Modification of Risk of Arsenic-Induced Skin Lesions by Sunlight Exposure, Smoking, and Occupational Exposures in Bangladesh

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Background: The risk of skin lesions associated with arsenic exposure from drinking water in Bangladesh is considerably greater in men than in women.

Methods: Using baseline data from 11,062 cohort members in the Health Effects of Arsenic Longitudinal Study in Araihazar, Bangladesh, we performed a cross-sectional analysis to evaluate whether the association between arsenic exposure from drinking water and the risk of skin lesions is modified by tobacco smoking, excessive sunlight, the use of fertilizer, and the use of pesticides. A time-weighted well arsenic concentration was estimated for each participant by incorporating history of well use. Relative excess risk for interaction (RERI) and its 95% confidence intervals (CIs) were estimated using adjusted prevalence odds ratios.

Results: We observed a synergistic effect between the highest level of arsenic exposure (>113 μg/L) and tobacco smoking on risk of skin lesions in men (RERI = 1.5 [95% CI = 0.3 to 2.7] overall and 1.7 [0.2 to 3.4] for the subpopulation with longer-term arsenic exposure). We also observed suggestive synergistic effects between higher levels (28.1–113.0 μg/L and 113.1–864.0 μg/L) of arsenic exposure and fertilizer use in men (RERI = 1.0 [−0.2 to 2.2] and 1.3 [−0.2 to 2.9] respectively). Furthermore, the risk of skin lesions associated with any given level of arsenic exposure was greater in men with excessive sun exposure. The patterns of effect estimates in women indicate similar-but-weaker interaction effects of arsenic exposure with tobacco smoking and fertilizer use.

Conclusions: These findings help explain why the risk of arsenic-related skin lesions was much greater in men than in women in Bangladesh. Because most arsenic-induced skin cancers arise from these skin lesions, treatment and remediation plans should take into consideration these etiologic cofactors.

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Inorganic arsenic is widely but unevenly distributed in the earth's crust. The presence of arsenic in groundwater has been recognized as a public health hazard in many countries. Epidemiologic studies have documented associations of high levels of arsenic exposure from drinking water with elevated risks of premalignant and malignant skin lesions,[1] internal cancers,[2] cardiovascular diseases,[3] diabetes mellitus,[4] and adverse reproductive outcomes.[5] In Bangladesh, more than 50 million persons have been chronically exposed to drinking groundwater with arsenic concentrations, exceeding the World Health Organization standard (10 μg/L).[6] There is a need to systematically assess not only the distribution of arsenic exposure but also the cofactors with which arsenic exposure synergistically interact to increase arsenic-related disease burden.

Cutaneous abnormalities, including hyperpigmentation (melanosis) and hyperkeratosis (keratosis), have long been known as early signs of chronic inorganic arsenic poisoning. Melanosis usually starts with changes in skin pigmentation in a raindrop pattern that is particularly pronounced on the trunk and extremities and has bilateral symmetrical distribution. Keratosis commonly appears on the palms and soles, with rough nodules at the early stages and raised, punctated, 2- to 4-mm skin lesions forming at later stages.[7] Leukomelanosis, in which the hypopigmented maculaes take a spotty, white appearance, usually occurs in the early stages of arsenic intoxication.[7] Unlike arsenic-related internal cancers, which have a long latency (ie, decades), these skin lesions may appear within a few years of exposure.[7,8] Because these lesions are considered precursors of arsenic-induced basal and squamous cell skin cancers,[9] prevention of these skin lesions is an important public health issue.

Arsenic exposure seems to be a necessary cause of the skin lesions observed in Bangladesh but it may not be a sufficient cause. The literature has documented marked inter-individual variability in susceptibility to adverse effects of arsenic exposure from drinking water. Specifically, numerous studies[10–13] have unequivocally observed that the risk of arsenic-associated skin lesions/cancers is greater among men

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as compared with women. Both tobacco smoking and ultraviolet radiation have been identified as independent risk factors of nonmelanoma skin cancer.[14–17] Although smoking and sunlight exposure have been suggested as possible contributors to the higher risk of arsenic-related skin lesions in men, the potential role of these factors as etiologic partners of arsenic exposure has not been formally evaluated in epidemiologic studies. Other lifestyle factors or occupational exposures also may modify the effects of arsenic exposure on skin lesions. In the present study, we tested the hypothesis that tobacco smoking, excessive sunlight exposure, and occupational exposures to pesticides and fertilizers modify the risk of skin lesions caused by arsenic exposure.

