–100, 101–400	Incidence	Hospital	OR	Smoking and age
Heck *et al.*, 2009[23]	US	North America	Case: 100/ control: 97	Toenail arsenic concentration (μg g^{-1})	<0.05, 0.05–0.0768, 0.0768–0.1137, ≥0.05	Incidence	Hospital	OR	Sex, age, race, educational attainment
Steinmaus *et al.*, 2010[25]	Cordoba, Argentina	South America	Case: 43/ control: 75	Highest (μg L^{-1})	<99, 100–199, ≥200	Incidence	Hospital	OR	Sex, age
Dauphiné *et al.*, 2013[26]	Nevada and Kings County, California	North America	Case: 90/ control: 147	Highest (μg L^{-1})	≤10, 11–84, ≥85	Incidence	Hospital	OR	Sex, age, education, smoking, other lung carcinogens
Ferreccio *et al.*, 2013[12,27]	Northern Chile	South America	Case: 215/ Control: 431	Average exposure (μg L^{-1})	0–59, 60–199, 200–799, ≥800	Incidence	Hospital	OR	—
Steinmaus *et al.*, 2013[12,26,27]	Northern Chile	South America	Case: 232/ Controls: 640	Average exposure (μg L^{-1})	<26, 26–79, 80–197, >197	Incidence	Hospital	OR	Age, sex, smoking, mining work, race, body-mass index, and socioeconomic status
Smith *et al.*, 2009[30]	Northern Chile	South America	Case: 140/ Control: 327	Average exposure (μg L^{-1})	10–59, 60–199, 200–399, 400–699, 700–999	Incidence	National/local cancer registry	OR	Age, sex, smoking status, employment in copper smelting, and socioeconomic status
Cohort study									
Chiou *et al.*, 1995[19]	Southwestern Taiwan	Asia	2256 (0.05–7.69 years)	Cumulative exposure μg L^{-1} year	0, 100–19 900, >20 000	Incidence	Hospital	IRR	Age, sex, smoking
Baastrup *et al.*, 2008[8,31]	Denmark	Europe	56 378 (6–10 years)	Average exposure (μg L^{-1})	0.05–25.3	Incidence	National/local cancer registry	IRR	Smoking, alcohol drinking, hormone therapy, occupation, diet
Chen *et al.*, 2010[24]	Northeast Taiwan	Asia	8086 (11 years)	Median (μg L^{-1})	<10, 10–49.9, 50–99.9, 100–299.9, ≥300	Incidence	National/local cancer registry	IRR	Age, sex, education, smoking, alcohol drinking
D'Ippoliti *et al.*, 2015[9]	Viterbo, Central Italy	Europe	138 800 (20 years)	Average exposure (μg L^{-1})	≤10, 10–20, >20	Mortality	National/local cancer registry	HR	Age, calendar period, socioeconomic level, occupation, smoking, radon exposure
Tsuda *et al.*, 1995[20]	Japan	Asia	454 (33 years)	Highest (μg L^{-1})	<50, 50–990, >1000	Standard mortality ratio	National/local cancer registry	SMR	NR
García-Esquinas *et al.*, 2013[28]	US	North America	3932 (2 years)	Urine arsenic concentration (μg g^{-1})	<6.91, 6.91–13.32, >13.32	Mortality	National/local cancer registry	HR	Region, age; sex, education, smoking, alcohol drinking and weight

Abbreviation: OR, odds ratio; IRR, incidence rate ratio; HR, hazard ratio; NR, not reported.

