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Risk of death from cardiovascular disease associated with low-level arsenic exposure among long-term smokers in a US population-based study

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Abstract

High levels of arsenic exposure have been associated with increases in cardiovascular disease risk. However, studies of arsenic's effects at lower exposure levels are limited and few prospective studies exist in the United States using long-term arsenic exposure biomarkers. We conducted a prospective analysis of the association between toenail arsenic and cardiovascular disease mortality using longitudinal data collected on 3939 participants in the New Hampshire Skin Cancer Study. Using Cox proportional hazard models adjusted for potential confounders, we estimated hazard ratios and 95% confidence intervals associated with the risk of death from any cardiovascular disease, ischemic heart disease, and stroke, in relation to natural-log transformed toenail arsenic concentrations. In this US population, although we observed no overall association, arsenic exposure measured from toenail clipping samples was related to an increased risk of ischemic heart disease mortality among long-term smokers (as reported at baseline), with increased hazard ratios among individuals with ≥ 31 total smoking years (HR: 1.52, 95% CI: 1.02, 2.27), ≥ 30 pack-years (HR: 1.66, 95% CI: 1.12, 2.45), and among current smokers (HR: 1.69, 95% CI: 1.04, 2.75). These results are consistent with evidence from more highly exposed populations suggesting a synergistic relationship between arsenic exposure and smoking on health outcomes and support a role for lower-level arsenic exposure in ischemic heart disease mortality.

Keywords

Arsenic; cardiovascular disease; ischemic heart disease; mortality; New Hampshire; smoking

Arsenic exposure via contaminated water and diet is a global health issue [1–3]. In the US, where over 15 million people rely on private wells as their primary water source, nearly 7%

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of these systems surpass the maximum contaminant level of 10μg/L for arsenic, a known carcinogen [3–5]. Recent studies have suggested that arsenic exposure is not limited primarily to those with contaminated drinking water but may be more common, as some everyday foods have been identified as potential sources of arsenic exposure, including rice and rice products, fruit juices and chicken [6–11].

According to the National Research Council's recent assessment of arsenic, cardiovascular disease (CVD) may be the most important non-cancer disease risk posed by environmental arsenic exposures, given the high incidence of cardiovascular disease worldwide [3]. Among adults chronically exposed to high levels of arsenic, substantial evidence has supported a relationship between arsenic exposure and risk of death from any CVD, particularly ischemic heart disease (IHD) [12]. Ecological studies have observed relationships between historic arsenic water contamination in Chile and the risk of deaths from acute myocardial infarction (historic arsenic level in public water supplies: ~850 μg/L) [13] and more recently, increased mortality rates for any CVD, IHD, and stroke in municipalities with arsenic concentrations in drinking water > 10μg/L compared to the overall population in Spain (mean arsenic level in public water supplies: 2.4 μg/L, range <1 to 118 μg/L) [14]. Early epidemiological evidence from Taiwan suggested a dose-response relationship between water arsenic exposure and CVD mortality [15]. These findings have been supported by prospective studies from Bangladesh using both well water (well arsenic median: 62 μg/L, range 0.1–864.0 μg/L) and urinary arsenic measures (urinary arsenic median: 199.0 μg/g creatinine, range 6.6–1100 μg/g creatinine) [12,16]. More recent data from the Strong Heart Study in the US also indicate that relatively low levels of arsenic exposure (urinary arsenic median: 9.7 μg/g creatinine, range 0.1–183.4 μg/g creatinine) may increase risk of CVD outcomes [17]. As studies of CVD mortality have primarily focused on populations with high levels of chronic arsenic exposure, understanding the relation between lower levels of arsenic exposure and CVD mortality requires further investigation. To address this issue, we leveraged exposure and health information from a US population-based study to examine CVD mortality among adults with a range of arsenic exposure, including lower levels of exposure that have been largely unexplored.

