

### Short Communication

## Arsenic Methylation Capacity and Skin Cancer<sup>1</sup>

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### Abstract

Chronic ingestion of arsenic from drinking water is associated with the occurrence of skin cancer. To clarify the role of arsenic methylation capacity in the development of arsenic-associated skin lesions, an epidemiological case-control study was conducted in the southwestern region of Taiwan, in which 26 skin disorder patients were matched with control subjects. The objective of this study was to determine whether arsenic methylation capacity of patients with skin disorders differed from that of matched controls. Both cases and controls had been exposed to similar high concentrations of arsenic in drinking water. Results indicated that skin lesion cases had higher percents of inorganic arsenic (InAs,  $13.1 \pm 3.7\%$ ), methylarsonic acid (MMA,  $16.4 \pm 3.2\%$ ), lower percent of dimethylarsinic acid (DMA,  $70.5 \pm 5.8\%$ ), and higher ratio of MMA to DMA (MMA/DMA,  $0.24 \pm 0.06$ ) than matched controls (InAs:  $11.43 \pm 2.1\%$ ; MMA:  $14.6 \pm 2.6\%$ ; DMA:  $73.9 \pm 3.3\%$ ; MMA/DMA:  $0.20 \pm 0.04$ ). Individuals with a higher percentage of MMA ( $>15.5\%$ ) had an odds ratio of developing skin disorder 5.5 times (95% confidence interval, 1.22–24.81) higher than those having a lower percentage of MMA. This association was not confounded by hepatitis B surface antigen, cigarette smoking, or alcohol and tea consumption. It is concluded that arsenic biotransformation including methylation capacity may have a role in the development of arsenic-induced skin disorders.

### Introduction

Epidemiological investigations have demonstrated associations between arsenic ingestion and blackfoot disease (1), cancers of skin, lung, liver, bladder, kidney, and prostate, and other non-

cancer end points (2–4). The IARC has classified arsenic as a human carcinogen, although there is inadequate evidence of its carcinogenic potential in animals (5).

Skin lesions are recognized as one of the most sensitive end points of chronic arsenicism. Investigations identified hyperpigmentation and hyperkeratosis in humans after exposure to high levels of arsenic (6). Bowen's disease, basal-cell carcinomas, and squamous cell carcinoma were reported among individuals chronically ingesting arsenic-contaminated water (6, 7). Tseng *et al.* (6) reported that people exposed to high arsenic-contaminated water in southwestern Taiwan had prevalence rates for hyperpigmentation, hyperkeratosis, and skin cancer of 183.5/1000, 71/1000, and 10.6/1000, respectively. Chen and Wang (8) reported a significant ecological correlation between the arsenic concentration in drinking water and the age-adjusted mortality from skin cancer in 314 townships throughout Taiwan.

The detailed mechanism of arsenic carcinogenicity and related susceptibility of humans is poorly understood. An important issue relates to the possible role of metabolism and more broadly, the methylation of arsenic (9, 10). The issue of arsenic methylation as a detoxification pathway has been discussed by numerous investigators (9–13). Arsenic methylation has been generally considered a detoxification process, because the methylated compounds are less genotoxic (14) and are excreted more rapidly in urine than inorganic forms (15). New evidence concerning possible modes of the toxic action of arsenic, such as effects on DNA repair and methylation, generation of reactive oxygen species, and modification of cellular proliferation, has suggested methylation is complex (16–21).

We have carried out a case-control study with subjects from the southwestern region of Taiwan who had been previously exposed to high concentrations of arsenic in drinking water. The objective of this study was to determine whether the arsenic methylation capacity of patients with skin disorders differs from that of matched controls. ORs for arsenic-associated skin lesions were estimated for individuals having high methylation capacity, compared with those having low methylation capacity. We examined patterns of urinary arsenic methylation capacity, and their relationship with potentially confounding factors, including gender, age, cigarette smoking, hepatitis B surface antigen, alcohol consumption, and regular tea intake.

### Materials and Methods

**Study Subjects.** Patients and matched controls were identified in the blackfoot disease endemic area in southwestern Taiwan. The cases were sampled from subjects who had been identified by dermatologists during 1994. Patients with basal cell carcinoma (2 cases), Bowen's disease (squamous cell carcinoma of the skin, 19 cases) or hyperkeratosis/hyperpigmentation (6 cases) were classified as "cases," whereas control subjects were matched by gender and age within 3 years. Both the case and control subjects had been exposed to artesian well water for approximately 30 years but had changed to piped water for

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more than 10 years. Currently, well water was not used for drinking but was still used for washing dishes, cleaning, watering plants, and occasionally for drinking in dry seasons.

