Response to Invited Commentary

Hsu and Chen Respond to “Implications for Prevention and Future Research”

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Abbreviations: CAE, cumulative arsenic exposure; NHI, National Health Insurance.

We thank Drs. Ahsan and Steinmaus (1) for their invited commentary. Because large populations worldwide face the public health challenge of having elevated levels of arsenic in their drinking water, examination of the association of early clinical markers (such as arsenical skin lesions) with subsequent internal cancers and other systemic diseases is important. This type of information could help in the identification of subjects susceptible to arsenic toxicity, planning efficient intervention for exposed individuals at high risk, and understanding the natural history of arsenic-related pathogenesis. We agree with Ahsan and Steinmaus about the need for such studies, and we are now conducting such a study of the long-term consequences of arsenic exposure. We plan to evaluate the association of hyperpigmentation and palmoplantar hyperkeratosis with diabetes mellitus, hypertension, cardiovascular diseases, respiratory diseases, and kidney diseases through linkage to Taiwanese National Health Insurance (NHI) databases from 1998 to 2009. The NHI database includes information on complete outpatient visits, hospital admissions, prescriptions, disease, and vital status for 99% of the 23 million persons living in Taiwan (2). To ensure the accuracy of case identification, we are trying to combine medical information including hospital admissions and prescriptions from several NHI database domains. We expect to have results soon after refining the analysis.

We realize the limitation of the research cohort from southwestern Taiwan, whereby an individual’s arsenic level from deep-well water consumption was estimated by using the median arsenic concentration of the resident village because residents used water from multiple wells when at work and at home. Furthermore, no biological markers of arsenic exposure (such as urine or hair arsenic concentrations) were used, and arsenic exposure from other sources (such as shallow-well water) was not taken into account. Ahsan and Steinmaus are concerned that the cumulative arsenic exposure (CAE) might not reflect an individual’s true exposure and that skin lesions classified as low exposure (CAE: <1.0 mg/L × years) were more likely to be incorrectly classified. We agreed with their points that these issues should be carefully considered in the study. However, misclassification of arsenic exposure was considered nondifferential between the subjects with or without arsenical skin lesions because 1) the median arsenic concentration of the resident village used for exposure estimation might either overestimate or underestimate an individual’s true exposure level and 2) the community health examination was held in a local activity center, and experienced dermatologists examined subjects’ skin status without knowledge of the subject’s resident village or estimated cumulative exposure level. Thus, their point that “at a given measured CAE level, those with skin lesions could actually have higher true exposures (and thus higher true risks of arsenic-related internal cancers) than those without skin lesions” (1, p. 214) might not always be true. Therefore, the extent of biased estimation for the reported relative risk in our paper might be small if nondifferential, misclassified arsenic exposure levels were considered in the analysis of subjects with and without skin lesions. A sensitivity analysis restricted to the skin cancer case-control subcohort, with the controls well matched to the cases on residence (within a 3-house neighborhood), also showed a similar magnitude of association. The other supportive evidence was that the magnitude of the association between arsenic lesions and internal cancers remained when several arsenic exposure indices were considered (3).

Our study revealed the interesting findings that these lesions are associated with increased risk of cancers of the prostate, esophagus, and pancreas (other gastrointestinal cancers), although the cancer cases were rare. In our opinion, the difference in diagnostic rate between subjects
with and those without skin lesions was small, because the
health-screening program provided by the local govern-
mment-authorized health authority was held regularly in this
area. Thus, overestimation of prostate cancer risk among
lesion patients might be small. However, longer follow-up
for more cases is needed in order to draw a conclusion.

In summary, our study highlights the great variation of
individual susceptibility to arsenic toxicity and a predictive
role of arsenic lesions for subsequent lung cancer (strong)
and urothelial carcinoma (moderate). Our future goal is to
examine the association of these markers with cardiovascu-
lar, respiratory, and other noncancer diseases, as well as the
interaction with other exposures for disease risk.

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