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ARSENIC AND SKIN LESION STATUS IN RELATION TO MALIGNANT AND NON-MALIGNANT LUNG DISEASE MORTALITY IN BANGLADESHI ADULTS

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Abstract

Background—Chronic arsenic exposure through drinking water is a public health problem affecting millions of people worldwide, including at least 30 million in Bangladesh. We prospectively investigated the associations of arsenic exposure and arsenical skin lesion status with lung disease mortality in Bangladeshi adults.

Methods—Data are from a population-based sample of 26,043 adults, with an average of 8.5 years of follow-up (220,157 total person-years). There were 156 non-malignant lung disease deaths and 90 lung cancer deaths ascertained through October 2013. We used Cox proportional hazards models to estimate adjusted hazard ratios and 95% confidence intervals (CIs) for lung disease mortality.

Results—Creatinine-adjusted urinary total arsenic was associated with non-malignant lung disease mortality, with persons in the highest tertile of exposure having a 75% increased risk for mortality (95% CI=1.15–2.66) compared with those in the lowest tertile of exposure. Persons with

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arsenical skin lesions were at increased risk of lung cancer mortality (hazard ratio=4.53 [95% CI=2.82–7.29]) compared with those without skin lesions.

Conclusions—This prospective investigation of lung disease mortality, utilizing individual-level arsenic measures and skin lesion status, confirms a deleterious effect of ingested arsenic on mortality from lung disease. Further investigations should evaluate effects on the incidence of specific lung diseases, more fully characterize dose-response, and evaluate screening and biomedical interventions to prevent premature death among arsenic-exposed populations, particularly among those who may be most susceptible to arsenic toxicity.

Exposure to arsenic through groundwater is a major public-health problem throughout the world, with people in South Asia (Bangladesh and West Bengal, India) most seriously affected.[1] An estimated 28 to 57 million people in Bangladesh have been chronically exposed to relatively high concentrations of arsenic in drinking water beginning in the 1970s, when about 10 million hand-pumped wells were installed to provide pathogen-free groundwater for the prevention of waterborne infectious diseases.[2] Unfortunately, in the 1990s it was realized that many of these wells yield drinking water that is naturally contaminated with arsenic.

Chronic exposure to arsenic in drinking water has been associated with a multitude of health effects, including increased risk of cancer, cardiovascular disease, peripheral neuropathy, and respiratory diseases.[3–6] In addition to lung cancer,[7–15] exposure to ingested arsenic has been associated with diminished lung function[16–21] and an increased prevalence of respiratory symptoms,[22–24] as well as, in ecologic studies, mortality from pulmonary tuberculosis,[25] bronchitis,[14] and bronchiectasis.[10]

Skin lesions are a classical sign of chronic arsenic toxicity, with epidemiologic evidence consistently reporting a dose-response relationship between arsenic levels in drinking water and risk of skin lesions.[26] Furthermore, previous epidemiologic studies have shown that persons with arsenical skin lesions or skin cancers are at increased risk of internal cancers and other chronic disease conditions.[27,28]

While prior studies provide evidence for an association between arsenic exposure and lung disease mortality, they were primarily ecologic or retrospective in design and conducted in populations with known moderate-to-high arsenic exposure levels.[10,14,25,29] Here we present data from adults with a wide range of arsenic exposure in rural Bangladesh who participated in two longitudinal studies – the Health Effects of Arsenic Longitudinal Study[30] and Bangladesh Vitamin E and Selenium Trial[28] – that used similar methods for assessing individual-level exposure, covariate, and outcome data. This provides an opportunity to prospectively investigate the associations of arsenic exposure and skin lesion status with lung disease mortality in a large population, incorporating individual-level arsenic exposure and relevant confounding and modifying factors.

METHODS

Study Design

The Health Effects of Arsenic Longitudinal Study, described previously in detail,[30] is a cohort study established to investigate health outcomes associated with chronic arsenic exposure from groundwater in a population sample of adults in Araihazar, Bangladesh. Eligibility criteria for participation included being married (to minimize loss to follow-up), aged 18 to 75 years, and resident in the study area for at least 5 years. Between October 2000 and May 2002, 11,746 men and women were enrolled in the cohort. Between July 2006 and August 2008, 8,287 new participants were added following the same study methodologies.