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Table 2 Newcastle-Ottawa quality assessment scale for case-control studies

	Selection				Comparability		Exposure		
Study	Is the case definition adequate?[a]	Representativeness of the cases[b]	Selection of controls[c]	Definition of controls[d]	Study controls for age, sex	Study controls for any additional factors (*e.g.* smoking)	Ascertainment of exposure[e]	Non-response rate[f]	Total
Steinmaus *et al.*, 2014[29]	1	1	1	1	1	1	0	0	6
Ferreccio *et al.*, 2000[21]	1	1	0	1	1	1	0	1	6
Mostafa *et al.*, 2008[22]	1	1	0	1	0	1	0	0	4
Heck *et al.*, 2009[23]	1	1	1	1	1	1	1	0	7
Steinmaus *et al.*, 2010[25]	1	1	1	0	1	0	0	0	4
Dauphiné *et al.*, 2013[26]	1	1	1	1	1	1	1	1	8
Ferreccio *et al.*, 2013[12,27]	1	1	1	1			0	0	4
Steinmaus *et al.*, 2013[12,26,27]	1	1	1	1	1	1	0	0	6
Smith *et al.*, 2009[30]	1	1	1	1	1	1	0	0	6

[a] Requires some independent validation (*e.g.*, >1 person/record/time/process to extract information or reference to primary record source such as X-rays or medical/hospital records). [b] All eligible cases with outcome of interest over a defined period of time, all cases in a defined catchment area, all cases in a defined hospital or clinic, group of hospitals, health maintenance organization, or an appropriate sample of those cases (*e.g.*, random sample). [c] Requires community controls (*i.e.*, same community as cases and would be cases if had outcome). [d] If cases are first occurrence of outcome, then it must explicitly state that controls have no history of this outcome. If cases have new (not necessarily first) occurrence of outcome, then controls with previous occurrences of outcome of interest should not be excluded. [e] Requires independent blind assessment. [f] Requires same rate for both groups.

Table 3 Newcastle-Ottawa quality assessment scale for cohort studies

	Selection				Comparability		Outcome			
Study	Representativeness of the intervention cohort[a]	Selection of the non-intervention cohort[b]	Ascertainment of intervention[c]	Demonstration that outcome of interest was not present at start of study	Study controls for age, sex	Study controls for any additional factors (*e.g.*, smoking)	Assessment of outcome[d]	Was follow up long enough for outcomes to occur[e]	Adequacy of follow up of cohorts	Total
Chiou *et al.*, 1995[19]	1	1	0	0	1	1	0	1	0	5
Baastrup *et al.*, 2008[8,31]	1	1	1	1	1	1	0	1	0	7
Chen *et al.*, 2010[24]	1	1	0	0	1	1	0	1	0	5
D'Ippoliti *et al.*, 2015[9]	1	1	0	0	1	1	0	1	0	5
García-Esquinas *et al.*, 2013[28]	1	1	1	0	1	1	0	1	0	6
Tsuda *et al.*, 1995[20]	0	1	0	0	0	0	0	1	1	3

[a] Truly representative of the average, elderly, community-dwelling resident. [b] Drawn from the same community as the intervention cohort. [c] Secure record (*e.g.*, health care record). [d] Independent blind assessment. [e] If median duration of follow-up ≥6 months.

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Table 4 Relative risk of lung cancer at different arsenic exposure levels in each study