METHODS

The Health Effects of Arsenic Longitudinal Study

The Health Effects of Arsenic Longitudinal Study is a prospective cohort study that investigates health effects of arsenic exposure from drinking water in Araihazar, Bangladesh. Detailed information on the study methodology has been presented elsewhere.[18] Briefly, we created a sampling frame by collecting water samples, geographic data, and basic demographic data on well owners and users from 5,966 contiguous wells serving nearly 66,000 people in a well-defined 25 km^2 area.[19,20] Between October 2000 and May 2002, 11,746 men and women ages 18 years and older were recruited from users of these 5,966 wells by trained research teams, with a participation rate of 97.5%.

The baseline interview included detailed inquires on water drinking patterns and history, demographics, and lifestyle characteristics. Information on diet was assessed using a newly developed food frequency questionnaire that has been validated in the study population.[21] In addition, trained physicians completed a comprehensive physical examination, with special emphasis on signs and symptoms of arsenic-induced skin lesions and skin cancers, using a structured clinical protocol. Presence/absence, type, size, and shape of skin lesions, as well as the extent of skin involvement, were recorded. Physicians were not aware of the arsenic level in participants' drinking wells.[18] Verbal consent was obtained from study participants. The study procedures were approved by the Columbia University Institutional Review Board and the Ethical Committee of the Bangladesh Medical Research Council.

The present analysis is a cross-sectional study using baseline data from the cohort study. The outcome of interest was defined as the presence of any of skin lesions, including melanosis and keratosis.

Measurements of Arsenic Exposure

In brief, water samples from all 5966 tube wells in the study area were collected in 50-mL acid-washed tubes after pumping the well for 5 minutes.[19] Total arsenic concentration was determined by graphite furnace atomic-absorption spectrometry (Hitachi Z-8200 System, Lamont-Doherty Earth Observatory of Columbia University, New York, NY).[19] Because the standard graphite furnace atomic-absorption spectrometry method has a detection limit of 5 μg/L, water samples found to have arsenic concentration at or below the detection limit were reanalyzed by inductively coupled plasma-mass spectrometry, which has a detection limit of 0.1 μg/L.[22]

Analyses for time-series samples collected from 20 tube wells in the study area showed that the standard deviation of groundwater arsenic concentrations was <10 μg/L over the course of 3 years.[23] Given that arsenic concentration in well water is relatively stable over time, we derived a time-weighted arsenic measure as a function of drinking durations and well arsenic concentrations. This arsenic measure (in μg/L) is defined as $\Sigma\ C_iT_i/\Sigma T_i$, where C_i and T_i denote the well arsenic concentration and drinking duration for the ith well. If the previous drinking well was one of the 5966 tube wells that we had already tested, drinking duration and well arsenic concentration of the previous well were taken into account in the calculation of arsenic exposure. Eighty-six percent of study participants used their current well as their exclusive source of drinking water. For participants who reported drinking water from a second well (14%), the average concentration of the 2 wells was considered for the same drinking duration in the calculation of arsenic exposure. The average time for which arsenic concentration was known was 10.0 years for men and 8.3 years for women, accounting for 25% of lifetime on average for both sexes.

Measurements of Occupational and Smoking Variables

In addition to demographic and socioeconomic characteristics, we collected information on occupational uses of fertilizers, chemical dyes, and pesticides, including current use status, duration of use, and specific product brands. Men with outdoor occupations were queried about daytime working duration and whether their bodies were covered by clothing while outside. Because women in Bangladesh universally wear traditional dresses that almost completely cover the skin of their trunk, sunlight exposure of female respondents was considered minimal and therefore was not assessed in the study.

Detailed information on smoking of tobacco products also was collected. Details of smoking cigarettes and bidis (filterless locally produced cigarettes) were asked together (past or current use, duration of use, age at start, and number of sticks per day). A separate set of questions were asked for hukka smoking (tobacco smoking using waterpipes). We observed a high correlation between hukka and cigarette use, such that 98% of the 1845 ever smokers of hukka were ever smokers of cigarettes/bidis. Therefore, we dichotomized subjects as never/ever smokers of cigarettes, bidis, or hukka. To define finer categories of smoking status, past and noncurrent users of any tobacco products were classified as past smokers, and current users of any tobacco products were considered current smokers. Although cigarettes and bidis frequently are sold individually in Bangladesh, we calculated "pack-years" (product of sticks of cigarettes/bidis per day and years of smoking, divides by 20) for ease in comparison with other

studies. Similarly, a "time-years" index (product of times per day and years of smoking) was calculated for hukka smoking. Median values of "pack-years" and "time-years" among all current smokers were used to define current moderate and heavy smokers.