The Bangladesh Vitamin E and Selenium Trial is a 2×2 factorial randomized chemoprevention trial evaluating the long-term effects of vitamin E and selenium supplementation on non-melanoma skin cancer risk.[28] Participants are residents of Araihazar (the same geographic area as the arsenic study participants), Matlab, and surrounding areas. Eligibility criteria included age 25 to 65 years, permanent residence in the study area, manifest arsenical skin lesions, and no prior cancer history. Between April 2006 and August 2009, 7,000 people were enrolled into the study.

These two studies use many of the same study protocols, including biospecimen collection and processing, as well as vital status assessment. Trained study physicians, unaware of participants' arsenic exposure, conducted in-person interviews and clinical evaluations and collected biological samples.

There were 26,043 people from the combined cohorts with complete exposure, covariate, and outcome data. There were 129 persons enrolled in both study cohorts; therefore, for the purposes of these analyses their exposure and questionnaire data from only the earlier assessment was used. The study protocol was approved by the institutional review boards of the University of Chicago, Columbia University, and the Bangladesh Medical Research Council. All study participants provided informed consent prior to participation.

Exposure Assessment

For all 26,043 study participants, urinary total arsenic concentration was measured in the baseline spot-urine sample, collected in an acid-washed specimen container, by graphite furnace atomic absorption spectrometry, with a detection limit of 2 μg/L, in a single laboratory (Trace Metal Core Laboratory at Columbia University).[31] Samples that fell below the limit of detection (n=18) were assigned a value of 2 μg/L. The laboratory participates in the quality-control program of the Institut de Sante Publique du Quebec and has consistently measured urinary arsenic concentration with reliability >0.97. Urinary creatinine was also measured for all 26,043 participants in the same laboratory by a colorimetric method based on the Jaffe reaction.[32] Urinary total arsenic was divided by creatinine to obtain a creatinine-adjusted urinary total arsenic concentration, expressed as μg/g creatinine. Urinary total arsenic, a good biomarker of aggregate ingested arsenic exposure, captures exposure from all sources including water, food, soil, and dust.[33] Previous studies of the distribution of urinary arsenic metabolites in a subset of 1,717 participants in the Health Effects of Arsenic

Longitudinal Study indicate that urinary arsenic concentration consisted, on average, of 16% inorganic arsenic, 13% monomethylated arsenic species, 68% dimethylated arsenic species, and only 3% arsenobetaine and arsenocholine.[34]

Arsenical skin lesion status was evaluated at the baseline skin examination by a study physician, described in detail elsewhere.[28,35] Arsenical skin lesions were categorized according to the presence of melanosis, leucomelanosis, or keratosis in body segments.[36] For the purposes of this analysis, we evaluated baseline skin lesion status as a proxy measure of cumulative arsenic exposure, as well as susceptibility to exposure.[27] Analyses were conducted by the presence of any skin lesion, which included 839 (4%) prevalent skin lesions among participants from the arsenic study and 6,834 (100%) prevalent skin lesions among participants from the vitamin trial. Analyses were also conducted by skin lesion severity, classified as less-severe skin lesions with no keratosis (melanosis and/or leucomelanosis only) if no body segment had keratotic lesions (n=3,133) and more-severe skin lesions with keratosis if one or more body segments had keratotic lesions (n=3,701). The 839 prevalent skin lesion cases from the arsenic study were excluded from analyses of skin lesion severity since keratotic lesions had been recorded only on the palms and soles, not the entire body surface.