METHODS

We conducted a prospective analysis of the relation between arsenic exposure and CVD mortality using follow-up data collected on participants in the New Hampshire Skin Cancer Study, an ongoing population-based study case-control study of keratinocyte cancers, described in detail previously [18]. Briefly, cases (n=2881) were 25–74 years old at the time of diagnosis and controls (n=1376) were frequency-matched on age and gender. Detailed covariate information was collected at baseline by a trained research interviewer during a personal interview, usually conducted in-home, and included questions about health history, smoking and alcohol use, lifestyle, and sociodemographic information. Data collection occurred in three phases, with refinement of the variables collected in each phase. All study protocols and materials were approved by the Committee for the Protection of Human Subjects of Dartmouth College. All participants provided written informed consent upon enrollment.

Toenail clippings were collected and analyzed from participants upon enrollment, as previously described [19,20]. Briefly, toenail samples were washed to remove external contamination, freeze-dried, and then stored in sealed vials until they were analyzed for arsenic at the University of Missouri Research Reactor Center using standard-comparator instrumental neutron activation analysis (NAA). The limit of detection (LOD) for arsenic in these samples was 0.01μg/g, with less than 5% of all samples below detection. Samples below the LOD were set to one-half the detection limit. Toenail arsenic, an integrated long-term biomarker of the previous 6–12 months of inorganic arsenic exposure and shown to be reliable in our population, served as our primary exposure measure [19–21]. Household water samples collected from participants (n=3099 overall participants, n=200 CVD deaths) were analyzed in the Dartmouth Trace Element Analysis Core using a Finnigan MAT GmbH ELEMENT high resolution inductively coupled mass spectrometer equipped with an MY hydride generator (Finnigan MAT GmbH, Bremen, Germany), as previously described [20]. The LOD for arsenic in these samples ranged from 0.001 to 0.2μg/L.

We ascertained vital status on study participants through December 31, 2013 by linkage with the National Death Index to identify deaths nationwide. Deaths that occurred prior to December 31, 2009 were secondarily confirmed with New Hampshire state death certificates, as previously described [22]. Analyses of disease-specific mortality were based on the primary cause of death as based on the International Classification of Diseases, 10th revision (ICD-10). The time interval for our analyses was the time from the reference date (diagnosis date of cases and matched date for controls) to either date of death or to December 31st, 2013, whichever came first, therefore only right censoring was present in this study. We used Cox proportional hazard models to estimate hazard ratios (HR) and 95% confidence intervals (CI) associated with the risk of death from any CVD (ICD I00-99), IHD (ICD I20-25), and stroke (ICD I60-69), in relation to natural-log (ln) transformed toenail arsenic concentrations. In our analyses, we adjusted for potential confounders, including educational attainment, BCC status, SCC status, and smoking behavior at baseline (pack-years). As the majority of participants did not have body mass index (BMI) information available (available for 158 of the 312 CVD deaths in our study population), we performed restricted analyses to examine the effect of this covariate on our results among those with BMI information. Given the growing literature suggesting a potential synergistic role of smoking and arsenic exposure in cancer and CVD [12,23,24], we conducted further analyses to assess multiplicative interaction between arsenic exposure and smoking status in CVD mortality. To obtain p-values for interaction, we added a cross-product term between continuous arsenic exposure (ln-transformed toenail arsenic concentrations) and each smoking status at baseline (former or current) or a cross-product term between continuous arsenic exposure and each continuous smoking variable (pack years, or years of smoking) alternatively to the overall model. For ease of interpretation, we estimated the hazard ratios associated with one unit increase in continuous arsenic exposure by smoking status at baseline (never, former, current), total years of smoking as of reference date (stratified at 31 years; median among CVD ever smoker cases), and pack-years as of reference date (stratified at 30 pack-years; median among CVD ever smoker cases). The hazard ratios were estimated with the ‘hazardratio’ statement within the SAS PHREG procedure, allowing the calculations in one model without stratifying the data. We used the distribution of smoking

behavior among CVD cases to determine median values, as it varied from that of the overall population. To account for missing data, we included missing indicator variables. The assumption of proportional hazards was examined by testing the cross product terms between covariate variables and log function of follow-up time. None of the P values for the terms were statistically significant (i.e. p >0.05), nor was a global test of proportionality, indicating that the assumption for use of a proportional hazards model was met. Analyses were performed using SAS 9.3 (SAS Institute, Cary, NC).

