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Lifetime exposure to arsenic in drinking water and bladder cancer: a population-based case–control study in Michigan, USA

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Abstract

Objective—Arsenic in drinking water has been linked with the risk of urinary bladder cancer, but the dose–response relationships for arsenic exposures below 100 μg/L remain equivocal. We conducted a population-based case–control study in southeastern Michigan, USA, where approximately 230,000 people were exposed to arsenic concentrations between 10 and 100 μg/L.

Methods—This study included 411 bladder cancer cases diagnosed between 2000 and 2004, and 566 controls recruited during the same period. Individual lifetime exposure profiles were reconstructed, and residential water source histories, water consumption practices, and water

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arsenic measurements or modeled estimates were determined at all residences. Arsenic exposure was estimated for 99% of participants' person-years.

Results—Overall, an increase in bladder cancer risk was not found for time-weighted average lifetime arsenic exposure >10 μg/L when compared with a reference group exposed to <1 μg/L (odds ratio (OR) = 1.10; 95% confidence interval (CI): 0.65, 1.86). Among ever-smokers, risks from arsenic exposure >10 μg/L were similarly not elevated when compared to the reference group (OR = 0.94; 95% CI: 0.50, 1.78).

Conclusions—We did not find persuasive evidence of an association between low-level arsenic exposure and bladder cancer. Selecting the appropriate exposure metric needs to be thoughtfully considered when investigating risk from low-level arsenic exposure.

Keywords

Age factors; Arsenicals; Environmental exposure; Residential mobility; Urinary bladder

Introduction

Inorganic arsenic exposure is a risk factor for a range of adverse health outcomes including vascular diseases, skin ailments, cancers, and diabetes [1]. Drinking water is the predominant source of elevated inorganic arsenic exposure for most individuals due to naturally elevated arsenic concentrations in aquifers around the world [2]. Tens of millions of the world's citizens are exposed, with much debate over quantifying risks at chronic, low-level exposures [1, 2].

Worldwide, bladder cancer is the ninth most frequent type of cancer, resulting in more than 350,000 new diagnoses each year [3]. Highest incidence occurs in industrialized regions of Western Europe and the United States where nearly all cases of bladder cancer are transitional cell carcinomas (TCC) [4]. Cigarette smoking and a host of occupational exposures are the major risk factors for TCC of the bladder; however, many cases remain unexplained [4].

The International Agency for Research on Cancer [5] considers there to be sufficient evidence for arsenic to increase risk of urinary bladder cancer in humans; yet risks related to exposure in the 10–100 μg/L range remain uncertain. Valid and reproducible animal models that may serve to explain how arsenic induces cancer do not exist [1, 6, 7]. Epidemiologic studies continue to be the primary source of data used to assess cancer risks for exposed populations [1].

Evidence in support of an association between arsenic and bladder cancer has been based on studies in high-arsenic regions (>150 μg/L) [8–11]. At lower levels of arsenic exposure (<100 μg/L arsenic in drinking water), epidemiologic studies have provided less evidence of increased risk for bladder cancer [12–20]. However, as others have noted, many of these studies have encountered two stumbling blocks for assessing risk from low-to-moderate arsenic concentrations: inadequate sample size and exposure misclassification which may bias results toward the null [15, 21, 22]. Carefully designed epidemiologic studies of low-level arsenic exposure <100 μg/L are critical for informed risk assessment and management [21]. Expected risk from low-level arsenic exposure remains uncertain.

In this report, we present results from a population-based bladder cancer case–control study which incorporate lifetime exposure assessment in a residentially stable population in Michigan. High rates of bladder cancer mortality have been reported for nearly 50 years in southeastern Michigan, yet these elevated rates are not well explained [23]. Concentrations

of arsenic ≥50 μg/L were first reported in Michigan groundwater in 1981 [24]. Since then, arsenic has been identified in unconsolidated and bedrock aquifers throughout southeastern Michigan, with concentrations frequently exceeding the new Maximum Contaminant Level (MCL) of 10 μg/L set by the U.S. Environmental Protection Agency [25]. This region of Michigan has a population of 2.8 million people, with 1.6 million people relying on groundwater as their source of drinking water. Approximately 8% of the southeastern Michigan population (~ 230,000 people) are exposed to arsenic >10 μg/L in their drinking water, making this one of the largest populations with moderately elevated exposure in the United States [26].

Materials and methods

A population-based bladder cancer case–control study was conducted in eleven counties of southeastern Michigan (Fig. 1). These counties included Genesee, Huron, Ingham, Jackson, Lapeer, Livingston, Oakland, Sanilac, Shiawassee, Tuscola, and Washtenaw and were selected to investigate risk based on moderately elevated arsenic concentrations in the groundwater (<100 μg/L). Participants were offered a modest financial incentive; research was approved by the University of Michigan IRB-Health Committee and participants provided written informed consent. A total of 411 cases and 566 controls were determined to be eligible and completed all aspects of the study.

Cases diagnosed with urinary bladder cancer between 2000 and 2004 were recruited from the Michigan Cancer Surveillance Program (the state cancer registry), within the Division of Vital Records, Michigan Department of Community Health. Eligibility criteria included residence in the eleven county study area for at least the previous 5 years, age at diagnosis between 21 and 80 years, and no history of cancer per histology report in the cancer registry database (except for basal cell and squamous cell carcinomas of the skin which were not recorded by the registry). Cases were reported to the state cancer registry approximately 3–23 months following diagnosis, depending on each hospital's reporting system. There were 1,634 potentially eligible cases. Approximately 22% died prior to contact; the registry was not permitted by hospital or physician to contact another 5% of cases. The remaining cases were mailed a letter by the registry asking for permission to release their name and contact information to the research team. Of these 1,178 cases, 50% agreed to have their name released. Among the 584 cases subsequently contacted by the research team, 411 cases (70%) completed all phases of participation, including telephone interview, in-person interview, and providing environmental and biological samples. Thus, of the 1,634 potentially eligible cases, 25% completed all phases of participation, resulting in 411 participating cases.