Outcome Assessment

Enrolled participants in both cohorts received in-person home follow-up visits by trained physicians every two years, as well as home visits (monthly for the arsenic study and semiweekly for the vitamin trial) by village health workers. All deaths and their immediate and underlying causes were ascertained in both cohorts on a continuous basis. Date of death was ascertained from relatives or neighbors of the deceased. We implemented a verbal autopsy questionnaire, developed by the World Health Organization (WHO) and modified for and validated in a Bangladeshi population by the International Centre for Diarrheal Disease Research, Bangladesh.[37] In brief, a trained physician—unaware of the arsenic exposure level of the deceased participant—conducted an in-person interview with the informant to complete the verbal autopsy questionnaire, which included questions regarding the decedent's history of chronic conditions and symptoms for a determination of cause of death. Verbal autopsies were reviewed by a panel of expert physicians, and a cause of death was assigned and coded using the tenth revision of the International Classification of Diseases (ICD-10). These methods have been successfully used in our cohort for similar recent investigations in relation to all-cause and cardiovascular mortality,[38,39] as well as in other rural Bangladeshi populations for mortality related to respiratory disease.[40]

We had endpoint data through October 2013. Follow-up time was calculated as the number of days between baseline interview and date of death, or, if alive, date of last interview or report of being alive. Participants were censored at the time of death from a cause other than lung disease or October 2013, whichever was earlier. Classifications of lung disease mortality are shown in eTable 1. Non-malignant lung disease mortality was classified as deaths with ICD-10 codes J00-J99 and I27 (n=156). Lung cancer mortality was classified as deaths with ICD-10 code C34 (n=90). "All lung-disease mortality" included all deaths in the disease categories mentioned above (n=246).

Covariates

Covariate data were derived from the baseline interview. We included sex, age (years), formal education (yes, no), attained level of education (years), smoking status (never, former, or current), study cohort, and body mass index (BMI; kg/m^2). Height and weight were measured as part of the baseline clinical examination.

Statistical Analysis

The Cox proportional hazards regression model was used to estimate hazard ratios (HRs) and their 95% confidence intervals (CIs) as measures of association between urinary total arsenic concentration at baseline and lung-disease mortality during the follow-up period. For the purposes of the main analyses, creatinine-adjusted urinary total arsenic concentration was divided into tertiles according to the baseline distribution of the cohort eligible for analysis. Tests for trend were assessed via a single ordinal exposure variable and the corresponding P-value of the coefficient was reported as the P for trend. Analyses were also conducted utilizing creatinine-adjusted urinary total arsenic concentration as a continuous measure, as well as urinary total arsenic concentration as a continuous measure with urinary creatinine as an independent covariate in the model.[41] For the continuous-exposure models, creatinine-adjusted urinary total arsenic concentration and urinary total arsenic concentration were standardized to have an overall mean of zero and standard deviation of 1. All models were adjusted for sex, age (years), BMI (kg/m^2), formal education (yes, no), years of education (years), smoking status (former/never, current/never), and study cohort. Models using urinary total arsenic concentration as the regressor were additionally adjusted for urinary creatinine concentration (mg/dL) in the model.

The associations between skin lesion status and severity in relation to lung-disease mortality were also evaluated using Cox proportional hazards regression models. Models were adjusted for sex, age (years), BMI (kg/m^2), formal education (yes, no), years of education (years), smoking status (former/never, current/never), and baseline urinary total arsenic concentration (indicator variables for tertiles).

We also evaluated effect modification of the associations between creatinine-adjusted urinary total arsenic or skin lesion status and lung-disease mortality by baseline covariates on both the additive and multiplicative scales. Baseline characteristics included sex, age, BMI, years of education, study cohort, smoking status, and skin lesion status. Continuous variables were dichotomized at their median value for the purposes of interaction analyses. Additive interaction was evaluated through the synergy index (SI) using multivariate adjusted estimates.[42] This was calculated as

$$SI = \exp(\beta 1+\beta 2+\beta 3) - 1 / \exp(\beta 1) + \exp(\beta 2) - 2.$$ [43]

Here β_1 is the coefficient of the ordinal arsenic-exposure measure (or dichotomous skin lesion status), β_2 is the coefficient of the dichotomous effect-modifier measure, and β_3 is the coefficient of the cross-product of the ordinal arsenic exposure (or dichotomous skin lesion status) and dichotomous effect-modifier measures.[43] CIs of the synergy index were calculated using the delta method described by Hosmer and Lemeshow.[44] Tests for multiplicative interaction were assessed via the P-value of the cross-product term of the

ordinal exposure variable (or dichotomous skin lesion status) and dichotomous effect modifier in the Cox proportional hazards model.