Study	Exposure metric	Exposure levels	RR (95%CI)
Case-control study			
Steinmaus *et al.*, 2014[29]	Average exposure (μg L^{-1})	111–800	0.95 (0.46–1.97)
		>800	1.32 (0.75–2.34)
Ferreccio *et al.*, 2000[21]	Average exposure (μg L^{-1})	10–29	1.60 (0.50–5.30)
		30–49	3.90 (1.20–12.30)
		50–199	5.20 (2.30–11.70)
		200–400	8.90 (4.00–19.60)
Mostafa *et al.*, 2008[22]	Average exposure (μg L^{-1})	11–50	1.25 (0.96–1.62)
		51–100	1.37 (0.92–2.03)
		101–400	1.65 (1.25–2.18)
Heck *et al.*, 2009[23]	Toenail arsenic concentration (μg g^{-1})	0.11–0.17	1.34 (0.71–2.53)
		0.17–0.25	1.10 (0.55–2.20)
		>0.25	0.89 (0.46–1.75)
Steinmaus *et al.*, 2010[25]	Highest (μg L^{-1})	0–99	0.46 (0.14–1.35)
		100–199	0.86 (0.26–2.69)
		≥200	2.20 (0.62–8.82)
Dauphiné *et al.*, 2013[26]	Highest (μg L^{-1})	11–84	0.75 (0.45–1.25)
		≥85	0.84 (0.41–1.72)
Ferreccio *et al.*, 2013[12,27]	Average exposure (μg L^{-1})	60–199	0.77 (0.49–1.21)
		200–799	1.38 (0.89–2.13)
		≥800	2.39 (1.61–3.54)
Steinmaus *et al.*, 2013[12,26,27]	Average exposure (μg L^{-1})	26–79	0.98 (0.62–1.53)
		80–197	1.70 (1.05–2.75)
		>197	3.18 (1.90–5.30)
Smith *et al.*, 2009[30]	Average exposure (μg L^{-1})	10–59	0.70(0.30–1.70)
	Average exposure (μg L^{-1})	60–199	3.40(1.80–6.50)
	Average exposure (μg L^{-1})	200–399	4.70(2.00–11.00)
	Average exposure (μg L^{-1})	400–699	5.70(1.90–16.90)
	Average exposure (μg L^{-1})	700–999	7.1(3.4–14.8)
Cohort study			
Chiou *et al.*, 1995[19]	Cumulative exposure μg L^{-1} year	50–700	2.10 (0.70–6.80)
		>710	2.70 (0.70–10.20)
Baastrup *et al.*, 2008[8,31]	Average exposure (μg L^{-1})	0.05–25.3	0.99 (0.90–1.08)
Chen *et al.*, 2010[24]	Median (μg L^{-1})	10–49.9	1.10 (0.74–1.63)
		50–99.9	0.99 (0.59–1.68)
		100–299.9	1.54 (0.97–2.46)
D'Ippoliti *et al.*, 2015[9]	Average exposure (μg L^{-1})	10–20	1.47 (1.17–1.86)
		>20	1.83 (1.41–2.39)
García-Esquinas *et al.*, 2013[28]	Urine arsenic concentration (μg g^{-1})	6.91–13.32	0.94 (0.51–1.72)
		>13.32	1.82 (1.00–3.31)
Tsuda *et al.*, 1995[20]	Highest (μg L^{-1})	<50	0.001 (0.001–2.43)
		50–990	2.33 (0.12–13.39)
		>1000	15.69 (7.38–31.02)

Abbreviation: RR, relative risk; CI, confidence interval.

that used urine concentrations for inorganic plus methylated arsenic species as biomarkers, low to moderate exposure to arsenic (median = 9.7 μg g^{-1} creatinine) was prospectively associated with increased mortality for lung cancer (adjusted HR = 1.56; 95% CI = 1.02–2.39).[28] Another American biomarker (toenail arsenic concentrations) study with a case-control design found that lower levels of arsenic exposure were significantly associated with an increased risk of two specific histologic types of lung cancer: small-cell and squamous-cell lung cancer.[23]

In contrast, a case-control study found that arsenic concentrations near 100 μg L^{-1} were not associated with markedly high relative risks of lung cancer among 196 cases and 359 controls matched on age and gender in the US.[26] A prospective Danish cohort of 57 053 persons also found no significant association between exposure to low levels of arsenic (mean = 1.2 μg L^{-1}) and risk for cancers of the lung.[8] In another prospective cohort study, there was also no apparent increased lung cancer risk at arsenic concentrations between 10 and 100 μg L^{-1} among 6888 participants followed for 11 years.[24]

In the subgroup meta-analysis of 13 included studies[9,12,20–26,28–31] that reported RRs of lung cancer at water arsenic concentrations below 100 μg L^{-1}, we did not observe a statistically increased lung cancer risk (RR = 1.18; 95% CI = 1.00–1.36; I^2 = 56.3%).