Controls were frequency matched to recruited cases by age (±5 years), gender, and race and were recruited by random digit dialing of age-weighted lists by the Michigan Public Health Institute (MPHI). Age-weighted lists purchased from Genesys Sampling Systems were weighted to be representative of the age distribution of cases in the study area and were generated from telephone directories, automobile and motorcycle registries, real estate listings, and driver's license data. Random calls were made to 11,463 potential controls, and eligibility was determined based on answers to screening questions (at least 5 years of residence in the study area, no history of cancer except non-melanoma skin cancer, and appropriate case-matched frequencies of age, race, and gender). A number was dialed fifteen times during different times of day and days of week before it was retired. Of those numbers dialed, 3,341 were non-working/non-residential or were never answered, 3,333 resulted in hang-ups prior to screening, and 4,748 resulted in successful screening. Of those screened, 2,616 were found to be ineligible. Among the 2,132 eligible controls, 69% refused to

participate, 4% failed to complete all requirements of participation, and 27% completed all phases of participation, resulting in 566 participating controls.

Participants answered a 30–45 min computer-aided telephone interview which included questions on water and other fluid consumption, dietary habits, smoking, and medical history. This was conducted by trained MPHI interviewers to ensure standardization of the administration of the survey questionnaire and response entry. With regard to fluid consumption, participants reported consumption of water, beverages made with water, and different types of fluids not made with water at home, at work, and at places other than home or work. Current and previous consumption patterns, including detailed characterization of major changes in fluid consumption were reported. These questions were used to estimate water consumption at home (water + beverages made with water measured in L/day) and total fluid intake over the adult lifetime.

In addition to the telephone interview, participants were mailed residential and occupational history forms; research team members met with participants at their home to review and collect the forms. Participants provided written residential and occupational histories of each home lived-in and each job, for at least 1 year. Individuals were asked to report name of employer, list job title and to describe the nature of the work activity for occupations held for at least 1 year. Duration of residence/occupation, drinking water source, change in water source, and street address were requested for each location. If exact street address was unknown, participants were asked to identify the closest cross streets. Written forms were double-entered into a database and checked for discrepancies. If discrepancies were found, the original document was checked and relied on. Each residence in the study area was geocoded and assigned a geographic coordinate in ArcGIS (Version 9.0; ESRI, Redlands, CA, USA); residences outside the study area were not geocoded. Geocoding settings were the following: spelling sensitivity of 70, minimum candidate score of 10, and minimum match score of 60.

Lifetime arsenic exposure assessment

The approach developed for individual lifetime exposure assessment has been previously described [27]. Briefly, locations of residences were used to generate lifetime exposure estimates; previous sensitivity analyses indicated limited exposure from food or drinking water at other locations (e.g., place of occupation) in this region [28]. The research team met with participants where they lived, and water samples were collected from sources used for drinking (including coffee) and cooking, as well as untreated well water if participants used a private well. Water samples were analyzed for arsenic using an inductively coupled plasma mass spectrometry unit (ICP-MS, Model 7500c, Agilent Technologies, Santa Clara, CA). Each batch of samples included a standard reference material (NIST SRM 1640, Trace Elements in Natural Water), and the set acceptance criterion was ± 10% of the certified arsenic concentration in the SRM. Non-detects (n = 40) were assigned a level of 0.02 μg/L, equal to half of the average instrument detection limit. Additional details about the analytic protocol can be found elsewhere [29].

A geostatistical model was developed for predicting arsenic concentrations at past residences on private well water [30]. A soft indicator kriging approach was adopted, incorporating the spatial pattern in the State's arsenic database (n = 6,050 private untreated wells in the eleven county study area from 1993–2002) as well as secondary data such as geographic boundaries of different types of bedrock and unconsolidated geologic formations. The geostatistical model predicts arsenic concentration for 500 × 500 m^2 pixels. This model was validated using a separate test dataset of 371 well water measurements, and showed a Pearson's correlation r = 0.61; predicting above or below a 10 μg/L threshold resulted in sensitivity = 0.62, specificity = 0.80, and 75% agreement [31].

To estimate arsenic concentrations at past residences on public water supplies, 1,675 arsenic measurements in public well water supplies in the study area were extracted from a Michigan state arsenic database (1983–2004). A water supply history between 1920 and 2003 was also obtained by calling each municipality in the study area that serves water to at least 1,000 people (135 water suppliers). Changes in water source from groundwater to surface water and shut-down of high-arsenic wells were most common. The state arsenic database was combined with the water supply history to generate an arithmetic mean of arsenic concentration for each public groundwater supply over applicable time periods. Public surface water supplies were assigned an arsenic concentration of 0.30 μg/L, which is the average measured level in surface water in this study population (range 0.20–0.64 μg/L).

Altogether, within the study area (a) arsenic was measured in drinking water at each participant's current residence, (b) estimates of arsenic were generated from a validated geostatistical model at past residences on private well water, and (c) average arsenic concentrations were derived for public water supplies from the State database and public water supply histories. Estimates of arsenic concentration in drinking water were linked to individual lifetime residential histories using automated functionality developed in space–time analytic software (STIS™, TerraSeer, Inc., Ann Arbor, MI). The procedure successively loops through each person's residential history in the study area, retrieves their water source history, and assigns an arsenic level for each space–time interval.

For public supplies outside the study area, most participants drank water from Detroit, measured as 0.30 μg/L (consistent with surface water measurements within the study area). Outside of Detroit, estimates were generated from arsenic data compiled for public water supplies in the United States [32]. If no data existed for a particular city, which was common for cities relying on surface water, then a level of 0.30 μg/L was assigned. For private wells outside the study area, arsenic was estimated using city averages from a US Geological Survey (USGS) database of well water arsenic levels [33]. All locations outside of the United States were assigned a level of 0.30 μg/L, because public data were not readily available. The majority of time spent outside the United States was in a military capacity, relying on water at a military base or on a navy ship in the 1940s, 1950s, or 1960s.