Statistical analyses were performed using SAS, including the procedure PHREG, release 9.2 (SAS Institute, Inc., Cary, North Carolina).

RESULTS

The mean follow-up time was 8.5 years (220,157 total person-years). Among the 26,043 participants, 1,278 deaths were ascertained through October 2013, including 156 non-malignant lung-disease deaths and 90 lung cancer deaths. Lung-disease mortality classifications based on cause of death are summarized in eTable 1.

Table 1 shows the distribution of demographic, clinical, and exposure characteristics for deceased participants according to lung-disease death classifications. In general, participants who died from lung disease were more likely to be male, be aged 31 years and older, have a low BMI (<18.5 kg/m^2), have no formal education, report a history of smoking, and have prevalent arsenical skin lesions.

Creatinine-adjusted urinary total arsenic concentration was associated with all lung-disease mortality and with non-malignant lung-disease mortality, as shown in Table 2. The mortality rates increased across creatinine-adjusted urinary total arsenic tertiles. Utilizing the continuous exposure data in the multivariate models, each one standard deviation (SD) increase in creatinine-adjusted urinary total arsenic concentration was associated with a 14% increase (95% CI=1.04–1.25) in all lung-disease mortality, an 11% increase (0.96–1.29) in non-malignant lung-disease mortality, and a 17% increase (1.05–1.32) in lung cancer mortality. Additionally, associations were modeled using urinary total arsenic (μg/L) as the exposure measure, with adjustment for creatinine as a covariate in the model. Results were not appreciably different from the creatinine-adjusted exposure models (data not shown). Association results are presented separately by study cohort in eTable 2, with no distinct differences in trends noted between studies. Sensitivity analyses were also conducted evaluating baseline well-water arsenic concentration in relation to lung-disease mortality among the arsenic study participants, with effects estimates only slightly weaker than those observed for urinary total arsenic concentration, as presented in eTable 2.

Associations between arsenical skin lesion status and severity in relation to lung-disease mortality are summarized in Table 3. Arsenical skin lesion status was associated with lung cancer mortality. Furthermore, arsenical skin lesion severity was associated with lung cancer mortality in a dose-dependent manner, with the greatest risk of mortality observed among those with the most severe arsenical skin lesions.

We evaluated whether the association between arsenic concentration and lung-disease mortality was modified by baseline characteristics (i.e., sex, age, BMI, education as a proxy of socioeconomic status, study cohort, smoking status, and skin lesion status) on the additive and multiplicative scales. Analyses for cigarette smoking were restricted to men since the prevalence of tobacco smoking in women is low (<5%). There was no evidence of additive or multiplicative statistical interactions in relation to lung disease mortality, summarized in

eTable 3. We also evaluated whether the associations between skin lesion status and lung-disease mortality were modified by baseline characteristics. Significant additive statistical interaction was observed for the joint effect of arsenical skin lesion status and age in relation to lung-disease mortality, as shown in eTable 4. On the additive scale, mortality was greater among persons aged 38 years and older with arsenical skin lesions than would be expected based on the additive independent effects of age and arsenical skin lesion status alone (synergy index=1.67 [95% CI=1.15–2.43]).

DISCUSSION

We observed dose-dependent associations between creatinine-adjusted urinary total arsenic concentration and non-malignant lung-disease mortality in a prospective cohort study, based on individual-level data. Additionally, there was increased risk of lung cancer mortality among persons with arsenical skin lesions as well as by skin lesion severity. Furthermore, there was evidence of statistical interaction on the additive scale between arsenical skin lesion status and older age (≥38 years) in relation to lung cancer mortality. We have previously reported increased all-cause and chronic disease mortality,[38] as well as cardiovascular disease mortality,[39] in relation to arsenic exposure in Bangladesh.