**Urine Samples and Demographic Data.** Twenty-four-h urine samples were collected. All of the participants were requested to not consume seafood for at least 48 h before urine sample collection. Questionnaires to collect demographic data, history of exposure, and types of preexisting diseases were collected at the time of sampling. Medical records were obtained from local hospitals.

**Reagents.** Sodium metaarsenite ( $\text{As}^{3+}$ ), arsenic acid ( $\text{As}^{5+}$ ), DMA,<sup>3</sup> sodium borohydride, and boric acid were obtained from Sigma Chemical Co., St. Louis, MO. These compounds were reported to be 98–99% pure. MMA was purchased from Chem Service Co., West Chester, PA; the purity was reported as 95%. Standard Reference Material 2670 was obtained from National Institute of Standard & Technology, Gaithersburg, MD. Other chemicals were certified or trace metal grade reagents from Fisher Scientific, Pittsburgh, PA.

**Analytical Methods.** Urine samples were analyzed with high performance liquid chromatograph-hydride generator-flame atomic absorption spectrophotometry with absorption cell (22). The mobile phase for chromatography was deionized water, 30 mM borate buffer (pH 9.5), and 30 mM ammonium dihydrogen phosphate (pH 2.2). The flow rate of effluents was 2.0 ml/min. The acid channel of the hydride generator was 2.5 M HCl at a flow rate of 2.0 ml/min. The other channel consisted of 2% sodium borohydride in 0.5% sodium hydroxide solution at the flow rate of 1.0 ml/min. The detection limits was obtained as the concentration of arsenic (in micrograms per liter) that gives a signal equal to twice the SD of a series of at least 10 determinations at the blank level (95% CI). The detection limits for arsenic species DMA, MMA, and InAs in urine were 1  $\mu\text{g/l}$ . The coefficient of variation of this method was less than 5%. An analysis of urinary arsenic of frozen dried urine SRM 2670 (480  $\mu\text{g/l}$ ) from National Bureau of Standard was used to insure the accuracy of this methodology. SRM 2670 (480  $\mu\text{g/l}$ ) was diluted to an appropriate concentration (0–100  $\mu\text{g/l}$ ) and was analyzed before each run of urinary arsenic analyses. The calibration and spiked samples were checked regularly.

**Statistical Methods.** Paired t tests were used to compare urinary arsenic metabolites between cases and controls. A conditional logistic regression model was applied to explore the association between methylation capacity and risk of arsenic-associated skin lesions. A stepwise strategy was used to build the model. General linear models were used to examine the relationship between arsenic methylation capacity variables and potential confounding variables. Statistical procedures from SAS Institute were used for all of the statistical analyses.

## Results

Among the matched pairs of cases and controls, there were 14 male and 12 female pairs with an average age of 63.4. Cases and control subjects were very similar in terms of cigarette smoking, consumption of alcohol beverages for at least 1 year before the study, status of hepatitis B surface antigen, and tea intake.

Skin lesion cases and matched controls had ingested sim-

Table 1 Conditional logistic regression of 26 arsenic-associated skin lesion cases and matched controls:<sup>a</sup> stepwise model selection of potential significant explanatory variables

Explanatory variable <sup>b</sup>	Score $\chi^2$	P
Total arsenic metabolites	0.084	0.772
InAs	0.072	0.788
MMA	0.028	0.868
DMA	0.190	0.663
% InAs <sup>c</sup>	2.778	0.0956 <sup>d</sup>
% MMA <sup>e</sup>	6.231	0.013 <sup>f</sup>
% DMA <sup>g</sup>	4.765	0.029 <sup>f</sup>
Ratio of MMA:DMA <sup>h</sup>	3.769	0.052 <sup>d</sup>
Hepatitis B surface antigen	0.500	0.480
Alcohol consumption	0.143	0.706
Tea intake	0.111	0.739

<sup>a</sup> Controls were matched with cases by sex and age (within 3 years).

<sup>b</sup> Smoking was excluded because 23 out of 26 pairs were matched.

<sup>c</sup> High versus low groups using 2.265% InAs as a cut point.

<sup>d</sup> Marginally significant ( $0.05 < P < 0.10$ ).

<sup>e</sup> High versus low groups using 15.5% MMA as a cut point.

<sup>f</sup> Statistically significant ( $P < 0.05$ ).