Statistical Analysis

Study participants were recruited from a list of regular users of all contiguous wells in the study area.[18] Eighty-nine percent of study participants shared tube wells with 0–5 other study participants, whereas the remaining 14% shared their wells with 6–13 individuals. To account for the correlation of arsenic exposure among participants who consumed water from the same well, logistic regression modeling of correlated data using generalized estimating equations[24] was used to estimate prevalence odds ratios (PORs) for skin lesions. Calculations of standard errors and 95% confidence intervals (CIs) were based on robust variance estimates with "exchangeable" correlation structure, which assumes that any 2 distinct participants from the same well have the same correlation coefficient for their arsenic exposure. Because distributions of tobacco use and the occupational exposures are very different by sex, sex-specific analyses were performed. Analysis with regard to sun exposure and pesticide use was only performed in men because sun exposure was not assessed in women and pesticide use was very rare in women (with only 7 cases of skin lesions who were ever-users of pesticides). PORs for skin lesions in relation to arsenic exposure were computed by categories of each potential effect-modifier, controlling for other effect-modifiers of interest in the present study as well as age, body mass index, educational attainment, and daily water consumption.

We assessed the presence of synergy (ie, epidemiologic interaction or interaction on an additive scale) between arsenic exposure and each of the potential effect-modifiers by testing whether the joint effect of exposure to both factors was greater than the sum of their independent effects. The arsenic exposure was categorized into 3 levels (low, moderate, high), each of them included 33% of overall study population. We hypothesized a priori a single reference group with the lowest risk of arsenic-induced skin lesions and estimated dose-specific relative excess risk for interaction (RERI)[25,26] using adjusted PORs as surrogates of incidence rate ratios.

RERI was calculated as follows

$$\text{RERI} \approx POR_{jk} - POR_{j0} - POR_{0k} + 1$$

where POR_{jk} indicates the POR for skin lesions for participants with arsenic exposure at k (moderate or high) level and a hypothesized more susceptible attribute j (eg, ever, past, current moderate, or current heavy smoking) as compared with the reference group with low level of arsenic exposure and a less susceptible attribute (eg, never smoking); POR_{0k} indicates the POR for skin lesions comparing participants with arsenic exposure at k level alone to the reference group; and POR_{j0} denotes the POR for skin lesions comparing participants with a more susceptible attribute j (eg, ever, past, current moderate, or current heavy smoking) alone to the reference group. 95% CIs of RERI were estimated for statistical inferences using the standard delta method described by Hosmer and Lemeshow[27] and a modified SAS (SAS Institute, Cary, NC) program developed by Lundberg et al[28] Because RERI is a measure of difference in risk ratios/rate ratios, there will be evidence of synergy of 2 risk factors at the $P < 0.05$ level if its 95% confidence intervals are positive and excludes zero.

We excluded cohort members with ambiguous skin lesion status at baseline (n = 96) or those who did not undergo the baseline physical examination (n = 212). Information on years of well use was not available for 436 participants because this question was added to the questionnaire a month after the study began. A total of 11,062 with data on time-weighted arsenic exposure and skin lesion status were included for the present cross-sectional analysis. Those with missing values on any of the variables of interest (n = 114; 73 women and 41 men) were excluded from multivariate analysis. Multivariate analysis was also performed in the subpopulation (n = 7997) with longer-term arsenic exposure, defined as those with ≥5 years for the duration with known well arsenic concentrations. In this subpopulation, the average duration with known well arsenic concentrations was 13.1 and 11.3 years for males and females, respectively, accounting for 32% of their lifetime on average in both sexes. The subpopulation was very similar to the overall population in terms of distributions of arsenic exposure levels and potential effect modifiers of interest (data not shown).

RESULTS

Table 1 shows distributions of sociodemographic variables, body mass index, smoking status, and occupational exposures by sex and status of skin lesions. The prevalence of current cigarette smoking was much greater in men (62%) than in women (4%). In men, there were more past smokers and more heavy current smokers of cigarettes/bidis in cases than in noncases of skin lesions. Although few female current smokers of cigarettes/bidis smoked heavily, the percentage of ever smokers in cases (15%) was more than doubled compared with that in noncases (6%). A similar pattern was observed for hukka smoking, although current smoking of hukka (2% in men and 1% in women) was much less prevalent. The use of fertilizers and pesticides was more prevalent in men than in women and also was more prevalent in cases than in noncases.