Arsenic concentration estimates inside and outside of the study area were combined for each participant to provide estimates of arsenic concentration in the drinking water over the life-course. In generating these estimates, we assume that arsenic concentrations were temporally stable within a particular well, an assumption supported by studies in our region, and in other areas, across seasons, years, and decades [29, 34, 35]. Arsenic exposure estimates were constructed independent of case–control status.

Two arsenic exposure metrics were investigated for each participant: (a) arsenic concentration estimates (μg/L) from the lifetime exposure assessment; (b) arsenic intake (μg/day) over the adult life-course. The second metric was calculated by multiplying arsenic concentration by the sum of intake of tap water, coffee, and all other beverages made with water at home as an adult. These metrics were used to construct time-weighted average (TWA) exposure measures for arsenic concentration (μg/L) over the life-course and arsenic intake (μg/day) over the adult life-course.

In addition to long-term TWA exposure measures, researchers often examine lag effects and/or calculate exposure over decade-wide time windows. However, given limited knowledge about the temporal relationship between arsenic exposure and bladder cancer, we were concerned that these approaches could result in misspecification of the appropriate etiologic period, thereby introducing non-differential misclassification and bias the results toward the null as cautioned by Rothman [36]. Therefore, given that a temporal hypothesis

could not be justified, we opted for an exploratory approach using temporally resolved exposure estimates. The two exposure metrics were calculated using moving 5 year averages over each year of a participant's life; arsenic estimates were assigned to the middle year of each 5-year average and called yearly exposure estimates.

Epidemiologic analyses

Odds ratios (OR) and 95% confidence intervals (CI) were calculated for TWA exposure estimates using unconditional logistic regression in SAS (Cary, NC). Arsenic was treated both as a continuous variable (modeled linearly per 5 μg/L increment) and categorized a priori into <1 μg/L, 1–10 μg/L, and >10 μg/L. This categorization permitted examination of risk in the low-to-moderate exposure range above the current MCL (10 μg/L), where little information currently exists. Unadjusted (crude) analyses were conducted, as were analyses adjusted for factors shown to be associated with bladder cancer in univariate models or otherwise deemed important: age, race (white, black, other), sex, smoking (never smoker, former <20 pack-years, former ≥20 pack-years, current <20 pack-years, current ≥20 pack-years), education (highest level attained), history of urinary bladder cancer in an immediate relative (parent, sibling, or child), and at least 5 years of employment in a high-risk occupation (dye workers and users, aromatic amine manufacturing, leather workers, painting, driving trucks or other motor vehicles, aluminum workers, machinists, and automobile assemblers) [4, 37]. Employment classifications were made using job titles, place of occupation, and using the U.S. Census Bureau Index of Occupation [38].

To investigate possible interactions, stratified analyses were conducted. To compare results with previous studies [13, 14, 20], and because smoking is the most important known risk factor for bladder cancer, analyses were stratified by ever/never smoking. In addition, we were concerned about error associated with self-reported fluid consumption, and recent evidence suggests that classifications using the median are less likely to result in misclassification of water consumption-related exposures [39]. Therefore, for the arsenic concentration metric (μg/L), home water consumption was split at approximately the median (1 L/day) for stratified analyses. In addition, Bates et al. [13] hypothesized that dividing water consumption by total fluid consumption accounts for possible dilution of arsenic in the urine; this was investigated by calculating the percentage of total fluid intake that includes water from home and conducting stratified analyses using the median value (26%). These strata are characterized as *above average home water consumption* and *above average percentage of fluids containing water from home*, respectively, in the "Results" and "Discussion" sections.

The above logistic regression analyses were also conducted using yearly exposure estimates, in an exploratory attempt to generate a temporal hypothesis about the relationship between arsenic exposure and bladder cancer. Yearly exposure estimates were analyzed using three different temporal measures: calendar year, participant's age, and years prior to diagnosis or interview. These are analogous to age-period-cohort models common in epidemiologic surveillance. Because of multiple testing, only signals that persisted for at least 5 years are reported.

Consistency of results was evaluated by conducting analyses for only those cases with transitional cell carcinoma (TCC) of the bladder (n = 400), and only those with papillary TCC (n = 306). Analyses were also repeated after removing the sixteen controls and ten cases who reported being diagnosed with non-melanoma skin cancer. Cumulative exposure estimates also were examined (as opposed to TWA). In addition, analyses were conducted using an arsenic concentration estimate of 0.30 μg/L (estimate of background exposure within the study area) for all residences outside of the study area (~ 33% of person-years),

and for past residences with private wells in study area which were not geocoded to exact address or nearest cross street, representing ~ 5% of person-years.

Results

Demographics and exposure assessment

As a result of frequency matching, distributions of gender, race, and age were similar between bladder cancer cases and controls (Table 1). Cases and controls both averaged 65 years of age. Compared with controls, cases smoked more cigarettes over their lifetime, completed fewer years of schooling, and were more likely to have worked for at least 5 years in an occupation at high risk for bladder cancer. Cases were more likely to have a family member diagnosed with bladder cancer, compared with controls, albeit this only reached borderline significance.

In general, distributions of arsenic exposures and residential histories were similar for cases and controls. Cases reported an average of 9.1 residences per person, and 9.0 residences were reported for each control (Table 2). This resulted in a total of 8,823 residences for the study population accounting for 64,040 person-years, reflecting an average of 65 years of residential history per person. Cases and controls did not report a residence for 1% of their person-years and reported similar distributions of person-years on private well and public water supply (Table 2). Participants spent approximately 66% of their person-years within the study area, and another 13% of their person-years drinking Detroit city water, just outside the study area. Within the study area, cases and controls spent both approximately 28% of their person-years drinking private well water and another 38% of person-years on a public water supply. Bottled water was rarely reported and represented <1% of person-years for cases and controls. Highest arsenic concentrations were found in private well water, with a 90% range of approximately 0.02–25 μg/L for cases and controls (Table 2). Past residences on public water supply were associated with higher arsenic concentrations than current residences because of recent changes (post-1983) to reduce arsenic in water supplies.