While arsenic exposure has been associated with impaired lung function, respiratory symptoms and disease, and mortality in previous epidemiologic studies,[7–25] the mechanisms and biological basis of these relationships have yet to be fully uncovered. Animal studies have demonstrated that low-dose ingested arsenic exposure results in the accumulation of arsenic metabolites in lung tissue.[45,46] Additionally, animal studies have shown decreased expression of genes associated with the extracellular matrix, including elastin and collagen, in animals with low-dose arsenic ingestion.[47] In vitro studies have shown arsenic to increase oxidative stress in lung cells.[48] Additionally, Josyula and colleagues[49] showed that pulmonary inflammatory markers, as measured by human sputum metalloproteinase concentrations, were associated with low-level arsenic exposure, suggesting lung inflammation as a possible mode of action. Parvez et al.[19] observed that serum Clara cell protein CC16 levels, a biomarker of early lung epithelial damage, was inversely associated with chronic arsenic exposure, indicating that lung injury and thus a decrease in CC16 protein levels may be present in people with elevated chronic arsenic exposure levels. This evidence provides biological rationale for ingested arsenic as a respiratory toxicant associated with acute and chronic pulmonary conditions, as well as impaired lung function. Additional investigations into these underlying pathways are needed.

While skin lesions are a classic sign of chronic arsenic toxicity, evidence has suggested that arsenic exposure itself fails to fully explain the presence of arsenical skin lesions in an exposed population and that genetic susceptibility may play an important role in determining sub-populations at higher risk of developing the disease at similarly exposed levels.[50] Furthermore, studies from Taiwan and Chile indicate that elevated cancer risk among arsenic exposed populations persists for several decades after cessation of exposure.[3,11,51] Therefore, the association between arsenical skin lesion status and lung cancer mortality may be attributable to skin lesion status either as a proxy for increased susceptibility to arsenic toxicity or as a proxy for past cumulative or peak arsenic exposure.

There are several strengths of this study. First, while previous studies have demonstrated associations between arsenic exposure and mortality due to pulmonary tuberculosis,[25] bronchitis,[14] and bronchiectasis,[10] this population-based study prospectively investigated the association between arsenic exposure and classifications of malignant and non-malignant lung disease mortality in a Bangladeshi population. Second, prior studies were conducted largely in populations exposed to high arsenic concentrations, and thus associations with arsenic dose could not be examined based on the study designs. In this study, the wide range of arsenic exposure afforded the opportunity to evaluate the dose-response nature of arsenic-associated mortality. Third, measurement of arsenic exposure on all 26,043 cohort members was assessed based on baseline urinary total arsenic concentration, a good aggregate biomarker of ingested exposure that captures exposure from multiple sources including drinking water, food, soil and air.[33] Finally, we also conducted analyses examining arsenical skin lesion status and severity in relation to lung disease mortality. Skin lesion severity itself is a construct that represents a composite of the extent of arsenic exposure (including potentially cumulative exposure effects) and susceptibility (e.g., genetic, nutritional) to exposure. Skin lesion status as a predictor of disease risk was an approach recently taken by Hsu et al. [27] in their analyses of internal cancer risk, as well as by us to examine chronic disease co-morbidities.[28]

There are limitations of this study that we also consider. We evaluated various classifications of lung-disease mortality; however, small numbers precluded our inclusion of additional categories of specific individual diagnoses, or analyses based on incident cases of chronic respiratory diseases. The verbal-autopsy instrument may allow some misclassification of cause-of-death. Any misclassification of cause-of-death is unlikely to be dependent on arsenic exposure status, and thus potential misclassification of the outcome would be expected on average to result in an underestimation of the true population effects.

The number of non-malignant lung disease (n=156) and lung cancer deaths (n=90) included in this analysis was small; thus, we did not have adequate statistical power to evaluate interactions for those endpoints individually. Additive interaction between arsenical skin lesion status and age in relation to lung-disease mortality was observed in these analyses; however, given the number of interactions evaluated, we interpret these results cautiously. A borderline association with lung cancer mortality was observed in the highest arsenic exposure tertile (HR=1.56 [95% CI=0.90–2.69]). The magnitude of this association was lower than expected based on the previous literature on arsenic-related lung cancer[52]; however, the association was in the expected direction, and the magnitude of the association may be a chance finding given the small number of lung cancer deaths. Analyses based on more refined arsenic dose categories, especially in the low-to-moderate dose range, will become feasible in future analyses of these cohorts as the number of deaths increases with the aging of the population.