Dose–response meta-analysis

Eight case-control studies[12,21–23,25–27,29] involving a total of 8026 participants provided the required data for dose–response meta-analysis. In analyses where water arsenic was modeled as restricted cubic splines of log-transformed arsenic

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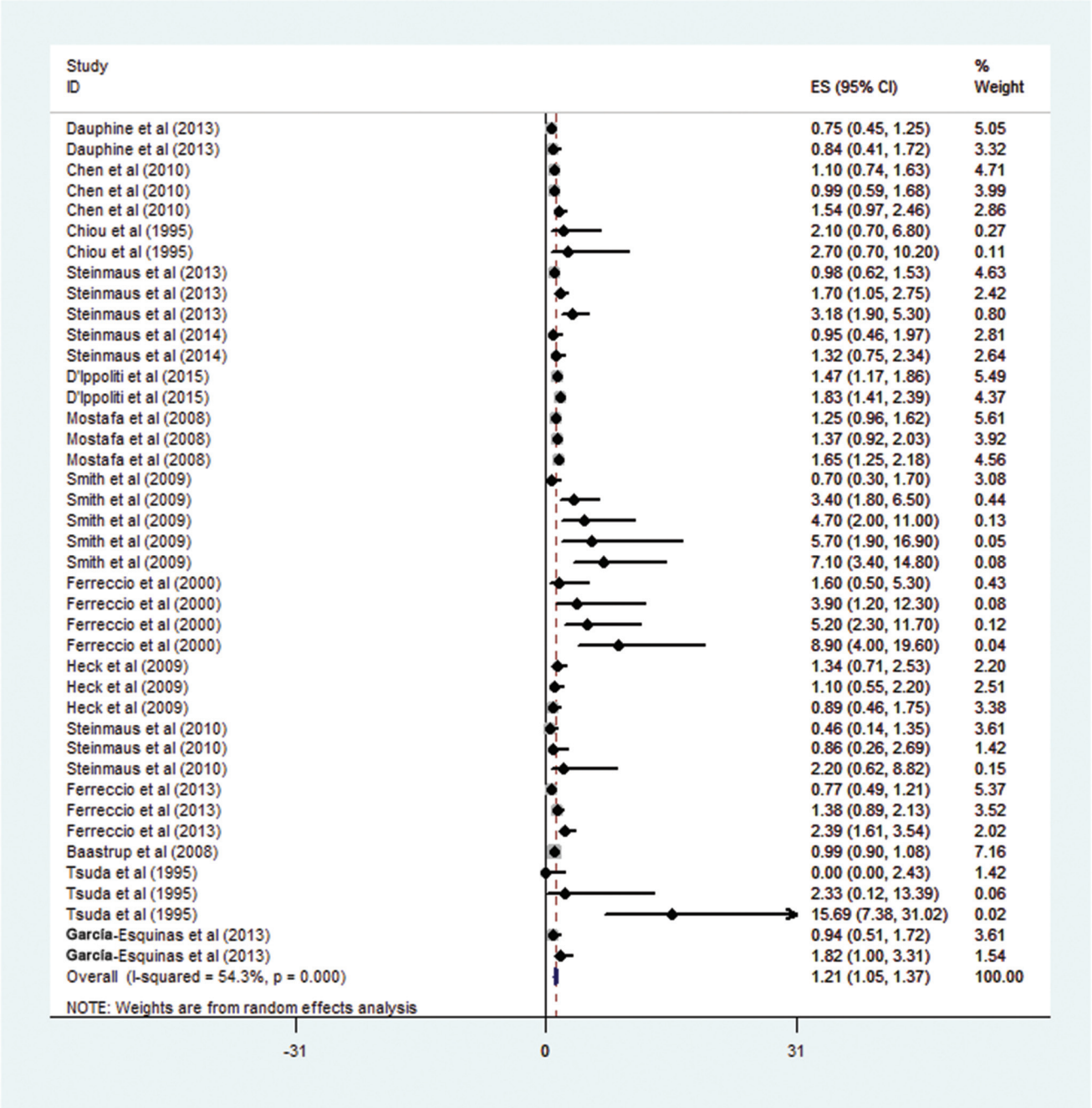

Fig. 2 Forest plot of 15 studies on the association between relative risks of lung cancer and full range arsenic concentrations (10 μg L^{-1}–1000 μg L^{-1}) in drinking water.

concentrations, we found no statistical evidence of a departure from a constant dose–response association (p value for non-linear trend = 0.64; Fig. 3). We found an increased risk of lung cancer with increasing exposure to arsenic in drinking water. The corresponding pooled RRs and their 95%CIs for exposure to 10 μg L^{-1}, 50 μg L^{-1}, and 100 μg L^{-1} water arsenic were 1.02 (1.00–1.03), 1.10 (1.04–1.15), and 1.20 (1.08–1.32), respectively. There was evidence of heterogeneity among studies (P value for heterogeneity <0.001).