Among men, at low level of arsenic exposure (<28.1 μg/L), smoking was not related to risk of skin lesions (Table 2). At high level of arsenic exposure (>113 μg/L), the risk of skin lesions was consistently higher in ever, past, and current smokers compared with never smokers. The pattern of PORs in the overall population was similar to that in the subpopulation with a longer-term arsenic exposure, and the interaction between tobacco smoking and arsenic exposure was stronger in the subpopulation. In the subpopulation, the joint effect of high level of arsenic exposure and ever-smoking was greater than the sum of their individual effects, with the RERI being 1.7 (95% CI = 0.2–3.4). When ever smokers were further grouped into past, current moderate, and current

TABLE 1. Distributions of Sociodemographic Variables, Body Mass Index, Smoking Status, Occupational Exposures, by Sex and Status of Skin Lesions*

	Men Skin Lesions		Women Skin Lesions	
	Yes (n = 572)	No (n = 4149)	Yes (n = 127)	No (n = 6214)
Age (yrs); mean ± SD	45.7 ± 9.6	41.0 ± 9.8	38.6 ± 8.9	33.5 ± 8.9
Body mass index (kg/m^2); mean ± SD	18.8 ± 2.6	19.5 ± 3.0	19.4 ± 3.0	20.0 ± 3.3
Education (yrs); mean ± SD	3.0 ± 3.6	4.1 ± 4.2	1.5 ± 2.8	3.1 ± 3.6
Cigarette/bidi smoking; %				
Nonsmokers	17	27	85	94
Past smokers	17	11	9	2
Current smokers (sticks/days)				
<11	36	36	5	3
11+	30	26	1	1
Hukka smoking; %				
Nonsmokers	44	67	93	97
Past smokers	50	31	6	2
Current users (times/d)				
<5	3	1	1	1
5+	3	1	0	0
Work outside; %				
No	66	75	—	—
Yes			—	—
Covered	24	21	—	—
Uncovered	10	5	—	—
Use of fertilizer; %				
Yes	80	67	26	17
Use of pesticides; %				
Yes	61	51	6	4

*Data on body mass index were missing for 3 men with skin lesions, 15 men without skin lesions, 1 woman with skin lesions, and 52 women without skin lesions. Data also were missing on education for, respectively, 0, 5, 0, and 1 subjects; on smoking for 0, 4, 0, and 5 subjects; on hukka smoking for 0, 5, 0, and 4 subjects; and on pesticide use for 0, 1, 0, and 2 subjects.

heavy smokers, the synergistic effects of high level of arsenic exposure with past smoking and current heavy smoking were stronger (RERI = 2.8 [95% = 0.1 to 5.6] and 2.0 [0.1 to 4.0] respectively, in the subpopulation). Female ever smokers in general smoked less intensively, with lower pack-years for cigarettes/bidis and time-years for hukka. Among women, PORs associated with high arsenic exposure levels were also greater in ever smokers than in never smokers. However, the joint effect of smoking and high level of arsenic exposure was not significantly greater than the sum of the individual effects.

Among men, at each level of arsenic exposure, PORs for skin lesions in ever-users of fertilizer were greater than those in never-users (Table 3). Joint effects of ever using fertilizer with moderate and high levels of arsenic exposure suggest similar synergistic effects (RERI = 1.3 [−0.2 to 2.8] and 1.3 [−0.6 to 3.2]). Similar patterns of PORs were observed when ever-users were categorized by duration of fertilizer use. In women, risk associated with each higher level of arsenic exposure was also greater in ever-users of fertilizers than in never-users. However, the joint effect of greater arsenic exposure and use of fertilizer did not suggest synergism.

In men, risks of skin lesions associated with moderate and high level of arsenic exposure were comparable in ever users and never users of pesticides (Table 3). The pattern of PORs did not suggest an influence of pesticide use in the relation between arsenic exposure and risk of skin lesions.

At any given level of arsenic exposure, risk of skin lesions was greater in men with excessive sun exposure (Table 3). For example, in the overall study population, compared with men who had a low level of arsenic exposure and no excessive sun exposure, PORs associated with moderate and high level of arsenic exposure in men without excessive sun exposure were 2.5 (95% CI = 1.9–3.5) and 3.8 (2.8–5.1), respectively; and the corresponding PORs were 4.5 (2.6–7.8) and 5.3 (3.0–9.3), respectively in men with excessive sun exposure. RERI estimates indicate that the joint effect of excessive sun exposure and higher levels of arsenic exposure did not exceed additivity.

DISCUSSION

In this study, we formally evaluated interaction of level of arsenic exposure with tobacco smoking, use of fertilizer,

TABLE 2. Skin Lesions in Relation to Smoking Status* and Levels of Time-Weighted Well Arsenic Concentration (TWA), by Sex

