Bronchiectasis in Persons With Skin Lesions Resulting From Arsenic in Drinking Water

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Background: Arsenic is a unique human carcinogen in that it causes lung cancer by exposure through ingestion (in drinking water) as well as through inhalation. Less is known about nonmalignant pulmonary disease after exposure to arsenic in drinking water.

Methods: We recruited 108 subjects with arsenic-caused skin lesions and 150 subjects without lesions from a population survey of over 7000 people in an arsenic-exposed region in West Bengal, India. Thirty-eight study participants who reported at least 2 years of chronic cough underwent high-resolution computed tomography (CT); these scans were read by investigators in India and the United States without knowledge of the presence or absence of skin lesions.

Results: The mean (± standard deviation) bronchiectasis severity score was 3.4 (± 3.6) in the 27 participants with skin lesions and 0.9 (± 1.6) in the 11 participants without these lesions. In subjects who reported chronic cough, CT evidence of bronchiectasis was found in 18 (67%) participants with skin lesions and 3 (27%) subjects without skin lesions. Overall, subjects with arsenic-caused skin lesions had a 10-fold increased prevalence of bronchiectasis compared with subjects who did not have skin lesions (adjusted odds ratio = 10; 95% confidence interval = 2.7–37).

Conclusions: These results suggest that, in addition to being a cause of lung cancer, ingestion of high concentrations of arsenic in drinking water may be a cause of bronchiectasis.

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Millions of people worldwide are exposed to drinking water containing naturally occurring arsenic.[1–9] These exposures have been linked to several diseases, including diabetes, liver disease, cardiovascular disease, skin lesions, and cancer.[10] Studies from Taiwan, Chile, Argentina, and Japan have reported associations between ingested arsenic and lung cancer, and the International Agency for Research on Cancer (IARC) has recently classified arsenic in drinking water as a group 1 lung carcinogen.[11] In addition to lung cancer, there is gradually emerging evidence that ingested arsenic may also cause nonmalignant respiratory disease. Studies from several countries have reported adverse respiratory effects in arsenic-exposed populations.[7,12–17] To date, these findings have come mostly from case series or studies assessing self-reported symptoms or chronic obstructive pulmonary disease mortality.

The goal of this study was to evaluate the association between arsenic ingestion (as assessed by characteristic skin lesions) and the presence of radiographic abnormalities of the lung using high-resolution computed tomography (CT). Chronic arsenic ingestion causes characteristic skin keratoses on the palms and soles as well as pigmentation changes on the limbs and trunk. There is a clear dose–response trend between the prevalence of these lesions and arsenic exposures in the study population.[18,19] The odds ratios (ORs) for skin lesions in subjects exposed to maximum arsenic concentrations of <50 (reference category), 50–99, 100–199, 200–299, and ≥300 μg/L were 1.0, 2.4 (95% confidence interval [CI] = 0.7–8.2), 6.7 (2.6–18), 9.9 (3.9–25), and 24.3 (9.7–61), respectively.[18]

In this investigation, we compared CT evidence of bronchiectasis, in subjects with arsenic-caused skin lesions,

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with CT findings in subjects without these lesions. Bronchiectasis is a widening and destruction of the larger airways of the lung. Known causes include cystic fibrosis, severe infections, and airway obstruction.[20]

METHODS

The subjects in this study were selected from 7683 individuals who participated in a 1995–1996 population-based cross-sectional survey of arsenic-caused skin lesions in South-24-Parganas, a rural district south of Kolkata, India.[19] We defined our exposed group as persons in the cross-sectional study who had arsenic-caused keratosis or hyperpigmentation and who were thought to be consuming water with arsenic concentrations above 400 μg/L at the time of the survey. As a comparison group, we randomly selected subjects without skin lesions who were consuming water with arsenic concentrations less than 50 μg/L at the time of the cross-sectional survey. These subjects were matched to skin lesion cases by age and sex. During the years 2001–2003, all participants were visited at home where they completed a study-specific questionnaire and underwent a physical examination. This study was approved by the Institutional Review Boards of the Institute of Post Graduate Medical Education and Research, Kolkata, India and the University of California, Berkeley. Informed consent was obtained from all subjects.

