Toxicology 317 (2014) 17–30

Contents lists available at ScienceDirect

Toxicology

journal homepage: www.elsevier.com/locate/toxicol

Arsenic exposure and bladder cancer: Quantitative assessment of studies in human populations to detect risks at low doses☆

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ARTICLE INFO

Article history:
Received 1 October 2013
Received in revised form
22 November 2013
Accepted 9 January 2014
Available online 21 January 2014

Keywords:
Arsenic
Drinking water
Bladder cancer risk
Meta-analysis
Risk assessment

ABSTRACT

While exposures to high levels of arsenic in drinking water are associated with excess cancer risk (e.g., skin, bladder, and lung), exposures at lower levels (e.g., <100–200 μg/L) generally are not. Lack of significant associations may result from methodological issues (e.g., inadequate statistical power, exposure misclassification), or a different dose–response relationship at low exposures, possibly associated with a toxicological mode of action that requires a sufficient dose for increased tumor formation. The extent to which bladder cancer risk for low-level arsenic exposure can be statistically measured by epidemiological studies was examined using an updated meta-analysis of bladder cancer risk with data from two new publications. The summary relative risk estimate (SRRE) for all nine studies was elevated slightly, but not significantly (1.07; 95% confidence interval [CI]: 0.95–1.21, *p*-Heterogeneity [*p*-H] = 0.543). The SRRE among never smokers was 0.85 (95% CI: 0.66–1.08, *p*-H = 0.915), whereas the SRRE was positive and more heterogeneous among ever smokers (1.18; 95% CI: 0.97–1.44, *p*-H = 0.034). The SRRE was statistically significantly lower than relative risks predicted for never smokers in the United States based on linear extrapolation of risks from higher doses in southwest Taiwan to arsenic water exposures >10 μg/L for more than one-third of a lifetime. By contrast, for all study subjects, relative risks predicted for one-half of lifetime exposure to 50 μg/L were just above the upper 95% CI on the SRRE. Thus, results from low-exposure studies, particularly for never smokers, were statistically inconsistent with predicted risk based on high-dose extrapolation. Additional studies that better characterize tobacco use and stratify analyses of arsenic and bladder cancer by smoking status are necessary to further examine risks of arsenic exposure for smokers.

1. Introduction

A considerable amount of epidemiological, experimental toxicology, medicinal, and in vitro mechanistic toxicology research has focused on evaluating arsenic's dose–response relationship for cancer and other health effects. A recent review reports that the weight of evidence collectively suggests a dose–response relationship for cancer that arises following non-cancer toxicity that progresses to tumor formation with sufficient dose and duration of exposure (Cohen et al., 2013). Such a mode of action may result in a non-linear dose–response relationship in which little risk of cancer would occur until exposure is sufficiently increased. A lower drinking-water exposure concentration at about 100–150 μg/L was estimated to result in a concentration of trivalent arsenical species in bladder cells that would be sufficient to exert toxic effects, and thereby to increase the risk of cancer (Cohen et al., 2013).

Ecological studies of cancer mortality in a large population in southwest (SW) Taiwan exposed to high arsenic levels in well water (Tseng, 1977; Tseng et al., 1968; Wu et al., 1989; Chen et al., 1992) have been the focus of dose–response assessments of arsenic cancer risk by the U.S. Environmental Protection Agency (EPA) (U.S. EPA, 1998). EPA's recent estimates of arsenic cancer risk have increased the slope of the dose–response assessment of arsenic carcinogenicity (e.g., 40 CFR 6976-7066 2001; U.S. EPA, 2007, 2008, 2010), based on a review and analysis conducted by NRC (2001). NRC (2001) estimated risks of bladder and lung cancer for arsenic in drinking water

Abbreviations: SRRE, summary relative risk estimate; SW, southwest; NE, northeast; RR, relative risk; ELR, excess lifetime risk; BLR, background lifetime risk; *p*-H, *p* value for heterogeneity; CI, confidence interval.

