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Cumulative arsenic exposure is associated with fungal infections: Two cohort studies based on southwestern and northeastern basins in Taiwan

Ling-I Hsu [b,1], Yu-Wen Cheng [a,1], Chien-Jen Chen [c], Meei-Maan Wu [d], Kuang-Hung Hsu [b,e], Hung-Yi Chiou [d], Chih-Hung Lee [a,*]

[a] Department of Dermatology, Kaohsiung Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Kaohsiung, Taiwan
[b] Laboratory for Epidemiology, Department of Health Care Management, and Healthy Aging Research Center, Chang Gung University, Taoyuan, Taiwan
[c] Genomic Research Center, Academia Sinica, Taipei, Taiwan
[d] School of Public Health, College of Public Health and Nutrition, Taipei Medical University, Taipei, Taiwan
[e] Department of Urology, Chang Gung Memorial Hospital, Taoyuan, Taiwan

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ABSTRACT

Long-term arsenic exposure results in atherosclerosis and cancers, along with aberrant immune responses. Animal-based and epidemiological studies indicate that arsenic exposure increases susceptibility to viral and bacterial infections. This study aimed to assess whether arsenic exposure is associated with the development of fungal infection, which is substantially attributed to as a cause of aberrant immunity. Based on two well-established cohorts from two basins in southwestern (SW; high arsenic area) and northeastern (NE; low arsenic area) Taiwan (n = 297 and 2738, respectively), the arsenic exposure in well water was estimated using HPLC-ICP-MS. Fungal infections were defined *via* clinical and mycological assessments (PCR of fungal 18S rRNA) of nail samples. Individuals in SW cohort with cumulative arsenic exposure >10,000 μg/L∗years had a higher risk of developing fungal infections (OR = 1.57, 95% CI = 1.08–1.92) after adjusting for diabetes and occupation. In NE cohort, female sex, alcohol consumption, and chronic kidney diseases were associated with toenail infections. In contrast, fingernail infections (OR = 1.33, 95% CI = 1.05–1.68) were highly associated with arsenic exposure in a dose-dependent manner. We are the first to report palmar and plantar hyperkeratosis upon low arsenic exposure in 3.9% and 6.7% individuals, respectively. This is the first large-scale study showing arsenic exposure is associated with fungal infections in a dose-dependent manner.

1. Introduction

Arsenic is a common metalloid in the Earth's crust. The major route of human exposure to arsenic is through drinking artesian water contaminated with arsenic (Lee et al., 2011a). Tens of millions of people are at risk of arsenic exposure globally, including regions in Bangladesh, Mongolia, India, and South America (Parvez et al., 2013). Arsenic induces several human cancers, including those of skin, lung, bladder, and liver (Lee et al., 2011b). In addition to its notorious effects in carcinogenesis, chronic arsenic exposure features characteristic skin manifestations, including variegated hyperpigmentation and palmoplantar hyperkeratosis. Moreover, arsenic exposure leads to systemic vascular effects; for instance, it increases the risk of several vascular diseases, including the cerebral vascular disease, myocardial infarction, and peripheral vascular diseases (Ren et al., 2011).

Compelling evidences have shown that arsenic impairs immune responses. In mice, arsenic enhances the susceptibility to influenza A infection by impaired migration of dendritic cells towards mediastinal lymph nodes (Ramsey et al., 2013; Kozul et al., 2009). This susceptibility to influenza infection was subsequently reproduced in humans (Farzan et al., 2013). The epidemiological studies in Bangladesh (Rahman et al., 2011) and US (Farzan et al., 2013) showed an increased risk of respiratory infections in infants of mothers exposed to arsenic. Experimentally, arsenic differentially affects the activation, function, differentiation, and apoptosis in different cell types of the immune system (Lee et al., 2011a; Dangleben et al., 2013). Clinically, the fact that arsenic exposure induces cancers in only about 10% of the population suggests that host immune responses interactively regulate the process of carcinogenesis. In patients with arsenical cancers, the *in vivo* delayed hypersensitivity response involving antigen presenting cells and T cells is impaired. We previously reported that arsenic selectively induces Fas-dependent apoptosis of Th2 lymphocytes (Liao et al., 2004). Moreover, arsenic was reported to impair the activation of monocytes and macrophages (Binet et al., 2009). In line with this, we have demonstrated that arsenic mobilizes the epidermal Langerhans cells and polarizes Th1 response in

* Corresponding author.
E-mail address: dermlee@gmail.com (C.-H. Lee).
[1] Equal contributions.

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arsenical cancers (Lee et al., 2012). Paradoxically, arsenic is the drug of choice for a specific form of acute leukemia, that is, acute promyelocytic leukemia, owing to its effect in regulating differentiation of the lymphoid blast cells (Novick and Warrell, 2000). These studies further indicate arsenic has profound multifaceted effects in the immune system. Taken together, these studies demonstrated that arsenic exposure affects the host immune system, particularly in the early stage of immune organ development, possibly leading to an increase in the susceptibility to respiratory infections.