Smoking Status TWA Levels (μg/L)	Smoking		Overall Study Population Skin Lesions				Subpopulation With Longer-Term Arsenic Exposure			
	Pack-Years (mean)§	Number-Years (mean)‖	TWA (mean; μg/L)	No. Cases/ Noncases	POR (95% CI)†	RERI (95% CI)	Time With Known Arsenic Level (Mean Years)	Skin Lesions: No. Cases/ Noncases	Skin Lesions: POR (95% CI)†	Skin Lesions: RERI (95% CI)
Men										
Nonsmokers										
0.1–28.0	—	—	8.1	16/384	1.0‡		11.0	10/282	1.0‡	
28.1–113.0	—	—	65.6	36/337	2.5 (1.3 to 4.4)		12.3	31/243	3.3 (1.6 to 6.8)	
113.1–864.0	—	—	229.9	40/384	2.5 (1.4 to 4.7)		12.0	30/271	3.2 (1.5 to 6.5)	
Ever smokers										
0.1–28.0	16.5	49.4	8.2	72/1090	1.0 (0.6 to 1.9)		11.0	59/806	1.4 (0.7 to 2.7)	
28.1–113.0	16.0	47.7	64.1	160/992	2.6 (1.5 to 4.5)	0.1 (−1.1 to 1.2)	12.3	131/726	3.4 (1.8 to 6.6)	−0.2 (−1.9 to 1.5)
113.1–864.0	15.5	50.8	220.9	245/930	4.1 (2.4 to 7.0)	1.5 (0.3 to 2.7)	12.0	211/712	5.3 (2.8 to 10.0)	1.7 (0.2 to 3.4)
Past smokers										
0.1–28.0	18.4	59.3	8.6	25/157	1.2 (0.6 to 2.5)		10.5	11/123	1.4 (0.7 to 2.7)	
28.1–113.0	17.9	61.3	64.8	28/163	2.1 (1.1 to 4.0)	−0.6 (−2.2 to 1.0)	11.8	24/122	2.9 (1.4 to 6.2)	−0.7 (−2.9 to 1.6)
113.1–864.0	18.5	56.1	231.8	51/149	4.6 (2.4 to 8.4)	1.9 (−0.1 to 3.8)	12.7	44/104	6.3 (3.1 to 13.0)	2.8 (0.1 to 5.6)
Current smokers										
Moderate										
0.1–28.0	8.0	41.5	8.2	30/499	1.0 (0.5 to 2.0)		11.1	24/359	1.4 (0.7 to 3.0)	
28.1–113.0	8.0	36.2	63.0	64/486	2.4 (1.3 to 4.2)	−0.5 (−2.0 to 1.1)	11.7	54/356	3.2 (1.6 to 6.4)	−0.8 (−3.0 to 1.5)
113.1–864.0	8.1	39.5	216.2	112/457	3.9 (2.2 to 6.9)	2.0 (0.1 to 4.0)	12.7	93/368	4.7 (2.4 to 9.1)	2.7 (−0.2 to 5.7)
Heavy										
0.1–28.0	25.6	52.6	8.1	27/434	1.2 (0.5 to 1.9)		11.1	24/324	1.3 (0.6 to 2.9)	
28.1–113.0	25.8	52.2	65.1	68/343	3.2 (1.8 to 5.8)	0.8 (−0.6 to 2.1)	12.5	53/248	4.0 (2.0 to 8.0)	0.4 (−1.6 to 2.4)
113.1–864.0	24.5	60.7	222.2	82/324	4.0 (2.2 to 7.0)	1.4 (0.0 to 2.9)	12.8	74/240	5.5 (2.8 to 10.9)	2.0 (0.1 to 4.0)
Women										
Nonsmokers										
0.1–28.0	—	—	8.1	15/1899	1.0‡		9.6	14/1340	1.0‡	
28.1–113.0	—	—	63.9	34/1943	2.3 (1.1 to 4.5)		10.1	34/1383	2.5 (1.2 to 5.0)	
113.1–864.0	—	—	223.9	57/1925	3.7 (1.9 to 7.1)		11.1	49/1372	3.4 (1.7 to 6.8)	
Ever smokers										
0.1–28.0	3.5	32.0	7.6	5/132	2.5 (0.8 to 7.5)		10.5	5/95	2.9 (1.0 to 8.8)	
28.1–113.0	4.3	30.4	64.6	4/123	2.2 (0.7 to 6.7)	−1.6 (−5.0 to 1.9)	11.8	4/92	2.5 (0.8 to 8.1)	−1.8 (−5.8 to 2.1)
113.1–864.0	3.7	33.0	218.9	11/129	5.5 (2.3 to 13.6)	0.4 (−3.8 to 4.6)	11.8	9/101	5.1 (2.0 to 13.2)	−0.1 (−4.4 to 4.2)

*Cigarettes, bidis, or hukka.
†PORs were adjusted for age, educational attainment (years), body mass index, betel nut use, pesticide use, fertilizer use, and daily water consumption. PORs in men were additionally adjusted for excessive sun exposure.
‡Reference category.
§Pack-years of cigarettes/bidis smoking.
‖Number-years of hukka smoking.