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http://dx.doi.org/10.1016/j.tox.2014.01.004

in the United States based on linear extrapolation of risk as a function of dose for the SW Taiwan population. NRC (2001) predicted that lifetime exposure to arsenic in drinking water at 10 μg/L (the revised U.S. drinking-water standard) would result in a bladder cancer risk of about 2 in 1000—far greater than the upper end of the EPA target risk range of 1 in 10,000 (55 Fed. Reg. 8665-8865).

Although case-control (e.g., Steinmaus et al., 2013) and cohort (e.g., Chen et al., 2010a,b) studies in other populations confirm the risk of bladder and lung cancer at high arsenic doses, the appropriateness and reliability of models that assume a linear increase in risk at low doses based on SW Taiwan has been questioned (Brown, 2007; Lamm et al., 2013; Cohen et al., 2013). Research on the toxicological mode of action of arsenic, which does not involve direct reactivity with DNA (Nesnow et al., 2002), likewise supports a non-linear dose–response relationship (Snow et al., 2005; Cohen and Arnold, 2011; Clewell et al., 2011; Yager et al., 2013; Cohen et al., 2013).

In addition, making inferences from ecological studies is problematic because of numerous methodological concerns, such as a lack of individual level data, confounding, and within-group misclassification. The study populations in SW Taiwan also differ from other populations (e.g., United States) in terms of levels of exposure, nutritional status, prevalence of liver dysfunction from hepatitis B virus, socioeconomic factors, access to medical care, lifestyle factors, and possibly genetic traits (Chen et al., 1986, 1988, 2001). Because of these limitations, generalizability to other populations is compromised.

Despite the positive associations observed in studies conducted among highly exposed populations, observational epidemiological studies of low-level exposures in the United States and other countries (e.g., <100–200 μg/L arsenic in drinking water) have generally not indicated a statistically significant increase in bladder cancer risk with arsenic exposure (e.g., Bates et al., 1995, 2004; Kurttio et al., 1999; Lewis et al., 1999; Steinmaus et al., 2003; Karagas et al., 2004; Lamm et al., 2004; Michaud et al., 2004; Baastrup et al., 2008; Mink et al., 2008). Compared to ecological studies of 40,000 people in SW Taiwan, studies of populations with low-level exposure may be limited by inadequate statistical power to identify statistically significant relative risk estimates between 1.2 and 2.0, and by potential misclassification of exposure (NRC, 2001; Gibb et al., 2011).

To address the issue of individual study power of low-level exposure studies, and to quantitatively summarize the associations by various sub-groups, we previously conducted a meta-analysis of cohort and case-control epidemiologic studies that examined low-level arsenic exposure and bladder cancer risk (Mink et al., 2008). The overall summary relative risk estimate (SRRE) was weakly elevated but not statistically significant for all studies combined (1.11; 95% confidence interval [CI]: 0.95–1.30). However, summary associations varied by smoking status; the SRRE for *ever* smokers was 1.24 (95% CI: 0.99–1.56), whereas a non-significant inverse association was observed for *never* smokers (0.81, 95% CI: 0.60–1.08).

The lack of a statistically significant increase in relative risks at low doses in the United States may still be consistent with the linear extrapolations from high doses using the SW Taiwan data, however, because of difficulty in distinguishing arsenic risks at lower exposures from the background rate of bladder cancer in the United States (NRC, 2001; Gibb et al., 2011). Less-than-lifetime exposure to elevated arsenic levels in drinking water for a more mobile U.S. population, compared to SW Taiwan, reduces associated risks because cancer risk is assumed to be proportional to arsenic dose and duration of exposure (NRC, 2001; U.S. EPA, 2001; Gibb et al., 2011). Similarly, higher background rates of bladder and lung cancer in the United States result in lower relative risks (i.e., an increase in risk relative to background risk) based on the modeling of NRC (2001) (Gibb et al., 2011). Low relative risks decrease the ability of epidemiological studies to statistically detect increased risks predicted by NRC (2001).