<sup>g</sup> High versus low groups using 72.2% DMA as a cut point.

<sup>h</sup> High versus low groups using 0.22 of MMA:DMA ratio as a cut point.

ilar concentrations of arsenic in drinking water and excreted comparable urinary arsenic metabolite concentrations. Cases and control subjects had drunk artesian well water at 0.77 and 0.98 ppm, respectively, which are not statistically significant different ( $P = 0.117$ ). Cases excreted 54.5 ppb total urinary arsenic metabolites (InAs + MMA + DMA) whereas the control subjects excreted 56.9 ppb. Cases excreted 6.5 ppb InAs, 8.7 ppb MMA, and 39.3 ppb DMA, whereas the control subjects excreted 6.3 ppb InAs, 8.5 ppb MMA, and 42.1 ppb DMA. These differences between cases and controls were not statistically significant ( $P > 0.6$ ).

There were statistically significant differences in the percent of InAs, MMA, and DMA among cases as compared with control subjects. Among the skin lesion cases, InAs and MMA contribute 13.1 and 16.4% of total urinary arsenic metabolites. The control subjects excreted 11.4% InAs and 14.6% MMA, which is marginally significant when compared with cases ( $0.05 < P < 0.06$ ). In contrast, the control subjects excreted significantly higher percent of DMA (73.9%) than the cases (70.5%,  $P = 0.017$ ). The mean of the ratios of MMA to DMA of the cases (0.24) was significantly higher than that of the controls (0.20,  $P = 0.027$ ). These results indicate that, despite current and past arsenic concentrations in water being similar, cases produce a greater proportion of InAs and MMA and a smaller percentage of DMA than control subjects.

The occurrence of arsenic-associated skin lesions is significantly related to the percentage of MMA and the percentage of DMA. Table 1 shows that the concentration of InAs, MMA, and DMA, and total arsenic metabolites are poorly correlated with arsenic-associated skin lesions ( $P > 0.6$ ). The percentage of MMA was found to be the most influential explanatory variable ( $P = 0.013$ ), whereas others showed no significant contribution. Table 2 shows that subjects with a higher percentage of MMA ( $>15.5\%$ ) had an OR of 5.5 (95% CI, 1.22–24.81) to develop arsenic-associated skin lesions, compared with those having a lower percentage of MMA ( $\leq 15.5\%$ ). The OR for the subjects having a lower percentage of DMA ( $\leq 72.2\%$ ) was estimated to be 3.25 (95% CI, 1.06–9.97), compared with those having a higher percentage of DMA ( $>72.2\%$ ). The OR for InAs and MMA/DMA as the single

<sup>3</sup> The abbreviations used are: DMA, dimethylarsinic acid (cacodylic acid); InAs, inorganic arsenic; MMA, methylarsonic acid (monomethylarsonic acid); OR, odds ratio; CI, confidence interval.

Table 2 OR and 95% CI of the conditional logistic regression of 26 arsenic-associated skin lesion cases and matched controls

Single explanatory variable	OR	95% CI
% MMA (high vs. low groups) <sup>a</sup>	5.50	(1.22–24.81)
% DMA (low vs. high groups) <sup>b</sup>	3.25	(1.06–9.97)
% InAs (high vs. low groups) <sup>c</sup>	3.50	(0.73–16.85)
MMA:DMA ratio (high vs. low groups) <sup>d</sup>	3.33	(0.92–12.11)

<sup>a</sup> High versus low groups using 15.5% MMA as a cut point.

<sup>b</sup> Low versus high groups using 72.2% DMA as a cut point.

<sup>c</sup> High versus low groups using 2.265% InAs as a cut point.

<sup>d</sup> High versus low groups using 0.22 of MMA:DMA ratio as a cut point.

explanatory variable was 3.5 and 3.33, respectively, but the results were not statistically significant.

Our analyses demonstrate gender, age, hepatitis B surface antigen, smoking, alcohol consumption, and tea intake are not associated with urinary arsenic methylation variables in a consistent manner. Hepatitis B surface antigen, age, smoking, and past exposure arsenic in drinking water was either marginally (hepatitis B,  $P = 0.058$ ) or significantly (others,  $P < 0.05$ ) associated with percentage of InAs among control subjects, but not among the cases. All of these potential confounding variables were poorly associated with percentage of MMA, percentage of DMA, and MMA:DMA ratio in both cases and control subjects ( $P > 0.1$ ).

