Invited Commentary: Arsenic and Cancer of the Urinary Tract

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Inorganic arsenic in drinking water is a recognized cause of cancers of the skin, lung, and bladder. In the absence of an animal model for studying arsenic carcinogenesis, epidemiologic studies provide the only quantitative data for guiding risk assessment at levels that commonly occur in drinking water. To date, most estimates of risk at low and moderate levels of exposure (<200 µg/liter) have been based on extrapolation from ecologic studies of populations exposed to much higher levels. Epidemiologic data from the prospective cohort study by Chiou et al. that appears in this issue of the Journal (Am J Epidemiol 2001;153:411–18) make an important contribution to improving the precision of the estimated risk of transitional cell carcinoma of the urinary tract associated with ingested arsenic from drinking water. The great strength of the study derives from having individually based measures of exposure and cancer diagnoses. Arsenic in water is a topic of great concern and controversy, and epidemiologic studies will continue to provide crucial information about the risks of cancer and other diseases associated with ingested arsenic. Am J Epidemiol 2001;153:419–21.

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Airborne arsenic is a well-established lung carcinogen. Inorganic arsenic in drinking water is recognized as a cause of cancers of the skin, lung, and bladder (1). However, there remain many questions about the carcinogenicity of arsenic in human populations. Outstanding issues include the risk of other cancers, the nature of the dose-response relation (especially at low or moderate exposure levels), the mode of carcinogenic action, the contribution of diet to total intake of inorganic arsenic; and how genetic factors influence susceptibility. In the absence of an acceptable animal model for studying arsenic carcinogenicity and the presence of uncertainties about carcinogenic mechanisms, epidemiologic studies provide the only available source of data for assessing the risk of cancer posed by arsenic in drinking water. This situation is quite unusual, and it places special demands on the design and conduct of epidemiologic studies.

To date, ecologic studies of arsenic-exposed populations in southwestern Taiwan, Chile, and Argentina have been the primary source of information implicating arsenic in cancers of skin, lung, bladder, and possibly other organs (2–5). It is remarkable that elevated risks for these cancers appear unambiguously in ecologic studies. This is probably related to the carcinogenic potency of arsenic and to very high exposure levels in these regions, where water concentrations of at least several hundred micrograms per liter are frequently observed. Risks at lower levels of exposure have not been established directly, and assessments of risk have been based on extrapolation from ecologic data (1). Caution in extrapolating these data on the part of risk assessors is due to the lack of individual-specific information on outcomes and exposures in large studies, as well as the need to extrapolate below directly observed risk levels. Although a few case-control studies with data on individuals have been completed (6–8), quantitative interpretation of the findings is hampered by small study size, imprecise exposure assessment methods, and unorthodox approaches to control selection. There is a great need for data from additional studies with individual information that employ careful approaches to exposure assessment.

 Taiwanese researchers have played a pivotal role in epidemiologic assessment of arsenic in drinking water. The earliest quantitative assessment of skin cancer and internal cancers came from southwestern Taiwan, where tens of thousands of people in more than 40 villages were exposed to elevated arsenic levels in drinking water from wells that had been installed as a substitute for microbiologically contaminated surface water supplies (2, 9, 10). It is tragic that a similar rationale motivated the more recent replacement of surface water supplies by groundwater in extensive regions of Bangladesh and West Bengal, India, where populations numbering in the millions are currently exposed to health-threatening levels of arsenic (11, 12). The first comprehensive large-scale studies of skin cancer in Taiwan were conducted by Tseng et al. (2) and provided early semiquantitative data on the dangers of arsenic in water. Chen et al. (13) published the first quantitative estimates of risk of mortality due to bladder, lung, kidney, liver, and other internal cancers associated with consumption of arsenic-contaminated waters in the same region. Research conducted by Chen and colleagues has expanded to include other endpoints (hypertension, cerebrovascular dis-
ease, and cardiovascular disease), as well as biologic measures of arsenic damage and genetic and metabolic aspects of exposure (14–19).