Given the continued scientific interest in and importance of resolving the dose–response for arsenic carcinogenicity at low doses for public health (Gibb et al., 2011; Lamm et al., 2013; Cohen et al., 2013; NRC, 2013), we conducted a comprehensive update of our previous review and meta-analysis of low-level arsenic exposure and bladder cancer to evaluate the epidemiological evidence and compare it to predicted non-linear regions of the dose–response relationship based on the mode of action for arsenic toxicity and carcinogenicity. In addition, we evaluated the limitations of the evidence from these low-level epidemiological studies to assess consistency with the risk estimates of NRC (2001) (as examined more recently by Gibb et al. (2011) and Lamm et al. (2013)), given issues such as exposure misclassification, effect of smoking, study power, less-than-lifetime exposure, and differences in background cancer rates between the United States and SW Taiwan.

2. Materials and methods

2.1. Literature search and study inclusion

We updated our prior review and meta-analysis (Mink et al., 2008) by conducting a comprehensive literature search through November 2013 using the Medline database to identify studies of exposure to arsenic in drinking water and bladder cancer incidence and/or mortality. Searches included the keywords "arsenic," "bladder cancer," "bladder neoplasms," "water," and "epidemiol*" (where * = wildcard for any other characters), with variations of similar terms. Citations of recently published studies and reviews were also examined for relevant articles. Our original analysis included eight cohort and case-control studies of low-level (e.g., <100–200 μg/L arsenic in water) arsenic exposure and bladder cancer from the United States (Bates et al., 1995; Lewis et al., 1999; Steinmaus et al., 2003; Karagas et al., 2004), Finland (Michaud et al., 2004; Kurttio et al., 1999), South America (Bates et al., 2004), and NE Taiwan (Chiou et al., 2001). Our inclusion criteria consisted of: (1) case-control or cohort studies; (2) having an arsenic exposure metric for drinking-water concentration (i.e., largely <100 μg/L) or pertinent biomarker(s) related to exposure that would be within the "low-level" range; (3) available relative risks (e.g., rate ratios, odds ratios) and measures of variability (i.e., 95% CIs); (4) analytical metric comparisons of varying categorical or cumulative levels of arsenic exposure and bladder cancer; (5) control for smoking if needed; and (6) studies conducted in nutritionally sufficient populations to enhance comparability with U.S. populations. Case-control and cohort studies were selected, rather than ecological studies, because of their assessment of exposure/disease associations at the individual level and more efficient study design for evaluating bladder cancer incidence and mortality. Studies conducted in severely nutritionally deficient regions, as shown in SW Taiwan (Chen et al., 2001) and other populations (Yang et al., 2002; Gamble et al., 2007; Pilsner et al., 2009), have increased arsenic toxicity, and thus were excluded. Given our inclusion criteria, two studies (Meliker et al., 2010; Chen et al., 2010a) that evaluated low-level arsenic exposure in association with bladder cancer risk were identified since our original analysis (Mink et al., 2008). In total, nine studies are included in the current meta-analysis.

Meliker et al. (2010) conducted a population-based case control study of 11 counties in southeastern Michigan, where approximately 230,000 people are exposed to arsenic water concentrations of 10–100 μg/L. The population studied was described as residentially stable. Bladder cancer cases ($n = 411$) diagnosed between 2000 and 2004 were matched to 566 controls based on age, gender, and race. This study measured current arsenic water concentrations for participants and estimated water concentrations at previous residences. The exposure concentration was calculated as a time-weighted average based on information on residence location of participants over their lifetime combined with drinking water consumption information, accounting for 99% of participants' person-years. Associations based on analyses for the total study population and stratified analyses by smoking status were reported.

Chen et al. (2010a) is an update of the Chiou et al. (2001) study, which was included in our original meta-analysis, and evaluates a cohort of 8086 people exposed to elevated arsenic levels in well water in NE Taiwan. The relevant data from this update included 36 incident cases of urothelial cancer, adjusted for smoking status (no stratification of smoking status). The exposure groups included in the Chen et al. (2010a) study had a considerable number of study participants with arsenic water concentrations in the 100- to 300-μg/L range and >300 μg/L (up to 3000 μg/L), which exceeds the inclusion criteria for low-level exposure. We therefore excluded exposure categories that were greater than 100 μg/L and that were "unknown" in the Chen et al. (2010a) study for the current analysis, resulting in 12 incident cases. Data from Chen et al. (2010a) replaced Chiou et al. (2001) in the updated meta-analysis.