The questionnaire asked about residential and job history, drinking water sources, demographic characteristics, cough, sputum production, and physician-diagnosed respiratory illnesses (such as bronchitis, asthma, tuberculosis, or pneumonia). To identify those with chronic cough, participants were asked if they currently cough during the morning, day, or night. If yes, they were asked, "Do you cough like this for 3 months in a year?" and if so, "For how many years have you been coughing like this?" Smoking questions covered age when smoking began, age of cessation (if applicable), total years of smoking, and typical number of cigarettes smoked per day.

Physical examinations were conducted by a physician following a written protocol. Emphasis was placed on chronic respiratory disease end points, including the presence of abnormal sounds on auscultation and percussion (eg, crepitation, wheezing, dullness). An examination of the skin was conducted in a well-lit area outdoors. Visible or palpable dermal lesions were documented noting the location and appearance of the lesions and whether the patterns were characteristic of arsenic-induced skin toxicity. Between the time of the original cross-sectional survey and the time of this physical examination, skin lesions in some cases had resolved and new lesions developed in others. The development and resolution of skin lesions was related to age and sex. Thus, the original matching on age and sex was lost, and so both age and sex were controlled for in the statistical analyses.

To estimate historic arsenic exposure, we measured arsenic concentrations in all wells that were still open and had been identified to have been used by each subject at home or work over the last 20 years. This assessment was much more extensive than that from the original cross-sectional study, which assessed arsenic exposure at one point in time only. Based on our more extensive assessment, some of the subjects without skin lesions were found to have had past arsenic exposures above 50 μg/L and some of the skin lesion cases were found to have had maximum exposures below 400 μg/L.

All subjects who reported chronic cough (more than 3 months per year for at least 2 years) were referred for CT in Kolkata. Initial review of the CT scans suggested that bronchiectasis was a frequent finding. Each CT scan was then read independently by 2 radiologists, 1 in West Bengal and 1 in the United States, neither of whom had information on skin lesion or arsenic exposure status. The severity of bronchiectasis in each lobe was ranked using a modification of the system described by Lynch et al.[21] Briefly, a 5-point grading system was used: 0 = no bronchiectasis; 1 = mild bronchiectasis (nontapering cylindrical internal bronchial diameter 1.5–3 times the diameter of the accompanying artery); 2 = moderate bronchiectasis (nontapering cylindrical internal bronchial diameter more than 3 times the diameter of the accompanying artery); 3 = varicose bronchiectasis; and 4 = cystic bronchiectasis. The lungs were divided into 6 lobes (considering the lingula as a separate lobe) and a score was assigned to each lobe. We assigned a single score to each subject by summing the bronchiectasis scores from each lobe.

Associations of arsenic-caused skin lesions with variables such as age, sex, smoking history, and with CT findings of bronchiectasis were first assessed using univariate analyses. We used X-square tests when data were dichotomous. Student t test was used to compare category means for continuous variables that were normally distributed (age); otherwise, the Wilcoxon rank sum test was used (for average cigarette use and bronchiectasis severity scores). Factors related to bronchiectasis were then assessed by stratification followed by logistic regression analyses to calculate adjusted ORs and 95% CIs for bronchiectasis comparing subjects with skin lesions with those without skin lesions. ORs were adjusted for factors found to be important in the univariate analysis including age (year), sex, smoking (ever vs never smoker), and a history of tuberculosis (yes or no). Adjusting for other age or smoking variables or for socioeconomic variables such as education or household crowding had no impact on the results.

In the crude and adjusted OR calculations, we defined bronchiectasis cases as all subjects given a bronchiectasis severity score of at least 1 by both readers. Subjects without chronic cough in the source population, and subjects with chronic cough but bronchiectasis severity scores less than 1 among the CT-referred participants, were considered not to

have bronchiectasis. In a separate analysis, we assigned each subject an overall bronchiectasis severity score by averaging the summed scores from each reader. These scores are presented graphically and were used to calculate and compare mean bronchiectasis severity scores in subjects with and without skin lesions. The correlation coefficient between the scores of the 2 readers was 0.69.