Skin infections are the most common form of infections in humans because the skin constitutes an extensive area of interface between outside environments and inside hosts. Among skin infections, superficial fungal infections (mycosis) are very common worldwide. They are believed to affect 20% to 25% of the world's population (Havlickova et al., 2008). The incidence of superficial fungal infection continues to rise owing to the recent global warming and climate change. Individuals can develop superficial fungal infections owing to the increased environmental humidity and heat (Kaur et al., 2008), reflecting the increased prevalence of superficial mycosis in tropical regions as compared to that in temperate regions. The most common superficial mycosis is caused by dermatophyte infections, causing tinea pedis (Athlete's foot), tinea unguium (onychomycosis), tinea capitis, tinea corporis, *etc.*, depending on the location of skin involved. These infections are common in tropical countries and additionally tend to occur in immunocompromised patients, including patients with diabetes, HIV, and those undergoing chemotherapy. Tinea pedis and tinea unguium are emerging more commonly because of changes in lifestyle, including increased urbanization, the use of communal bathing facilities, and occlusive footwear.

Recently, global warming has led to a public concern about increased fungal infections to the subtropical and temperate regions. In addition, the increased survival of patients with AIDS and diabetes leads to an overall increased prevalence of fungal infections. Scientific evidences have suggested that aberrant immune responses might play a role in disease progression, immune modulation, and disease susceptibility in arsenic-exposed hosts. Therefore, in this study, we aimed to investigate whether arsenic exposure is associated with the susceptibility to dermatophytosis. We adopted two approaches. First, based on an established 30-year cohort in the southwestern (SW) Taiwan, an area with well-documented arsenical cancers and blackfoot disease (BFD), we estimated the prevalence of superficial fungal infections by clinical inspection and investigated its association with arsenic exposure. This cohort is characterized by high level of arsenic exposure with high concentrations of arsenic in the well water being consumed. Second, using another recently established cohort with several thousands of subjects in northeastern (NE) coast of Taiwan, we conducted the molecular diagnosis of dermatophytosis with clipped fingernails and toenails using fungal ribosomal 18S PCR. We aimed to validate the findings from the first cohort using the results for the second cohort with lower levels of arsenic in the well water being consumed. In both cohorts, arsenic exposure was estimated by the year of residence multiplied by arsenic concentration in underground well water in specific areas.

Table 1
Demographics of superficial mycosis in the SW cohort (n = 297) with community-based skin examination in 2009.

	Infection subjects/subtotal	Fungal infection (%)	p value
Age (2009, years)	185/297	62.3	
<65	66/125	52.8	
65–74	80/118	67.8	
>74	39/54	72.2	0.0137
Gender			
Male	81/120	67.5	
Female	104/177	58.8	0.1271
Fishery-related occupation (yrs)			
<5	57/102	55.9	
5–29	60/98	61.2	
≧30	68/97	70.1	0.1135
Diabetes mellitus (2009, from questionnaire)			
No	39/63	61.9	
Yes	143/231	61.9	1.0000
Cumulative arsenic exposure (μg/L∗years)			
<500.0	21/43	48.8	
500.0–9999.9	29/42	70.0	
10,000.0–17,999.9	63/83	75.9	
>18,000.0	36/60	60.0	
Not available	36/69	52.2	0.0087*

* Indicates a significant association between the fungal infections and the covariate.

Table 2
The association of superficial mycosis and the arsenic exposure (SW cohort, 2009 community health screening).

	OR	95% CI	p value
Age (2009, years)			
<65	1		
65–74	1.86	1.10–3.13	0.02
>74	2.24	1.12–4.50	0.02
Sex			
Male	1		
Female	0.70	0.43–1.15	0.16
Diabetes			
No	1		
Yes	1.21	0.67–2.20	0.53
Fishery-related work (yrs)			
<5	1		
5–29	1.13	0.64–2.01	0.68
>30	1.11	0.54–2.30	0.77
Cumulative arsenic exposure (μg/L∗years)			
<500.0	1		
500.0–9999.9	1.46	0.86–2.49	0.07
10,000.0–17,999.9	1.57	1.08–1.92	0.04
>18,000.0	1.26	0.74–2015	0.39
Not available	1.09	0.64–1.88	0.74
Ptrend			0.0065

Table 3
The demographic data from 2738 subjects from a cohort in the northeastern region of Taiwan (NE cohort, 2011–2014 community health screening).

	Variables	Frequency	Percentage
Age (years)	55–69	891	32.5
	70–76	963	35.2
	>77	884	32.3
Gender	Male	1189	43.4
	Female	1549	56.6
Town	C	1194	43.6
	D	319	11.7
	J	619	22.6
	W	606	22.1
Body mass index	<20	289	10.6
	20–25	1297	47.4
	>25	1051	38.4
	Not available	101	3.6
Smoking	No	1849	67.5
	Yes	889	32.5
Alcohol drinking	No	2302	84.4
	Yes	426	15.6
Wet work	No	2295	86.1
	Yes	373	14.0
Keratosis	Hand	106/2738	3.9
	Feet	178/2658	6.7
Pitted skin	Yes	418/2668	15.7