RESULTS

On average, participants were followed for 14 years (mean: 14.0, SD: 3.8, range 6–20). A total of 3,939 individuals contributed 55,034 person-years of observation. A total of 1081 deaths were observed, of which 312 were classified as CVD deaths. Of these, 154 (49% of total CVD deaths) were classified as IHD deaths and 43 (14% of total CVD deaths) as stroke deaths. Participants who were men, older, or SCC cases at baseline were more likely to die from any CVD (Table 1).

The average toenail arsenic in the overall population (mean (SD): 0.12 (0.14) ppm; median (range): 0.09 (0–3.26) ppm) was similar to average levels among those who died from CVD (mean (SD): 0.10 (0.08) ppm; median (range): 0.08 (0–0.67) ppm). The average home water arsenic level overall (n=3099) was 2.6 μg/L on average (SD: 9.4, median (range): 0.29 (0–158.1)), with approximately 6% of samples above 10μg/L. Among participants who were classified as dying from CVD, about two-thirds (n=200) had provided water samples for arsenic assessment. These individuals had home water arsenic levels similar to the overall population (mean (SD): 2.3 (7.2) μg/L; median (range): 0.25 (0.01–59.8) μg/L) and approximately 7% of samples exceeded the maximum contaminant limit of 10μg/L. Overall, we did not detect any significant associations between ln-toenail arsenic concentration and the risk of deaths from any CVD, IHD or stroke, after adjustment for age, sex, educational attainment, smoking history, or case status (Table 2).

In stratified analyses, we observed associations between ln-toenail arsenic concentration and IHD death among those with a longer duration of smoking, higher number of pack-years of smoking, and current smokers. In particular, a one unit change in ln-toenail arsenic in current smokers was associated with an increased risk of IHD death (HR: 1.69; 95% CI: 1.04, 2.75, *P*-interaction = 0.03, Table 3), as compared to individuals who reported never smoking (HR: 0.84; 95% CI: 0.58, 1.21) or being a former smoker (HR: 0.82; 95% CI: 0.61, 1.10). We also found that a one-unit increase in ln-transformed toenail arsenic was related to an increased risk of IHD death with a HR of 1.52 (95% CI: 1.02, 2.27) among those who smoked for 31 or more years, as compared to those who were never smokers (HR: 0.82, 95% CI: 0.54, 1.23) or smoked for less than 31 years (HR: 0.79; 95% CI: 0.62, 1.01; *P*-interaction = 0.0005, Table 3). Similarly, when we stratified by pack-years of smoking we observed increased hazard ratios for IHD death for 30 or more pack-years of smoking (HR: 1.66; 95% CI: 1.12, 2.45), as compared to never smokers (HR: 0.82, 95% CI: 0.54, 1.23) or those with less than 30 pack-years of smoking (HR: 0.77; 95% CI: 0.63, 0.94, *P*-interaction = 0.0009, Table 3). We did not find any clear associations between arsenic exposure on

overall CVD or stroke mortality in any stratum of cigarette smokers (i.e., by duration, pack-years or recency) (data not shown).

In a restricted analysis among those with known BMI (n=158), we did not observe any difference in the hazard ratio for cardiovascular disease mortality with additional adjustment for this variable, as compared to models that did not include BMI as a covariate among this subgroup.

DISCUSSION

We examined CVD mortality in relation to a long-term biomarker of arsenic exposure in a US population. Over an average of 14 years of follow-up, we found that higher arsenic concentrations were associated with increased IHD mortality among smokers. The data support a synergistic effect between cigarette smoking and arsenic exposure on cardiovascular mortality [12].

The literature supports the hypothesis that cigarette smoking may increase the risk of arsenic-related health outcomes [12,23–25]. Exposure to both arsenic and cigarette smoking has been associated with increased risks of bladder and lung cancers [26–29], as well as skin lesions [30,31]. Importantly, there is evidence from the HEALS in Bangladesh that among arsenic exposed individuals, cigarette smoking may increase risks of CVD morbidity and mortality [12,25]. In that large prospective analysis, among individuals with a moderate level of well water arsenic exposure (25.3–114.0 μg/L), the joint effect of arsenic exposure and cigarette smoking on mortality from heart disease was greater than the sum of their individual effects, with approximately 59% of heart disease deaths potentially attributable to the interaction between moderate levels of arsenic exposure and smoking [12]. In a more recent study of participants in HEALS, lower arsenic methylation capacity appears to modify the association between cigarette smoking and risk of both fatal and nonfatal CVD, especially heart disease [25]. Despite our smaller sample size and relatively low levels of arsenic exposure, similar increases in arsenic-related IHD among long-term smokers were observed.