Overall, geocoding accuracy was similar for cases and controls in the study area. Nearly 54% of controls' person-years were geocoded to exact address or closest cross streets, and 11% geocoded to town center. Among cases, 53% were geocoded to exact address or closest cross streets, and 14% geocoded to town center. The remaining person-years outside the study area were not geocoded.

Epidemiologic findings

TWA life-course arsenic concentration and arsenic intake exposure metrics were not associated with the risk of bladder cancer in unadjusted or multivariate adjusted analyses (Table 3). The TWA life-course arsenic concentration metric resulted in higher ORs than the arsenic intake metric. Multivariate-adjusted analyses stratified by ever smoking also produced no significant findings (Table 4); these results held for both exposure metrics. However, among never-smokers, risk was significantly elevated for higher levels of TWA life-course arsenic concentration using continuous measures (OR = 1.29; 95% CI: 1.03, 1.63, per 5 μg/L increase). Results were non-significantly elevated among never-smokers using categorical measures of arsenic concentration, or the arsenic intake metric.

Effect of TWA life-course arsenic concentration was also investigated in strata of home water consumption to examine interaction between water consumption and arsenic concentration in drinking water (Table 5). In multivariate-adjusted analyses, among those with home water consumption >1 L/day, arsenic approached a significant association with bladder cancer in continuous analyses (OR = 1.17; 95% CI: 0.94, 1.44, per 5 μg/L increase). Additionally stratifying into the subpopulation consuming a greater than average percentage

of fluids containing water from home (>26%) resulted in an elevated, but non-significant association between arsenic and bladder cancer (OR = 2.62; 95% CI: 0.83, 8.25) for participants with home drinking water arsenic concentrations above 10 μg/L when compared to those with levels <1 μg/L (Table 5). Continuous analyses were also elevated, but not significantly (OR = 1.21; 95% CI: 0.91, 1.61, per 5 μg/L increase).

In addition to the TWA life-course exposure estimates, yearly estimates of exposure were analyzed for a relationship with bladder cancer. No significant results were observed in unstratified multivariate analyses using age, calendar year, or years prior to diagnosis/interview as temporal measures (results not shown). In analyses stratified by water consumption >1 L/day, multivariate analyses indicated that exposures occurring when participants were between 45 and 52 years old were associated with peaks in estimated risk using continuous or categorical measures of arsenic exposure (categorical measures shown in Fig. 2). Over this 8 year age-at-exposure period, 30–32 cases and 20–25 controls were in the above average water consumption and high-arsenic (>10 μg/L) strata contributing to these findings. Age at diagnosis did not influence these findings; cases contributing to the significant results included those diagnosed from age 50 (~ 5 years following peak exposure) through age 79 (~ 30 years following peak exposure). Although not significant for all years, risk was elevated for exposures between ages 30 and 55. Further stratification by above average percentage of fluids that contain water from home revealed a similar time period of elevated risk. Analyses using other temporal measures did not produce a significant relationship, nor did analyses limited to ever-smokers.

We also investigated whether the results were specific to arsenic, or if private well use also produced an elevated OR in stratified analyses. In multivariate-adjusted analyses, private well use was not associated with bladder cancer in full analyses (OR = 1.01; 95% CI: 0.76, 1.32); or among strata >1 L/day home water consumers (OR = 1.16; 95% CI: 0.78, 1.73), or among strata of above average home water consumers who also consumed a greater than average proportion of fluids from their home water source (OR = 1.13; 95% CI: 0.63, 2.04).

Analyses were conducted using subsets of the cases defined by TCC or papillary TCC. The effect estimates were consistent with those reported from analyses of the entire dataset, as were results among those not diagnosed with non-melanoma skin cancer. Similar results were also observed when using arsenic concentration estimates of 0.30 μg/L for all residences outside of study area (32.7% of person-years for cases, 34.8% for controls) and for past residences on private wells that were not geocoded to exact address or nearest cross street in study area (5.9% of person-years for cases, 4.8% for controls). Cumulative exposure estimates over the life-course also produced similar results.

Discussion

This case–control study included a detailed lifetime exposure assessment and had good statistical power to investigate the relationship between low-level arsenic exposure and bladder cancer. Our null findings from analyses of the full dataset are generally consistent with results from other epidemiologic studies of low-level arsenic and bladder cancer [12–20]. We also identified suggestive, albeit underpowered, evidence of a relationship between arsenic exposure and bladder cancer in analyses stratified by above average water consumption at home and above average percentage of total fluids that came from water at home. These variables were treated categorically, and analyses were stratified to address possible misclassification in self-reported fluid consumption, which could potentially bias results toward the null [40]. These analyses included small numbers of cases and controls in the high-exposure group (Table 5) highlighting the need to expand such studies. It is important to note that treating these fluid consumption variables in a continuous fashion and

incorporating them directly into an exposure metric did not produce elevated associations. Other investigators of arsenic-bladder cancer relationships have not used categorical measures of fluid consumption variables, so we are unable to compare our results. Nonetheless, it is plausible that exposure to arsenic in home drinking water might produce stronger effects among individuals who consume more water from home. Furthermore, those who consume greater percentages of water from home out of total fluids would have less potential for dilution of arsenic in the bladder, as has previously been hypothesized [13, 14].

In addition to cumulative and TWA exposure measures, we opted to investigate temporally specific exposure estimates. When exploring varying induction-latency intervals and varying risk levels in relation to age-at-exposure intervals, we considered that cumulative measures alone would not have adequate sensitivity to demonstrate associations at low levels of exposure [36]. Lacking a suitable a priori temporal hypothesis, we investigated yearly averages of arsenic exposure using age, calendar year, and years prior to diagnosis/interview as temporal measures. A relationship between arsenic and bladder cancer was only observed using age as the temporal measure, with risk elevated for exposures occurring during ages 30–55 (significantly so for ages 45–52). These results appeared using strata defined by above average home water consumption or above average percentage of fluids containing water from home, and at a wide range of ages at diagnosis (ages 50–79), suggesting that age at diagnosis did not influence these findings. Previous studies have not examined whether participants' ages of exposure affected the relationship between arsenic and bladder cancer. In light of our exploratory approach, which may be prone to spurious results due to the large number of statistical analyses carried out, we interpret these findings cautiously. Thus, the window of exposure that was identified should be examined using hypothesis-driven analyses in future studies.