The effect of inclusion of six pairs of hyperkeratosis/hyperpigmentation cases with skin cancer cases on the estimate of the OR was minimal. When the six noncancer cases and their matched controls were excluded, the percentage of MMA was still the most statistically significant explanatory variable in conditional logistic regression analyses ( $P = 0.035$ ). The OR for contrasting high and low percentage of MMA in terms of occurrence of skin cancer was 4.5 (95% CI, 0.97–20.83). This was similar to that estimated when the six pairs were included (OR, 5.5; 95% CI, 1.22–24.81; Table 2), which suggested that the inclusion of the six pairs of hyperkeratosis/hyperpigmentation cases did not substantially distort our results.

## Discussion

The primary objective of this study was to determine whether skin lesion patients had differences in urinary arsenic methylation capacity in comparison with matched controls. We found cases had higher percentage of InAs, percentage of MMA, and MMA:DMA ratio, and lower percentage of DMA than matched controls. Subjects with a higher percentage of MMA had a stronger tendency to develop arsenic-associated skin lesions than individuals having a lower percentage of MMA, with an OR as high as 5.5. The association was not confounded by other variables such as gender, age, hepatitis B surface antigen, smoking, alcohol consumption, or tea intake.

The OR estimated in this study is consistent with previous studies. Hsueh *et al.* (23) reported that the incidence of skin disorders was strongly associated with high cumulative arsenic ingestion from drinking water and high percentage of MMA excretion, with an OR of about 21–24. The former factor contributed an OR of about 3, whereas the latter contributed about 8. The OR of 5.5 in this study is consistent with that of Hsueh's study. Del Razo *et al.* (24) found exposed individuals with cutaneous signs had a higher percentage of InAs and percentage of MMA, but a lower percentage of DMA than those individuals with normal skin. These findings were consistent with the results from this study.

There were differences in study design between Del Ra-

zo's, Hsueh's, and our investigations. First, subjects were exposed to high concentration of arsenic in the exposed group and low concentrations in control group in Del Razo's study; whereas both skin lesion cases and matched controls were exposed to high levels of arsenic in drinking water and subsequently exposed to low levels of arsenic in Hsueh's and our studies. Second, cases and controls were distinguished by exposure status on a group basis in the Del Razo's study; whereas these two groups were differentiated by disease status matched by sex and age individually in our study and on a group base in Hsueh's study. Third, the subjects in Del Razo's study were currently drinking water with high concentrations of arsenic and excreted large quantity of arsenic metabolites in the urine. Despite these differences, these studies demonstrate consistent findings.

The possibility of selection bias was not known. In this study, both patients and matched controls were identified in the same blackfoot disease endemic area in southwestern Taiwan. These subjects were matched by gender and age within 3 years. The study population was selected from southwestern Taiwan where Chen and his colleagues (1) investigated the relationship between excess risk for a number of cancers and arsenic ingestion and demonstrated a relationship between arsenic exposure and arsenic-associated skin lesions. However, the differences found in this study are small, and, although the subjects were selected from the same region, there is no guarantee that significant individual differences between cases and controls might occur. In this regard we have no evidence whether dietary factors may have played a role in the pharmacokinetic differences between cases and controls.

Wei *et al.* (25) have recently reported DMA acts as a urinary bladder carcinogen in male F344 rats. Previous investigations that have examined the dose dependence of DMA formation have indicated that the percentage of DMA decreases with increasing concentrations of InAs (24, 26–28). Hsueh *et al.* (23), Del Razo *et al.* (24), and this study indicated that skin lesion cases have a lower yield of DMA relative to controls. The significance of these findings versus bladder cancer requires further investigation.

We note with interest the recent report by Zakharyan and Aposhian (29), which indicated arsenite methylation by methyl vitamin B12 and glutathione does not require an enzyme. Our own laboratory-based research with C57/BL mice would seem to suggest that arsenite depletes DNA methylation in a dose-dependent manner, and therefore, arsenic metabolism may be relevant in terms of the depletion of methyl stores available for DNA methylation with subsequent implication for carcinogenesis related to hypomethylation.

Vahter *et al.* (30) have reported the metabolism of InAs in native women in four Andean villages in northern Argentina with elevated levels of arsenic in drinking water. In these women, there was very little MMA in their urine (2.2%), with the median fraction of excreted InAs being as high as 25%. None of the women had signs of arsenic-associated skin lesions. These authors suggest the existence of genetic polymorphisms in the methylation of arsenic, similarly suggested by others (9, 24, 27, 31). Thus, the issue of biotransformation of arsenic and carcinogenicity is complex but warrants continued investigation.

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