While limited, there are other data that suggest an association between low to moderate levels of arsenic exposure and CVD [17,32]. In the Strong Heart Study urinary arsenic levels were associated with increased risk of both fatal and nonfatal CVD, coronary heart disease and stroke among American Indian men and women [17]. The potential effects of arsenic on CVD occurrence is further supported by a growing body of literature indicating that arsenic may affect subclinical indicators of CVD, such as carotid intima media thickness and elevated blood pressure [32–37]. Additional studies suggest that arsenic impacts endothelial function, reactive oxygen signaling and levels of inflammatory mediators [38–41]. Further, arsenic has been associated with prolonged QT interval duration, a risk factor for sudden cardiac death, in studies from high and lower exposure areas [42,43], including the US-based Normative Aging Study [44].

Limitations of our study include the quality of cause of death information in death certificates, which is prone to misclassification [45–47]. Such errors, however, are unlikely

to have been affected by toenail arsenic levels, and thus likely, if anything, led to a bias towards the null. However, we cannot rule out the possibility that arsenic exposure and smoking behavior may be related to competing causes of death in this population [22]. Second, toenail clippings can have limitations as biomarkers due to variability in growth rate among individuals, the risk of external contamination, and protocols for collection and analysis [48], but we attempted to minimize such issues by collecting toenails immediately after bathing, washing them prior to analysis, and using standardized analytical procedures for all subjects. Third, arsenic has been previously associated with diabetes, which could be a potential mediator of cardiovascular effects [49–51]. However, we lacked information to evaluate the extent to which the effects we observe may be related to arsenic's impact on diabetes. Fourth, we only obtained information on smoking behavior upon enrollment into the study, thus we were unable to account for changes in smoking status after enrollment, which may have biased our results toward the null. Information on secondhand smoke exposure was not routinely collected in earlier phases of the study, therefore we were unable to include it our analyses. Further, although it is possible that some arsenic measured in toenails may be in part contributed by cigarette smoking, previous work has suggested that smoking behavior does not significantly impact levels of arsenic in toenails [20]. In this population, we examined differences in toenail arsenic levels between ever smokers and never smokers, as well as differences in toenail arsenic levels between individuals with different lengths of smoking history by pack-years and found that there were no statistically significant increases in toenail arsenic associated with ever smoking or pack-years of smoking (data not shown).

Lastly, our work was not initially designed for testing the association between arsenic exposure and CVD mortality, but to examine the risk factors for keratinocyte cancers. While this may somewhat limit the generalizability of our findings, this would not have impacted the internal validity of the findings, as this was a prospective analysis and we adjusted for case-status.

Taken together with the previous literature, our study suggests that arsenic may be a contributing risk factor for IHD in the United States, particularly among long-term smokers. Nonetheless, additional studies are needed, particularly to examine low to moderate levels of arsenic exposure. Given that arsenic is present in both drinking water and food supplies worldwide and that nearly one-third of US deaths are attributable to CVD, even small arsenic-related increases in CVD morbidity and mortality in susceptible populations, such as long-term smokers, could substantially impact public health.

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Highlights

- Arsenic (As) has been associated with increased cardiovascular disease (CVD) risk
- Little is known about CVD effects at lower levels of As exposure common in the US
- Few have investigated the joint effects of As and smoking on CVD in US adults
- We examine chronic low-level As exposure and smoking in relation to CVD mortality.
- Arsenic exposure may increase ischemic heart disease mortality among smokers in US

Table 1

Baseline characteristics among New Hampshire Skin Cancer Study participants and relation to cardiovascular disease mortality, 1993–2013.