One of the earlier epidemiologic studies of arsenic and bladder cancer identified increased risk among smokers [13]; however, more recent work from members of the same research team failed to find any interaction with smoking, using more detailed estimates of lifetime arsenic exposure [14]. While a couple studies have reported higher risk among smokers [16, 20], others have not [15, 19]. Our null findings among ever-smokers are not inconsistent with the weight of evidence available. Among never smokers, we found arsenic to be significantly associated with bladder cancer in continuous analyses, but not significant when treated categorically; these results were driven by only eleven highly exposed never-smoking cases. The significant finding among never smokers is inconsistent with the existing literature and requires confirmation before inferring that risk from arsenic exposure is higher among never-smokers.

One stumbling block for assessing cancer risk in such epidemiologic studies is characterization of individual-level long-term exposure to arsenic in drinking water [21, 22]. In addition to our study, three others involving relatively low-level arsenic exposure have incorporated long-term (30+ year) individual-level exposure reconstruction tracing residential histories [12, 14, 20]. Our study builds on these efforts by collecting lifetime residential history and assessing exposure inside and outside our study area using a combination of arsenic measurements and statistical predictions. In particular, two strengths of our study include the limited lifetime mobility of Michigan residents and our individual-level exposure reconstruction methodology. Residential histories were collected for 99% of case and control person-years, with an average 80% of person-years being spent in southeastern Michigan. Arsenic concentrations in drinking water were directly measured at then-current residences and modeled at past residences using historical databases compiled from MDEQ and municipal water suppliers, along with a geostatistical model that was validated using a separate test dataset. With respect to past private wells where residential information was inadequate for geocoding (~ 5% of person-years), analyses for consistency

were conducted and logistic regression analyses revealed similar results whether arsenic concentrations were estimated from the geostatistical model or from background values (0.30 μg/L). Nonetheless, exposure misclassification is still possible; future work will involve deriving estimates of exposure uncertainty and propagating that uncertainty into epidemiologic analyses. Those efforts not withstanding, exposure misclassification is likely to be non-differential, and bias results toward the null.

In addition to exposure misclassification, selection bias could have occurred. Given that some potentially eligible individuals chose not to participate, we evaluated whether systematic selection bias was present among cases. In multiple logistic regression analyses, participating cases were compared with potentially eligible cases, and there was no evidence that the populations had different geographic distributions using counties or metropolitan statistical areas to represent urbanicity (6% vs. 7% rural, $p = 0.39$). No differences were observed with respect to race or gender between participating and non-participating cases. However, participating cases were younger ($p < 0.0001$; average age in their 60 s at time of diagnosis, as opposed to their 70 s) and more likely to be diagnosed with less invasive, papillary TCC of the bladder ($p = 0.0004$; 75% vs. 66%) than their non-participating counterparts. These results suggest that our findings are applicable to younger cases with papillary TCC of the bladder. Given that 22% of cases died prior to contact, we also compared participating and deceased cases. Results from this comparison were similar to those described above between participating and potentially eligible cases, although deceased cases were more likely to come from rural areas ($p = 0.02$, 6% vs. 10%). We therefore cannot discount the possibility that arsenic exposure, being more prevalent in rural areas, may have contributed to earlier death and lack of participation by some individuals, thereby biasing our results toward the null. A study of arsenic-related chromosomal alterations in bladder cancer found evidence of more aggressive bladder tumors in arsenic-exposed patients compared with unexposed patients [41], and a hospital-based study reported poorer survival among bladder cancer patients living in a high-arsenic region of Taiwan [42], supporting the possibility that exclusion of early deceased cases may have biased results toward the null.

We evaluated the possibility of selection bias in controls using similar methods. Information pertaining to non-participating eligible controls was not available; therefore, controls were compared with the background population in relation to water source and county at current residence. Controls were not compared by age, race, or gender with the background population, because these variables were matched to the case population. Participating controls were better educated than the background age 45 and over population of the study area ($p < 0.0001$; 47% vs 32%). Participating controls were geographically representative of the background population whether compared by county or urbanicity ($p = 0.95$; 5% rural in both participants and non-participants). Nearly 95% of the population in the study area lived in a metropolitan statistical area at time of diagnosis/recruitment; nonetheless, groundwater was commonly used for drinking water throughout the region, even in suburban areas. Estimates of county-specific population on private well water were derived from US Census 2000 and Michigan Department of Environmental Quality population on public water supply database. Controls were more likely to use private well water at their current residence than the general population ($p < 0.0001$; 43% vs. 29%). Higher rates of private well use at current residence were reported by participants in every county other than two of the least populated, Shiawassee and Tuscola. Perhaps private well owners were more interested in participating in the study, because they were offered results of the water analyses as an incentive. Since controls had a higher percentage of private well users than the background population, and arsenic concentrations are highest in private well water, this again is likely to bias the results toward the null.

Recall bias also may be a concern in case–control studies. In our study, self-reports of water consumption history and residential mobility may be a source of recall bias. By knowing that the study was about arsenic in drinking water, cases might have recalled greater water consumption and had greater compliance with the residential history form. However, analysis demonstrates that this was not the case. Cases reported less water consumption at home over their adult lives than controls ($p = 0.27$), and both cases and controls reported mobility histories for 99% of their person-years, suggesting little evidence of bias from differential recall. This type of recall bias does not seem to be a problem in our study.