TABLE 3. Skin Lesions in Relation to Fertilizer Use Status, Pesticide Use (Men Only), Excessive Sun Exposure (Men Only), and Levels of Time-Weighted Well Arsenic Concentration

	Overall Study Population				Subpopulation With Longer-Term Arsenic Exposure			
		Skin Lesions				Skin Lesions		
Exposure Status TWA Levels (μg/L)	TWA (mean; μg/L)	No. Cases/ Non-Cases	POR (95% CI)	RERI (95% CI)	TWA (Mean; μg/L)	No. Cases/ Noncases	POR (95% CI)	RERI (95% CI)
Fertilizer use among men*								
Never-users								
0.1–28.0	8.0	17/512	1.0§		8.0	12/379	1.0§	
28.1–113.0	63.8	35/412	2.3 (1.3 to 4.0)		65.1	26/296	2.3 (1.2 to 4.5)	
113.1–864.0	221.3	69/441	3.5 (2.1 to 6.1)		219.6	52/327	4.1 (2.2 to 7.4)	
Ever-users								
0.1–28.0	8.3	71/962	1.5 (0.8 to 2.6)		8.2	57/709	1.8 (1.0 to 3.3)	
28.1–113.0	64.7	161/917	3.7 (2.2 to 6.4)	1.0 (−0.2 to 2.2)	65.2	136/673	4.4 (2.4 to 8.1)	1.3 (−0.2 to 2.8)
113.1–864.0	224.2	222/873	5.3 (3.1 to 9.1)	1.3 (−0.2 to 2.9)	227.7	189/656	6.2 (3.4 to 11.2)	1.3 (−0.6 to 3.2)
Duration of use								
<9 yr								
0.1–28.0	7.8	30/435	1.5 (0.8 to 2.7)		7.7	26/312	1.9 (1.0 to 3.6)	
28.1–113.0	63.6	64/410	3.9 (2.2 to 6.8)	1.1 (−0.4 to 2.6)	65.6	56/282	4.7 (2.5 to 8.8)	1.5 (−0.5 to 3.5)
113.1–864.0	224.3	91/397	5.6 (3.3 to 9.6)	1.6 (−0.3 to 3.4)	230.4	77/296	6.0 (3.3 to 11.0)	1.1 (−1.1 to 3.3)
9+ years								
0.1–28.0	8.7	40/526	1.6 (0.9 to 2.9)		8.5	30/396	1.7 (0.9 to 3.4)	
28.1–113.0	65.6	96/506	3.9 (2.2 to 7.0)	1.1 (−0.4 to 2.5)	64.9	79/390	4.3 (2.2 to 8.1)	1.2 (−0.5 to 2.9)
113.1–864.0	224.1	131/475	5.7 (3.2 to 10.0)	1.5 (−0.4 to 3.4)	225.6	112/360	6.3 (3.4 to 11.9)	1.6 (−0.7 to 3.9)
Fertilizer use among women*								
Never-users								
0.1–28.0	7.9	16/1751	1.0 §		7.8	15/1244	1.0 §	
28.1–113.0	63.9	27/1687	1.8 (0.9 to 3.6)		64.6	27/1201	2.0 (1.0 to 4.0)	
113.1–864.0	223.9	50/1652	3.4 (1.8 to 6.4)		226.9	43/1180	3.1 (1.6 to 6.1)	
Ever-users								
0.1–28.0	9.0	4/280	1.4 (0.5 to 4.5)		9.5	4/191	1.7 (0.5 to 5.2)	
28.1–113.0	63.8	11/379	3.1 (1.3 to 7.2)	0.8 (−1.7 to 3.2)	62.7	11/274	3.5 (1.5 to 8.4)	0.8 (−2.0 to 3.6)
113.1–864.0	222.7	18/402	4.3 (2.0 to 9.2)	0.5 (−2.3 to 3.3)	223.5	15/293	4.0 (1.8 to 8.9)	0.1 (−2.6 to 2.7)
Pesticide use among men†								
Never-users								
0.1–28.0	7.9	33/760	1.0§		7.8	26/558	1.0§	
28.1–113.0	63.8	85/627	3.0 (2.0 to 4.6)		65.2	68/452	3.0 (2.0 to 4.6)	
113.1–864.0	222.1	103/620	3.7 (2.4 to 5.6)		221.8	85/461	3.7 (2.4 to 5.6)	
Ever-users								
0.1–28.0	8.5	55/714	1.0 (0.7 to 1.7)		8.5	43/530	1.0 (0.6 to 1.7)	
28.1–113.0	65.0	111/702	2.3 (1.4 to 3.5)	−0.8 (−1.9 to 0.3)	65.1	94/517	2.3 (1.4 to 3.5)	−0.8 (−1.9 to 0.3)
113.1–864.0	224.3	182/694	3.7 (2.4 to 5.7)	0.1 (−1.3 to 1.3)	228.0	156/522	3.7 (2.4 to 5.7)	0.1 (−1.2 to 1.6)