RESULTS

Table 1 shows the demographic characteristics, the number of subjects with chronic cough, and the mean bronchiectasis severity scores in the 108 subjects with arsenic-caused skin lesions and 150 subjects without skin lesions. The proportion of subjects with a history of tuberculosis was somewhat higher among those with skin lesions than those without lesions (OR = 1.7; 95% CI = 0.7–4.2), although the proportion of ever smokers and the mean number of cigarettes smoked per day were similar. The median highest arsenic drinking water concentration was 330 μg/L (standard deviation [SD] = 881 μg/L) in subjects with skin lesions and 28 μg/L (SD = 147 μg/L) in subjects without lesions. Women comprised 33% of the subjects with skin lesions and 45% of those without lesions. The average (± SD) age was 46 years (± 14) in subjects with skin lesions and 43 years (± 15) in subjects without lesions.

Thirty-three (31%) subjects with skin lesions and 18 (12%) subjects without lesions reported chronic cough (OR = 3.2; CI = 1.7–6.1) (Table 1). Of these, 1 subject with lesions and 2 subjects without lesions were physically unable to travel to Kolkata for CT; 5 subjects with skin lesions and 5 subjects without skin lesions refused referral for CT; and 27 of the subjects with skin lesions and 11 of the subjects without lesions agreed to travel to Kolkata for CT. Overall, the participation rate was 82% in subjects with skin lesions and 61% in subjects without skin lesions. Participation rates (excluding those subjects who were physically unable to travel to Kolkata for CT) were 84% in subjects with skin lesions and 69% in subjects without lesions. For both subjects with skin lesions and subjects without skin lesions, those who agreed to referral were similar to those who declined or were physically unable to travel in terms of mean age, sex distribution, smoking history, history of tuberculosis, duration of cough, sputum production, and shortness of breath.

Among those subjects who underwent CT, the average (± SD) bronchiectasis severity score (averaged over the 2 readers) was 3.4 (± 3.6) in subjects with skin lesions and 0.9 (± 1.6) in subjects without lesions (Table 1). Differences in bronchiectasis severity scores between persons with skin lesion and those without were also present when the scores from the 2 CT readers were analyzed separately. Figure 1 shows the distribution of average scores among subjects with and without arsenic-caused skin lesions. Only 1 subject without skin lesions had a score above 2, whereas 14 skin lesion subjects had a score above 2.

In unadjusted analyses, those with bronchiectasis were more likely to be men and to have a history of tuberculosis (Table 2). The unadjusted odds ratio for

TABLE 1. Associations Between Study Variables and Arsenic-Caused Skin Lesions

	Skin Lesions (n = 108)	No Skin Lesions (n = 150)	Unadjusted OR (95% CI)
Age; mean ± SD	46 ± 14	43 ± 15	
Sex; %			
Women	33	45	
Men	67	55	
Cigarette smoking; %			
Never*	61	62	1.0
Ever	39	38	1.1 (0.7–1.9)
Cigarettes per day†; mean ± SD	12 ± 9	11 ± 9	
Tuberculosis‡; %			
No*	89	93	1.0
Yes	11	7	1.7 (0.7–4.2)
Chronic cough§; %			
No*	69	88	1.0
Yes	31	12	3.2 (1.7–6.1)
Sputum production; %			
No*	70	87	1.0
Yes	30	13	2.9 (1.5–5.5)
CT referral¶; %			
Accepted	82	61	
Physically unable	3	11	
Refused	15	28	
Bronchiectasis‖; mean ± SD			
Average score	3.4 ± 3.6	0.9 ± 1.6	
Reader 1 score	3.2 ± 4.1	0.7 ± 1.4	
Reader 2 score	3.6 ± 3.6	1.3 ± 2.4	
Highest known arsenic exposure (μg/L)**; mean ± SD	330 ± 881	28 ± 147	

*Reference category.
†Mean number of cigarettes smoked per day in smokers only.
‡Self-reported history of physician-diagnosed tuberculosis.
§Self-reported cough for 3 months or more per year for at least 2 years.
¶All subjects who reported chronic cough were asked to travel to Kolkata for CT.
‖Includes only those 27 subjects with arsenic-caused skin lesions and 11 subjects without skin lesions who had chronic cough and underwent CT.
**Median concentration. For each subject, arsenic concentrations were measured in all still-functioning tube wells that were used at home or work, for 6 months or more, over the last 20 years. This value is the median concentration of the highest arsenic concentration linked to each subject.