Discussion

This meta-analysis adds to the evidence for the significant association between increased lung cancer risks and full range (10 μg L^{-1}–1000 μg L^{-1}) and low to moderate range (<100 μg L^{-1}) of arsenic concentrations in drinking water. The dose–response meta-analysis also found increased pooled RRs of lung cancer in relation to log transformed arsenic concentrations across low, moderate, and high levels of arsenic in

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Table 5 Subgroup meta-analyses of relative risk of lung cancer exposed to arsenic *via* drinking water

Stratified variable	k^a	Relative risk (95%CI)	$I^{2,b}$ %
Study design			
Cohort studies	16	1.24 (0.97–1.52)	60.7
Case-control studies	26	1.15 (0.95–1.36)	43.9
Geographic location			
North America	7	1.21 (1.05–1.37)	0
South America	21	1.50 (1.20–1.88)	55.5
Europe	5	1.39(0.88–1.39)	88.3
Asia	9	1.26(0.99–1.54)	35.2
Exposure measurement			
Cumulative	2	1.24 (0.42–2.05)	42.9
Average	22	1.38 (1.15–1.82)	66.7
Biomarker	5	1.08 (0.81–1.50)	0
Median	4	1.14 (0.82–1.45)	0
Highest	8	0.88 (0.21–1.05)	22.0
Analysis			
Adjusted	33	1.21(1.05–1.37)	49.8
Unadjusted	9	1.25 (0.40–2.09)	74.6
Determination of cases			
Diagnostic method	24	1.19 (0.98–1.40)	45.4
Record	18	1.28 (0.98–1.55)	64.9

Abbreviation: CI, confidence interval. [a] The number of individual effect sizes. [b] Heterogeneity among studies; I^2 values of near or less than 25%, near 50% and near or higher than 75% represent low, moderate and high heterogeneity, respectively.

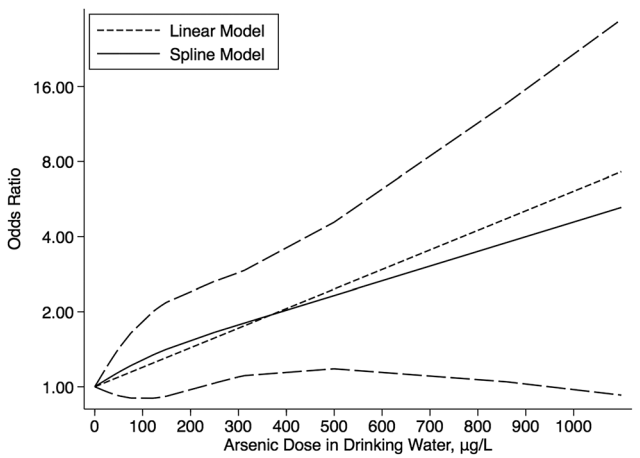

Fig. 3 Dose–response meta-analysis of log-transformed arsenic in drinking water and relative risks of lung cancer based on 8 case-control studies. Both linear and nonlinear regression lines are shown. The black solid curve and thin dashed straight line represents estimates of adjusted relative risk of lung cancer across average arsenic levels in drinking water relative to a reference level of 0 μg L^{-1}. The region between two thick dashed lines represents the 95% CI around the regression line. The vertical axis is on a log scale.

drinking water. We found no statistical evidence of non-linear dose–response association, although the non-linear association cannot be excluded because of our limited statistical power.