(*Continued*)

TABLE 3. (*Continued*)

Exposure Status TWA Levels (μg/L)	Overall Study Population				Subpopulation With Longer-Term Arsenic Exposure			
		Skin Lesions				Skin Lesions		
	TWA (mean; μg/L)	No. Cases/ Non-Cases	POR (95% CI)	RERI (95% CI)	TWA (Mean; μg/L)	No. Cases/ Noncases	POR (95% CI)	RERI (95% CI)
Excessive sun exposure among men‡								
No								
0.1–28.0	8.1	76/1406	1.0 §		8.0	60/1034	1.0 §	
28.1–113.0	64.6	175/1274	2.5 (1.9 to 3.5)		65.4	146/930	2.5 (1.8 to 3.5)	
113.1–864.0	221.9	257/1252	3.8 (2.8 to 5.1)		223.8	221/932	3.8 (2.7 to 5.2)	
Yes								
0.1–28.0	9.9	12/68	2.0 (1.0 to 3.9)		9.4	9/54	1.9 (0.9 to 4.1)	
28.1–113.0	61.8	21/55	4.5 (2.6 to 7.8)	0.5 (−2.5 to 3.5)	61.0	16/39	3.8 (2.0 to 7.2)	0.3 (−2.3 to 3.0)
113.1–864.0	246.5	28/62	5.3 (3.0 to 9.3)	0.9 (−1.7 to 3.5)	248.6	20/51	4.4 (2.3 to 8.3)	−0.3 (−3.3 to 2.6)

*PORs were adjusted for age, educational attainment in years, body mass index, betel nut use, pesticide use, tobacco smoking status, and daily water consumption. PORs in men were additionally adjusted for excessive sun exposure.
†PORs were adjusted for age, educational attainment in years, body mass index, betel nut use, fertilizer use, tobacco smoking status, excessive sun exposure, and daily water consumption.
‡PORs were adjusted for age, educational attainment in years, body mass index, betel nut use, fertilizer use, tobacco smoking status, pesticide use, and daily water consumption.
§Reference category.

use of pesticide, and excessive sun exposure on the risk of skin lesions in men and women separately. We found an apparent synergistic effect between high level of arsenic exposure and tobacco smoking in men. In addition, risk of skin lesion associated with any given level of arsenic exposure was greater in men who reported excessive sunlight exposure and in men who were ever-users of fertilizer. Patterns of PORs indicate similar-but-weaker influences of tobacco smoking and fertilizer use on risk associated with arsenic exposure in women compared with men.

Epidemiologic studies that have investigated the interaction between arsenic exposure and cigarette smoking on other health outcomes found similar patterns of joint effects. Studies that suggest a greater risk of bladder cancer in smokers were mainly conducted in areas with very high levels of arsenic exposure from drinking water (>300 μg/L).[29–32] In Western United States, Steinmaus et al[30] identified a greater risk of bladder cancer only in smokers with the highest intake of arsenic (median 177 μg/Day). Similarly, a recent study in New Hampshire[33] found an elevated risk of bladder cancer in smokers with the highest category of toenail arsenic. Another study of 192 cases of arsenic-related skin lesions and 213 controls in West Bengal,[34] however, found a greater proportion of current smokers in controls, as well as same proportion of past smokers in cases and controls. Importantly, information on the intensity of smoking and levels of arsenic exposure was not given, nor were sex-specific comparisons performed in that study.

The present analysis is population-based, with a large sample size and detailed information on smoking pattern. We performed sex- and dose-specific analysis, and we found a synergistic effect between a high level of arsenic exposure and tobacco smoking, especially with past and current heavy smoking in men. The synergy between tobacco smoking and a high level of arsenic exposure from drinking water suggests potential public health implications of smoking cessation and arsenic exposure reduction. We estimated the RERI of the highest level of arsenic exposure and ever-smoking in men to be 1.5 (95% CI = 0.3–2.7). The corresponding attributable proportion caused by interaction (AP = RERI/POR for joint exposures) is 37%, indicating that 37% of skin lesion risk among men who were ever smokers with highest level of arsenic exposure was attributable to the synergistic effect of these 2 exposures. The high prevalence of tobacco smoking in Bangladesh has been noted as a major public health problem.[35,36] In light of the findings from the present study and other studies, an emphasis on smoking-cessation programs in Bangladesh would be prudent, particularly in areas with high levels of arsenic exposure.