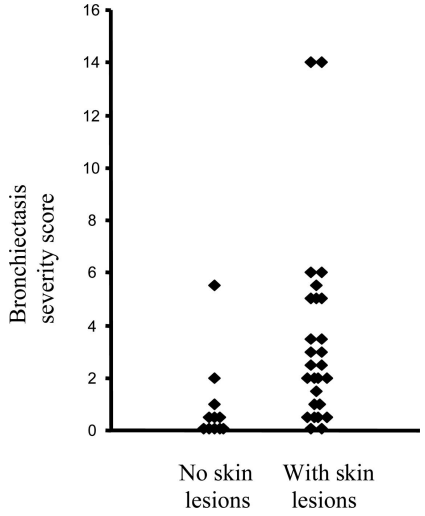

FIGURE 1. Bronchiectasis severity scores (average of 2 reviewers) in subjects with (n = 11) and without (n = 27) arsenic-caused skin lesions who have chronic cough.

TABLE 2. Associations Between Study Variables and Bronchiectasis Found on CT

	Bronchiectasis*		Unadjusted OR (95% CI)
	Yes (n = 21)	No (n = 227)	
Age; mean ± SD	46 ± 14	44 ± 15	
Sex; %			
Women†	19	43	1.0
Men	81	57	3.2 (1.0–9.8)
Cigarette smoking; %			
Never†	52	64	1.0
Ever	48	36	1.6 (0.7–4.0)
Cigarettes per day;‡ mean ± SD	14 ± 10	11 ± 9	
Tuberculosis;§ %			
No†	76	94	1.0
Yes	24	6	5.1 (1.6–16)
Skin lesions;¶ %			
No†	14	62	1.0
Yes	86	38	10 (2.9–35)

*Bronchiectasis was defined as present ("yes") when a subject had both chronic cough and bronchiectasis on CT. Bronchiectasis was defined as absent ("no") in subjects who did not have chronic cough and in subjects with chronic cough who did not have bronchiectasis on CT. This table excludes the 13 subjects who had chronic cough but refused or were physically unable to travel to Kolkata for CT.

†Reference category.

‡Mean number of cigarettes smoked per day in smokers only.

§Self-reported history of physician-diagnosed tuberculosis.

¶Arsenic-caused skin lesions.

TABLE 3. Associations of Arsenic-Caused Skin Lesions with Bronchiectasis Found on CT

	Bronchiectasis*		Unadjusted OR (95% CI)	Adjusted OR† (95% CI)
	Yes	No		
All subjects				
No skin lesions‡	3	140	1.0	1.0
Skin lesions	18	84	10 (2.9–35)	10 (2.7–37)
Men				
No skin lesions‡	2	76	1.0	1.0
Skin lesions	15	52	11 (2.4–50)	13 (2.6–62)
Women				
No skin lesions‡	1	64	1.0	1.0
Skin lesions	3	32	6.0 (0.6–60)	6.1 (0.6–62)

*Only those subjects with chronic cough underwent CT. Thus, bronchiectasis was defined as present when a subject had both chronic cough and bronchiectasis on CT. Bronchiectasis was defined as absent in subjects who did not have chronic cough and in subjects with chronic cough who did not have bronchiectasis on CT.

†Adjusted for age (year), sex, smoking (ever smoker vs never smoker), and self-reported history of physician-diagnosed tuberculosis (yes or no).

‡Reference category.

bronchiectasis was 10 (CI = 2.9–35) in subjects with arsenic-caused skin lesions compared with subjects having no lesions. The corresponding adjusted odds ratio was 10 (2.7–37) (Table 3). The adjusted odds ratio was 13 (2.6–62) in men and 6.1 (0.6–62) in women.

DISCUSSION

This study is the first published investigation of CT findings in a population exposed to high levels of arsenic in drinking water. In a previous study, we had shown that arsenic-caused skin lesions in this population were strongly associated with the consumption of arsenic-contaminated drinking water.[18] In this study, we have found that persons with these lesions have a 10-fold higher rate of bronchiectasis. Despite the relatively small number of people who received CT, this association is not likely to be the result of chance. Because the highly characteristic skin lesions result from the consumption of arsenic-contaminated drinking water, our findings provide evidence that long-term ingestion of arsenic results in increased risk of nonmalignant pulmonary disease, in particular, bronchiectasis.