Another strategy for investigating the influence of bias that we employed was to compare our results when analyzing established risk factors for bladder cancer with results in other publications. Current smokers of >20 pack-years show a three- to five-fold increase in risk [43] consistent with our results (OR = 4.79, Table 1). In recent decades, bladder cancer risks from high-risk occupations have typically been less than two-fold [4], similar to what we see here (OR = 1.92, Table 1). Approximately 6% of cases and 4% of controls report family history of urinary bladder cancer [44], similar again to the distribution reported here (5% of cases, 3% of controls (Table 1)). The male-to-female ratio of bladder cancer in our study is 3.3, close to the expected ratio [4]. Overall, these comparisons provide little evidence of bias.

Selecting the appropriate exposure metric and time period for investigating an exposure–disease relationship is one of the major challenges in environmental epidemiologic research. This is especially true in studies of low-level exposures where improper evaluation of the exposure time–disease relationship may mask any true findings [45]. In our study, we considered time-aggregated measures (cumulative and TWA), time-specific estimates (as defined by age, calendar year, and years prior to diagnosis/interview), and different arsenic exposure metrics at times stratified by fluid consumption measures and smoking history. Incorporating this breadth of exposure measures allows for a rigorous analysis of the dataset, yet also introduces the possibility of spurious findings. Recognizing the frequency of false positive results in cancer epidemiology, we have interpreted our results cautiously and seek other verification [46].

Our findings indicate that, overall, low-level TWA arsenic concentration in drinking water and arsenic intake were not associated with bladder cancer. However, in underpowered stratified analyses, effects were suggested for people consuming >1 L/day of water containing arsenic >10 μg/L and who drink an above average percentage of fluids containing water from home. Exploratory time-specific analyses produced results consistent with those from the time-aggregated stratified analyses and suggested that arsenic exposure levels >10 μg/L among individuals ages 30 and 55 with above average home water consumption were associated with subsequent development of bladder cancer. Follow-up studies are needed to investigate effects of low-level arsenic exposure in analyses stratified by fluid consumption and to establish whether there are one or more age-specific intervals of exposure susceptibility.

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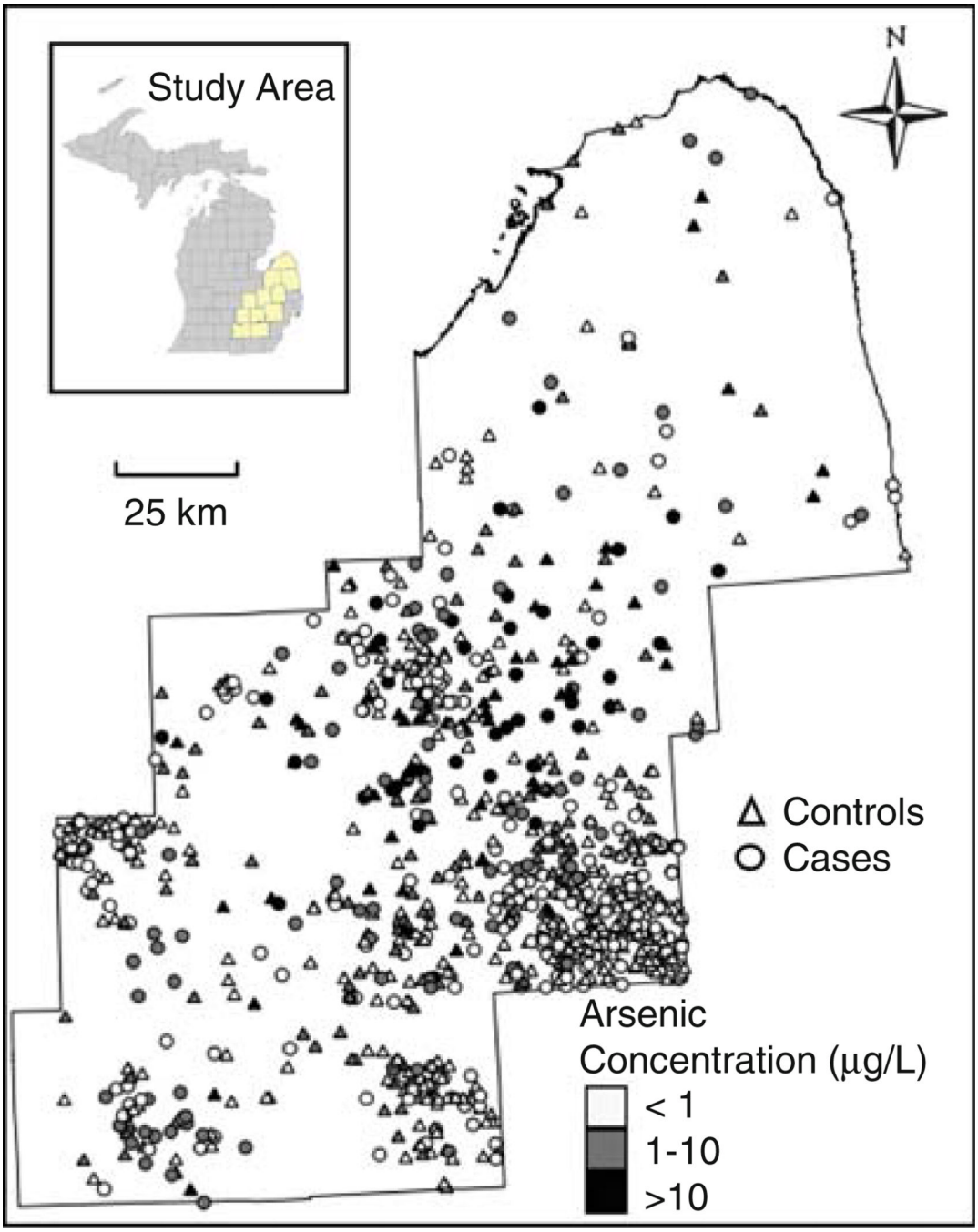

Fig. 1.
Arsenic concentrations in drinking water at current residence of cases and controls in eleven county study area of Southeastern Michigan, Enrolled 2002–2006