We acknowledge that the measure of arsenic exposure used in these analyses (urinary total arsenic concentration at baseline assessment) has some limitations. While a measure of well-water arsenic concentration was available for the arsenic-study participants, this information was not available for the vitamin-trial participants. Urinary arsenic concentration is reflective of recent exposure; however, baseline urinary total arsenic and well-water arsenic

concentrations in this population have good correlation (Spearman correlation coefficient=0.73). Subset analyses did not show appreciably different results for lung-disease mortality in relation to well-water or urinary total arsenic concentrations (eTable 2). Lifetime arsenic exposure data are not currently available for all study participants; therefore, latency patterns for arsenic exposure with lung-disease mortality cannot be explicitly examined in this study.

To overcome potential limitations of evaluating a single baseline assessment of arsenic exposure, we also conducted analyses by skin lesion status, which may be better than the baseline urinary total arsenic assessment as a proxy for cumulative or past peak arsenic exposure. Skin lesions (a proxy for arsenic exposure and susceptibility) appeared to be a good predictor for lung cancer mortality. This may be partly attributed to skin lesion status representing cumulative or past arsenic exposure levels more relevant than the baseline arsenic exposure assessment for the latency period of lung cancers.

We previously observed that, once a person is chronically exposed, decreasing exposure for a short amount of time did not reduce overall risk of mortality.[38] For the subset of participants in the arsenic study with repeated measures of urinary arsenic, we did not observe an effect of short-term changes of arsenic exposure in relation to lung-disease mortality (data not shown). This is consistent with the patterns we previously reported for all-cause and chronic disease mortality,[38] as well as with other studies that have shown mortality attributed to chronic diseases did not begin to decline until several decades after cessation of exposure to high-arsenic well water.[53–55] While short-term changes in exposure did not decrease lung-disease mortality risk, we will continue to evaluate the modification of risk as the cohort is followed for a longer period of time.

While initiatives to reduce exposure to arsenic through drinking water are ongoing, investigation into solutions to mitigate the resulting health effects of this catastrophe are also needed. Future research utilizing prospectively collected data on specific lung-disease incidence, mortality, and individual-level changes in arsenic exposure will strengthen our understanding of these associations and help identify effective avenues of prevention.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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TABLE 1

Baseline Characteristics of Study Sample in relation to Lung Disease Mortality

Characteristic	Lung Disease Mortality (n=246)		Non-malignant Lung Disease Mortality (n=156)		Lung Cancer Mortality (n=90)	
	No. of deaths	HR (95% CI)	No. of deaths	HR (95% CI)	No. of deaths	HR (95% CI)
Sex						
Women[a]	55	1.00	43	1.00	12	1.00
Men	191	2.53 (1.85–3.46)	113	1.67 (1.15–2.44)	78	5.69 (3.06–10.58)
Age (years)						
18–30[a]	7	1.00	4	1.00	3	1.00
31–40	28	3.08 (1.34–7.06)	20	4.03 (1.37–11.83)	8	1.99 (0.53–7.54)
41–50	70	10.00 (4.58–21.83)	39	10.80 (3.84–30.37)	31	9.19 (2.80–30.14)
51–75	141	36.81 (17.08–79.32)	93	51.84 (18.79–143.08)	48	22.70 (7.02–73.39)
Body mass index (kg/m^2)						
<18.5[a]	173	1.00	122	1.00	51	1.00
18.5–24.9	66	0.36 (0.27–0.48)	31	0.24 (0.16–0.36)	35	0.64 (0.42–0.99)
≥25.0	7	0.32 (0.15–0.69)	3	0.19 (0.06–0.59)	4	0.68 (0.25–1.89)
Education (years)						
0[a]	130	1.00	90	1.00	40	1.00
1–5	63	0.77 (0.57–1.04)	39	0.71 (0.49–1.04)	24	0.90 (0.54–1.49)
6+	53	0.74 (0.54–1.03)	27	0.57 (0.37–0.89)	26	1.08 (0.65–1.78)
Cigarette smoking status[b]						
Never[a]	13	1.00	7	1.00	6	1.00
Former	51	3.12 (1.67–5.80)	40	4.27 (1.88–9.68)	11	1.59 (0.58–4.39)
Current	127	3.03 (1.71–5.37)	66	2.76 (1.26–6.03)	61	3.43 (1.47–7.97)
Study cohort						
Arsenic study cohort[a]	172	1.00	130	1.00	42	1.00
Vitamin trial cohort	74	1.82 (1.33–2.50)	26	0.79 (0.50–1.26)	48	5.12 (3.08–8.50)
Arsenical skin lesions[c]						