Previous systematic reviews of arsenic in drinking water and lung cancer risks have identified strong evidence on the increased lung cancer risks at high levels of arsenic in drinking water. However, they have been inconclusive about the lung cancer risks at low to moderate arsenic concentrations (<100 μg L^{-1}). In this review, subgroup meta-analysis and dose–response meta-analysis identified a significant increase in lung cancer risks at arsenic concentrations below 100 μg L^{-1}. This finding is consistent with a previous meta-analysis including five studies of lung cancer, in which there are about 4.51 estimated lung cancer cases per 100 000 people for a maximum arsenic contamination level of 10 μg L^{-1}.[6] However, in comparison, this review included ten more studies through an updated search, so the enlarged sample size enhanced our statistical power to provide a more reliable estimate. In contrast, two previous reviews found no increase in lung cancer risks at low arsenic levels by conducting meta-regression analyses based on six and seven studies of lung cancer, respectively.[10,11] This disparity is likely due to the use of different data and methodology. Again, this review included more studies, all of which were cohort or case-control designs, unlike one of the previous meta-regression analyses that also included ecological studies that are generally susceptible to bias and are likely to dilute the real effects because of the lack of individual data.[10]

However, the interpretation of our findings is restricted by several limitations. First, this meta-analysis was based on observational studies, and substantial heterogeneity among studies was observed. Possible important sources of heterogeneity include differences in population characteristics (*e.g.*, genetic susceptibility, nutrition, pre-existing disease, or smoking status), study design and quality, exposure measurement, outcome ascertainment, and control for confounding. However, the investigation of heterogeneity *via* subgroup analysis may improve the understanding of the degree of comparability across studies.[32] As indicated by our subgroup analyses, geographic location and arsenic exposure definition contribute to the significant heterogeneity observed in total analysis, which was absent in North American studies and studies that used median or biomarkers of arsenic. Second, to ensure study quality and best inform the dose–response assessment, we excluded ecological studies and cross-sectional studies. However, these study designs remain informative for the overall assessment of the association between arsenic and lung cancer risks. Although cohort studies are generally superior to case-control studies in terms of examining incident endpoints, they were excluded from our dose–response meta-analysis due to the lack of required data.

We found no evidence of a non-linear dose–response relationship between log-transformed arsenic concentrations in drinking water and increased lung cancer risks, which is consistent with a previous meta-regression analysis.[11] However, it seems that we were underpowered to characterize the non-linear relationship due to the small number of studies and few exposure categories of each study. According to mechanism studies on arsenic carcinogenesis, there is a non-linear threshold dose–response at low dose arsenic exposures.

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The associated group proposed a theory of modes of action; this theory explains that the development of arsenic-related cancer is initiated and enhanced by regenerative cell proliferation induced by the cytotoxicity of inorganic arsenic.[33] The assignment of a single value for all participants within a wide exposure range may not result in robust and precise dose–response relationship water, particularly at low water arsenic levels.[11] The approach of estimating median arsenic concentrations for two biomarker studies[23,28] may also result in exposure misclassification. Hence, we were unable to estimate a safe threshold for arsenic concentrations in drinking water based on available epidemiological data.

Given the inherent limitations of meta-analyses based on published data from observational epidemiological studies, larger longitude studies with careful measurement of arsenic in drinking water distinguished from other sources (*e.g.*, food or air) may be needed to comprehensively assess the potential non-linear relationship at low-dose arsenic levels. Examining arsenic exposure *via* a biomarker (*e.g.*, toenail or urine) is an ideal option in terms of determining the internal dose and capturing low to moderate levels of arsenic in drinking water. However, biomarkers should be collected prospectively as the association between arsenic in a biomarker and drinking water is complex. This is because the association might be determined by both the concentrations and exposure duration of arsenic in drinking water; also, the results might get affected by individual differences in body weight, metabolism, toenail growth, and urine dilution.[34]

In conclusion, our meta-analysis found a significant increase in lung cancer risks among people exposed to inorganic arsenic *via* drinking water. We found no statistical evidence of a non-linear dose–response association between arsenic in drinking water and lung cancer risks; although the statistical power was limited. Reducing arsenic levels in drinking water even under the current EPA standard of 10 μg L^{-1} may be necessary given the widespread exposure to arsenic in many parts of the world.

Conflicts of interest

There are no conflicts to declare.

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