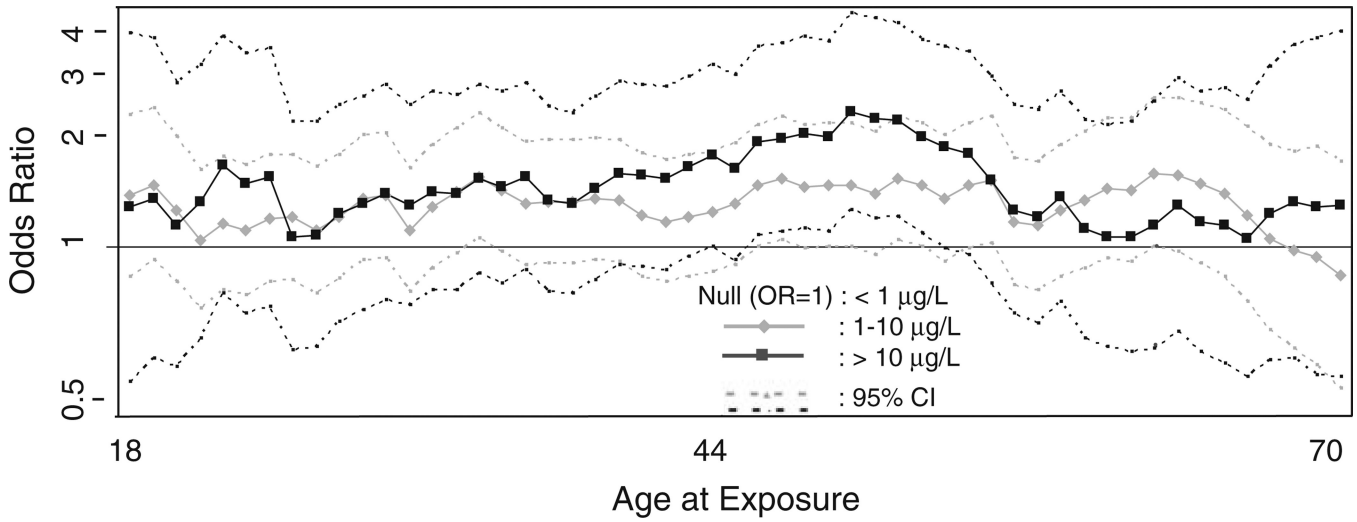

Fig. 2.

Multivariate-adjusted odds ratios and 95% confidence intervals for arsenic in drinking water and bladder cancer, among those who consume >1 L/day of water from home, by age of exposure; Southeastern Michigan, Enrolled 2002–2006. Adjusted for cigarette smoking history, education, history of employment in high-risk occupation, family history of bladder cancer, age, race, and sex. Exposure >10 µg/L between ages 45 and 52 significantly associated with bladder cancer

Table 1

Demographic characteristics of bladder cancer cases and controls, Southeastern Michigan, Enrolled 2002–2006

	Cases (*n* = 411) (No. (%))	Controls (*n* = 566) (No. (%))	*p* value[a]
Gender[b]			
Male	315 (76.6)	418 (73.9)	0.32
Female	96 (23.4)	148 (26.1)	
Race[b]			
White	380 (92.5)	518 (91.5)	0.81
Black	11 (2.7)	15 (2.7)	
Other	20 (4.8)	33 (5.8)	
Age[b]			
< 45	10 (2.4)	26 (4.6)	0.29
45–54	58 (14.1)	62 (11.0)	
55–64	113 (27.5)	158 (27.9)	
65–74	135 (32.9)	190 (33.5)	
75 or >	95 (23.1)	130 (23.0)	
Cigarette smoking in pack-years			
Nevers	104 (25.3)	263 (46.5)	<0.0001
Former <20	80 (19.5)	128 (22.6)	
Former ≥20	142 (34.5)	120 (21.2)	
Current <20	6 (1.5)	13 (2.3)	
Current ≥20	79 (19.2)	42 (7.4)	
Education			
High school or less	154 (37.5)	155 (27.4)	<0.0001
Some college	123 (29.9)	145 (25.6)	
College graduate or more	134 (32.6)	266 (47.0)	
Worked ≥5 Years in high-risk occupation[c]			
No	329 (80.1)	501 (88.5)	0.0003
Yes	82 (20.0)	65 (11.5)	
History of bladder cancer in immediate[d] family members			
No	390 (94.9)	550 (97.2)	0.07
Yes	21 (5.1)	16 (2.8)	
Usual[e] home water consumption >1 L/day[f]			
No	169 (42.5)	214 (39.9)	0.27
Yes	229 (57.5)	322 (60.1)	
Usual[e] percentage of fluid intake that includes water at home above median[g,h]			
No	163 (53.4)	161 (48.1)	0.21
Yes	142 (46.6)	174 (51.9)	
Usual[i] home water source			

	Cases (*n* = 411) (No. (%))	Controls (*n* = 566) (No. (%))	*p* value[a]
Public supply	213 (51.8)	304 (53.7)	0.56
Private well	198 (48.2)	262 (46.3)	
Exposed to arsenic >10 μg/L at ≥1 residence over life-course			
No	296 (72.0)	430 (76.0)	0.16
Yes	115 (28.0)	136 (24.0)	

[a] Derived using a 2-sided chi-square test

[b] Frequency matched between cases and controls

[c] High-risk occupations include dye workers and users, aromatic amine manufacturing, leather workers, painting, driving trucks or other motor vehicles, aluminum workers, machinists, and automobile assemblers

[d] Siblings, parents, or children

[e] Refers to average amount over adult life

[f] Missing data from 17 cases and 40 controls for calculating average home water consumption

[g] Median value = 26%

[h] Missing data from 106 cases and 231 controls for calculating percentage of fluid intake that includes water from home

[i] Refers to predominant water source over adult life

Table 2

Arsenic distribution by water supply and residential history strata for lifetime exposure reconstruction of cases and controls, South-eastern Michigan, Enrolled 2002–2006