Characteristic	Lung Disease Mortality (n=246)		Non-malignant Lung Disease Mortality (n=156)		Lung Cancer Mortality (n=90)	
	No. of deaths	HR (95% CI)	No. of deaths	HR (95% CI)	No. of deaths	HR (95% CI)
Skin lesions absent[a]	142	1.00	111	1.00	31	1.00
Skin lesions present	101	1.65 (1.26–2.17)	43	0.90 (0.62–1.31)	58	4.22 (2.66–6.70)
Creatinine-adjusted urinary arsenic (μg/g)						
Tertile 1: <132.5[a]	58	1.00	35	1.00	23	1.00
Tertile 2: 132.5–331.9	95	1.60 (1.16–2.22)	59	1.59 (1.05–2.42)	36	1.63 (0.96–2.75)
Tertile 3: ≥332.0	93	2.01 (1.45–2.80)	62	2.29 (1.51–3.48)	31	1.61 (0.93–2.76)

Adjusted for sex, age, and study cohort.

[a]Reference category.

[b]Reported for men only.

[c]Missing for 121 participants. Not adjusted for study cohort.

TABLE 2

Multivariate Associations Between Creatinine-adjusted Urinary Total Arsenic and Lung Disease Mortality

Outcome	Creatinine-adjusted urinary total arsenic tertiles, μg/g						Test for trend
	<132.5[a]		132.5–331.9		≥332.0		
	No.	HR	No.	HR (95% CI)	No.	HR (95% CI)	
Lung disease mortality	58	1.00	95	1.44 (1.04–2.00)	93	1.67 (1.20–2.32)	*P*=0.003
Non-malignant lung disease mortality	35	1.00	59	1.37 (0.90–2.08)	62	1.75 (1.15–2.66)	*P*=0.008
Lung cancer mortality	23	1.00	36	1.61 (0.95–2.73)	31	1.56 (0.90–2.69)	*P*=0.116

Adjusted for sex, age, body mass index, education, smoking status, and study cohort.

[a]Reference category.

TABLE 3

Multivariate Associations between Skin Lesion Severity and Lung Disease Mortality

Predictor	Lung Disease Mortality			Non-malignant Lung Disease Mortality			Lung Cancer Mortality		
	No.	HR (95% CI)[a]	HR (95% CI)[b]	No.	HR (95% CI)[a]	HR (95% CI)[b]	No.	HR (95% CI)[a]	HR (95% CI)[b]
Model 1									
No skin lesions[c]	142	1.00	1.00	111	1.00	1.00	31	1.00	1.00
Any skin lesion	101	1.71 (1.30–2.24)	1.58 (1.19–2.10)	43	0.93 (0.64–1.36)	0.81 (0.55–1.20)	58	4.45 (2.81–7.05)	4.53 (2.82–7.29)
Model 2									
No skin lesions[c]	142	1.00	1.00	111	1.00	1.00	31	1.00	1.00
Melanosis/leucomelanosis	17	1.23 (0.72–2.09)	1.11 (0.64–1.92)	5	0.43 (0.17–1.08)	0.35 (0.14–0.89)	12	4.34 (2.05–9.19)	4.69 (2.17–10.14)
Keratosis	57	2.76 (1.93–3.94)	2.57 (1.78–3.72)	21	1.25 (0.75–2.10)	1.08 (0.63–1.82)	36	8.34 (4.61–15.10)	9.00 (4.88–16.60)

[a] Adjusted for sex, age, body mass index, education, and smoking status.

[b] Additionally adjusted for creatinine-adjusted urinary total arsenic concentration.

[c] Reference category.