	Overall participants N (%)	CVD deaths N (%)[a]	Hazard ratio (95% CI)[a]
N	3939	312	
Age			
Median, years	61	69	
Mean (SD), years	58.5 (11.6)	67.3 (6.5)	
25–59	1829 (46.4)	32 (10.2)	1.0
60–68	1092 (27.7)	116 (37.2)	3.2 (2.2–4.7)
69–74	1018 (25.8)	164 (52.6)	4.9 (3.3–7.1)
Gender			
Male	2198 (55.8)	236 (75.6)	1.0
Female	1741 (44.2)	76 (24.4)	0.5 (0.4–0.7)
Marital Status[b]			
Married	3091 (80.6)	243 (79.7)	1.0
Single, divorced, widowed	744 (19.4)	62 (20.3)	1.2 (0.9–1.6)
Smoking[b]			
Mean (SD) years[c]	24.9 (14.6)	31.9 (14.4)	
Mean (SD) pack-years	28.1 (27.0)	36.3 (27.4)	
Never	1539 (39.2)	94 (30.3)	1.0
Former	1774 (45.2)	161 (51.9)	1.0 (0.7–1.3)
Current	615 (15.7)	55 (17.7)	1.2 (0.9–1.7)
Highest education[b]			
Any high school	1463 (37.3)	156 (50.3)	1.0
Any college	1480 (37.7)	99 (31.9)	0.9 (0.7–1.2)
Graduate school or higher	982 (25.0)	55 (17.4)	0.7 (0.5–1.0)
Skin cancer status[d]			
Control	1376 (34.9)	108 (34.6)	1.0
BCC	1505 (38.2)	89 (28.5)	0.8 (0.6–1.1)
SCC	1058 (26.9)	115 (36.9)	1.5 (1.1–1.9)

Abbreviations: 95% CI, 95% confidence interval; BCC, basal cell carcinoma; SCC, squamous cell carcinoma.

[a] HR among cardiovascular mortality deaths only, adjusted for educational attainment, marital status, cancer status (case, control), and smoking (pack-years).

[b] Seven cases were missing marital status information, two cases were missing smoking status and two were missing education level.

[c] Years smoked prior to reference date.

[d] Case status in parent New Hampshire Skin Cancer Study.

Table 2

Hazard ratios for mortality from cardiovascular disease in the NH Skin Cancer Study, per 1 unit increase in ln-transformed toenail arsenic.

	Person-years	N*	HR (95% CI)**
All cardiovascular disease	55034	312	0.88 (0.76–1.03)
Ischemic heart disease	55034	154	0.94 (0.74–1.19)
Stroke	55034	43	0.90 (0.61–1.33)

* N represents number of deaths.

** HR among cardiovascular mortality deaths, adjusted for educational attainment, BCC status, SCC status, and smoking (pack-years). Estimates were calculated using continuous ln-transformed arsenic.

Table 3

Hazard ratios for mortality from ischemic heart disease per 1 unit increase in ln-transformed toenail arsenic, stratified by smoking behavior.

	Person-years	N*	HR (95% CI)**	P-interaction
Smoking status†				
Never	21167	47	0.84 (0.58–1.21)	
Former	25278	80	0.82 (0.61–1.10)	
Current	8589	27	1.69 (1.04–2.75)	**0.03**
Years of smoking†				
0 years	21202	47	0.82 (0.54–1.23)	
> 0 to < 31 years	20877	50	0.79 (0.62–1.01)	
≥ 31 years	11420	53	1.52 (1.02–2.27)	**0.0005**‡
Pack-years of smoking†				
0 years	21202	47	0.82 (0.54–1.23)	
> 0 to < 30 pack-years	20697	49	0.77 (0.63–0.94)	
≥ 30 pack-years	11600	54	1.66 (1.12–2.45)	**0.0009**‡

*N represents number of deaths.

**HR among ischemic heart disease mortality deaths only, adjusted for educational attainment, BCC status, and SCC status.

†HRs were calculated from a single model with continuous ln-transformed arsenic and categorical smoking status.

‡P-values for interaction were estimated from models that included cross-product terms for continuous toenail arsenic and continuous smoking years (or pack-years).