	Cases		Controls	
	Person-years (%)	**Arsenic distribution (μg/L) (5%, 50%, 95%)**	**Person-years (%)**	**Arsenic distribution (μg/L) (5%, 50%, 95%)**
Measurements at current residence				
Private well	11.6	0.1, 5.3, 37.4	11.8	0.02, 1.8, 27.7
Public supply	15.7	0.1, 0.3, 3.6	15.0	0.02, 0.3, 3.5
Bottled water	0.6	0.02, 0.2, 1.0	0.6	0.02, 0.20, 0.20
Past residences[a] in study area				
Private well[b]	16.4	0.02, 4.0, 24.9	16.0	0.02, 4.3, 21.7
Public supply[c]	23.0	0.3, 0.3, 11.1	21.8	0.3, 0.9, 8.4
Past residences[a] outside of study area				
Detroit public supply	12.8	0.3, 0.3, 0.3	13.8	0.3, 0.3, 0.3
Other public supply[d]	12.0	0.3, 0.3, 4.6	14.7	0.3, 0.3, 4.1
Private wells[e]	5.7	0.3, 0.3, 5.0	4.8	0.3, 0.3, 8.0
International	1.2	0.3, 0.3, 0.3	1.0	0.3, 0.3, 0.3
Residence not provided	1.0		0.5	
Residences				
Total	3,741		5,082	
Average per person	9.1		9.0	

[a] Bottled water not reported at past residences

[b] Arsenic estimates from geostatistical model

[c] Arsenic estimates from Michigan Department of Environmental Quality database, and water supplier history

[d] Arsenic estimates from Natural Resources Defense Council database of arsenic in public water supplies

[e] Arsenic estimates from United States Geological Survey database of arsenic in groundwater

Table 3

Unadjusted and multivariate-adjusted odds ratios and 95% confidence intervals for arsenic in drinking water and bladder cancer, Southeastern Michigan, Enrolled 2002–2006

	Unadjusted analyses				Multivariate-adjusted analyses[a]			
	Cases (no.)	Controls (no.)	OR	95% CI	Cases[b] (no.)	Controls[b] (no.)	OR	95% CI
Arsenic concentration in water (TWA)								
Continuous (per 5 μg/L increase)	411	566	1.11	0.98, 1.25	407	564	1.05	0.92, 1.20
Categorical								
<1 μg/L	188	264	1.00		187	264	1.00	
1–10 μg/L	185	263	0.99	0.76, 1.29	182	180	0.84	0.63, 1.12
>10 μg/L	38	39	1.37	0.84, 2.22	38	37	1.10	0.65, 1.86
Arsenic intake from water (TWA)[c]								
Continuous (per 5 μg/day increase)	398	536	1.06	0.97, 1.17	394	534	1.01	0.92, 1.12
Categorical								
<1 μg/day	190	254	1.00		189	252	1.00	
1–10 μg/day	165	234	0.99	0.75, 1.29	162	234	0.83	0.62, 1.11
>10 μg/day	43	48	1.25	0.80, 1.96	43	48	1.01	0.62, 1.64

OR odds ratio; *CI* confidence interval; *TWA* time-weighted average life-course exposure estimate

[a] Adjusted for cigarette smoking history, education, history of employment in high-risk occupation, family history of bladder cancer, age, race, and sex

[b] Differences in numbers of cases and controls in adjusted analyses attributable to missing pack-year data from six participants

[c] Differences in numbers of cases and controls for arsenic intake metric attributable to missing water consumption data

Table 4

Multivariate-adjusted odds ratios and 95% confidence intervals for arsenic in drinking water and bladder cancer, among ever- and never-smokers, Southeastern Michigan, Enrolled 2002–2006

	Ever smoker				Never smoker			
	Cases (no.)	**Controls (no.)**	**OR**	**95% CI**	**Cases (no.)**	**Controls (no.)**	**OR**	**95% CI**
Arsenic concentration in water (TWA)								
Continuous (per 5 μg/L increase)	311	306	0.95	0.81, 1.11	100	260	1.29	1.03, 1.63
Categorical								
<1 μg/L	136	139	1.00		52	125	1.00	
1–10 μg/L	148	144	0.96	0.68, 1.36	37	119	0.72	0.43, 1.20
>10 μg/L	27	23	0.94	0.50, 1.78	11	16	1.62	0.68, 3.87
Arsenic intake from water (TWA)[a]								
Continuous (per 5 μg/day increase)	303	295	0.97	0.86, 1.09	95	241	1.14	0.94, 1.37
Categorical								
<1 μg/day	139	128	1.00		51	126	1.00	
1–10 μg/day	133	135	0.88	0.62, 1.25	32	99	0.80	0.47, 1.35
>10 μg/day	31	32	0.74	0.41, 1.31	12	16	2.01	0.87, 4.68

Adjusted for education, history of employment in high-risk occupation, family history of bladder cancer, age, race, and sex

OR odds ratio; *CI* confidence interval; *TWA* time-weighted average

[a]Differences in numbers of cases and controls for arsenic intake metric attributable to missing water consumption data

Table 5

Multivariate-adjusted odds ratios and 95% confidence intervals for arsenic in drinking water and bladder cancer, stratified by home water consumption and percentage of fluids that include water from home, Southeastern Michigan, Enrolled 2002–2006

	Home water consumption above 1 L/day				Home water consumption above 1 L/day and above median percentage of fluids that contain water from home[a]			
	Cases (no.)	Controls (no.)	OR	95% CI	Cases (no.)	Controls (no.)	OR	95% CI
Arsenic concentration in water (TWA)								
Continuous (per 5 μg/L increase)	202	262	1.17	0.94, 1.44	101	120	1.21	0.91, 1.61
Categorical								
<1 μg/L	79	123	1.00		36	58	1.00	
1–10 μg/L	104	124	1.05	0.69, 1.59	52	55	1.29	0.68, 2.45
>10 μg/L	19	15	1.62	0.72, 3.64	13	7	2.62	0.83, 8.25

Adjusted for cigarette smoking history, education, history of employment in high-risk occupation, family history of bladder cancer, age, race, and sex

OR odds ratio; *CI* confidence interval; *TWA* time-weighted average

[a]Percentage of fluids that contain water from home: Median = 26%