Several other investigations have also linked arsenic ingestion with nonmalignant pulmonary disease. In the survey used to recruit subjects for this study, self-reported symptoms and physical examination signs of respiratory disease were increased in subjects with arsenic-caused skin lesions and high arsenic drinking water concentrations.[13] In that study, positive dose–response trends with increasing

arsenic concentrations were seen for cough, shortness of breath, and crepitations and rhonchi.

Studies from Antofagasta, Chile, have also reported links between arsenic ingestion and lung disease, although the methods were not presented in detail. Antofagasta is a city in northern Chile with more than 200,000 inhabitants. From 1958 to 1970, the drinking water had arsenic concentrations over 500 μg/L.[15] In a 1968–1969 survey of 398 children, 38% had chronic cough and 14% had a history of bronchopulmonary disease.[15] By comparison, among 200 unexposed children from Santiago, chronic cough and bronchopulmonary disease was reported for 6% and 8%, respectively. The prevalence of cough among children in Antofagasta decreased to 7% after an arsenic removal plant was installed in 1970. The prevalence of bronchiectasis confirmed by bronchography was reportedly 11% (n = 38 cases) among Antofagasta children with skin lesions and 0.5% among the general population of Chilean children, although few details of this investigation were provided.[22] Associations between arsenic ingestion and nonmalignant respiratory disease have also been reported in Bangladesh, where millions of people are exposed to arsenic-contaminated drinking water. For example, in an analysis of 218 subjects with arsenic exposures near 600 μg/L, a prevalence ratio for chronic bronchitis of 3.0 (95% CI = 1.6–5.3) was reported in subjects with arsenic-caused skin lesions compared with unexposed subjects without skin lesions.[23]

Two studies have identified associations between mortality from nonmalignant lung disease and chronic arsenic ingestion. In an ecologic analysis in region II of Chile (the region that includes Antofagasta), chronic obstructive pulmonary disease mortality was elevated in subjects who were children at the time of peak arsenic exposures (standardized mortality ratio [SMR] = 11; 95% CI = 5.3–20).[7] In an ecologic analysis from Taiwan, mortality from bronchitis was increased in the arsenic-exposed blackfoot region (in men, SMR = 1.48 [95% CI = 1.25–1.73]; in women, 1.53 [1.30–1.80]), although no increases in asthma and emphysema mortality were identified.[16]

These studies provide a gradually emerging body of evidence that arsenic is a potent respiratory toxicant, even after ingestion. This observation has some biologic plausibility. For example, studies reporting associations between arsenic-contaminated drinking water and lung cancer provide evidence that ingested arsenic can reach the respiratory tract and can damage lung tissue.[10] Several other known lung carcinogens such as silica, asbestos, chromium, beryllium, and tobacco smoke also cause nonmalignant pulmonary disease. Other compounds such as paraquat and amiodarone have been linked to lung injury in humans after oral intake, but they do so primarily in acute poisoning events and operate through distinct mechanisms.[24,25] Arsenic is unique in that it is the only agent linked to both malignant and nonmalignant lung disease after chronic ingestion.

To assess the potential impact of bias on our study results, we evaluated several of the diagnostic and selection procedures used in this study. One issue is that only those subjects with chronic cough were referred for CT. Thus, subjects with bronchiectasis who did not report chronic cough were not identified as cases. However, because cough is seen in almost all diagnosed cases of bronchiectasis,[20] it is not likely that many cases were missed. In addition, because our selection criteria were the same for those with and without skin lesions, the impact of missing cases would likely be nondifferential and cause bias toward the null rather than producing spurious associations. Another selection bias issue was the possibility of differences between the CT participants and the 13 subjects with chronic cough who did not receive CT. Because CT participation rates were different between those with and without skin lesions, some selection bias is possible, and correcting for this potential bias would result in somewhat lower relative risk estimates. However, given the large magnitude of the relative risks we report, this bias could account for only a small part of the observed association.

In conclusion, the results of this study provide evidence that consuming water containing high levels of arsenic may lead to increased risks of bronchiectasis. Future research is needed to confirm these findings and investigate the mechanisms by which arsenic could cause these effects. Our study population included only adults. Information from exposed regions in Chile, however, suggests that children may be particularly susceptible to the respiratory effects of drinking water arsenic.[7,12,15,22,26] Further research on identifying and quantifying risks in potentially susceptible subpopulations such as children may be helpful in assessing the safety and effectiveness of current arsenic drinking water regulation.

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