Inorganic arsenic can be first ingested as either arsenite [As(III)] or arsenate [As(V)], which are methylated first to monomethylarsonate and then further to dimethylarsinate. Methylation of arsenic has been hypothesized as a detoxification process.[37] A cross-sectional study in Chile[38] found that cigarette smoking is associated with a lower methylation capacity of arsenic, as indicated by a higher ratio of urinary monomethylarsonate to dimethylarsinate in smokers. The immunosuppression caused by tobacco smoking[39,40] also

may play a role in the observed interaction. In addition, bidis, the filterless locally produced cigarettes with raw tobacco that are popular in rural areas in Bangladesh, may contain large amounts of substances that promote the onset of arsenic-induced skin lesions. It has been reported that carcinogenic substances were detected in greater amounts in bidis than in cigarettes.[41,42] Moreover, tobacco smoking may increase the requirement of folate,[43] a critical cofactor in one-carbon metabolism through which arsenic is enzymatically methylated.[44]

We found that the risk of skin lesions associated with any given level of arsenic exposure was greater in men with excessive sun exposure. This observation is in line with the mounting evidence from animal and experimental studies that arsenic may cause skin tumors by enhancing the mutagenicity of ultraviolet radiation possibly through inhibiting DNA repair and/or enhancing positive growth signaling.[45,46] Skin tumors occurring in mice given ultraviolet radiation plus arsenite appeared earlier and were much larger and more invasive than in mice given ultraviolet radiation alone.[45] In a recent case–control study in an Arsenic-exposed area in southwestern Taiwan,[12] skin cancer patients reported greater sunlight exposure than controls. In the present analysis, excessive sun exposure was dichotomized; men who worked outside with a bare upper body were categorized as having excessive sun exposure. In the follow-up visits of participants in our study, multiple categories of sunlight exposure were defined, and we will have the opportunity to examine this issue in greater detail in future prospective investigations of this topic.

We also found that ever users of fertilizers were more prone to arsenic-induced skin lesions. There are few reports of fertilizers causing occupational contact dermatitis.[47–49] Although the irritation of chemical fertilizers may increase skin sensitivity to the effects of arsenic exposure, the exact mechanism by which exposures to fertilizers and arsenic interact to increase the risk of skin lesions is not clear. It also remains unknown whether exposure to fertilizer would increase the malignant progression of arsenic-induced skin lesions.

Patterns of PORs indicate that among women the influences of tobacco smoking and fertilizer use in the risk of arsenic-related skin lesions are similar but much weaker. Tobacco smoking and fertilizer use are both infrequent and of lower intensity among Bangladeshi women. Our findings suggest that various lifestyle and occupational factors, rather than simply a detection bias, contribute to the much higher risk of arsenic-related skin lesions in men that has been observed in other studies.[10–13] In our study, both male and female physicians performed the clinical examinations to minimize detection bias between male and female study participants. The adjusted PORs for skin lesions comparing men to women did not differ by locations of the skin lesions (POR = 4.0 [95% = 2.1 to 7.6] for skin lesions in the trunk and 3.9 [2.9 to 5.2] for skin lesions in the extremities), suggesting that differences in the diagnosis of skin lesion between covered and uncovered areas of the body did not result in the observed sex differences in risk of skin lesions. Similarly, the adjusted PORs for early-staged and advanced skin lesions comparing men to women were also similar (data not shown).

The wide range of arsenic exposure (0.1–864 μg/L) in the study population, the large sample size, and the detailed individual-level data provided us a unique opportunity to evaluate in depth the influences of smoking and occupational exposures in arsenic toxicity. Epidemiologic studies that investigate interaction effects often are criticized for dichotomizing exposure levels. Importantly, we assessed dose-specific interaction on the additive scale and showed that the influence of tobacco smoking on risk of arsenic-related skin lesions is only apparent at a high level of arsenic exposure. Although we did not have a complete history of well use, patterns of PORs in the subpopulation with longer-term measure of arsenic exposure suggest similar, if not stronger, synergistic effects between arsenic exposure and smoking, fertilizer use, and sun exposure. While other potential modifications such as age and body mass index were evaluated in a separate analysis,[50] these factors were controlled for in the present analysis. One potential limitation of the study is the cross-sectional nature of the study design. However, arsenic-induced skin lesions are usually chronic with prolonged exposure and in general are not life-threatening. We used self-reported information on well-use history, sun exposure, smoking habits, and other occupational exposures. Validity of self-reported well use history was good; the correlation between arsenic concentration in the well water and urine was 0.70 in our study population.[18]

The identification of factors that render an individual more likely to be affected by arsenic exposure may help to unravel disease mechanisms and to design appropriate remediation measures. In conclusion, our findings suggest that use of fertilizer and excessive sun exposure increase the susceptibility to the risk of skin lesions due to arsenic exposure from drinking water and that tobacco smoking and high level of arsenic exposure synergistically increase the risk of skin lesions. Because most the arsenic-induced skin cancers would arise from these skin lesions, our findings suggest that arsenic exposure may increase the risk of skin cancer, particularly in these subgroups.

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