The prospective cohort study of an arsenic-exposed population by Chiu et al., which appears in this issue of the Journal (20), is the most recent contribution of this productive research group. The paper is a valuable addition to the literature on arsenic and risk of urinary tract cancers. The study was conducted in the Lanyang Basin in northeastern Taiwan, an area recently discovered to have elevated levels of arsenic in drinking water. In earlier ecologic studies from southwestern Taiwan, exposure assessment was done on a village level, and villages were grouped into broad exposure categories (<300, 300–590, and ≥600 μg/liter). With a minor exception (21), the studies of internal cancers from southwestern Taiwan and other places have focused on mortality rates as the outcome. In contrast, the study by Chiu et al. (20) relied on measured levels of arsenic in water samples from individual wells collected at cohort enrollment, and the outcome was newly diagnosed cancer. In both cases—exposure ascertainment and outcome measure—the Chiu et al. study improves upon previous work. The observed dose-response pattern supports the observation of other investigators that arsenic is a urinary tract carcinogen (3–5, 13, 22), and the paper provides quantitative estimates that go beyond those of earlier work. Of special interest is the finding that risk of urinary tract cancer, and of transitional cell carcinoma in particular, increased monotonically starting at arsenic levels above the baseline exposure level of <10.0 μg/liter (20). Few studies have attempted to directly measure risk at these relatively low levels of exposure (6, 7).

However, limitations remain that may influence interpretation of these study findings. Although Chiu et al. measured arsenic in 3,901 residential wells at the time of the recruitment and home interview of cohort members, these levels were used to represent these individuals’ past exposures. The practice of using current or recent measures of environmental exposures, especially water contaminants, to represent long-term historical levels is common to many studies and warrants critical scrutiny. The method has also been used in studies of nitrate and disinfection byproducts in water. The assumption that arsenic levels in individual wells did not vary much over the previous several decades is probably reasonable, especially if the water was drawn from deep aquifers minimally influenced by seasonal fluctuations in rainfall and surface water flows. However, there are few data that address this issue, and the question of historical consistency of arsenic levels in subsurface aquifers deserves exploration. Collection of sequential arsenic measurements from individual wells in varying geologic settings and improvements in geochemical and hydrogeologic knowledge regarding the issue would bolster confidence in the accuracy of this assumption.

Exposure assessment was not complete for all enrolled cohort members. Fourteen percent (n = 1,136) of the 8,102 persons in the cohort lacked arsenic measurements because their private residential wells had been closed, and these people were not included in the analysis. An additional 26 percent (n = 2,119) of the subjects had changed wells prior to enrollment, and the authors used information from current wells to represent historical exposure levels. If a subject’s current well had been used for many decades, use of these data was probably justified (assuming consistency of historical arsenic levels). However, misclassification of exposure may have occurred among individuals who had switched water sources more recently. Data on the duration of current well use in this group were not included in the article by Chiu et al. (20); such data would be quite informative.

In 1993, the World Health Organization published a provisional guideline for inorganic arsenic in drinking water of 10 μg/liter (23). As this commentary was being revised for publication, the US Environmental Protection Agency issued a regulation establishing a new maximum contaminant limit of 10 μg/liter for arsenic in US public drinking water supplies (24)—a decrease from the previous level of 50 μg/liter, which had been in effect since the 1940s. This regulation was based, in part, on the ecologic data from Taiwanese studies, with adjustment for differences between US and Taiwanese populations in average body size and fluid ingestion patterns. The newly established level also considered detection limits of available measurement methods, estimates of arsenic levels in food, and economic feasibility. Based on linear extrapolation from the ecologic data, the lifetime risk of dying from cancer of the lung, bladder, kidney, or liver associated with consumption of 1 liter/day of water containing arsenic at 50 μg/liter has been estimated as 13 per 1,000 persons (25). This estimate of risk is many orders of magnitude beyond that considered acceptable in other contexts. There are few data that directly address cancer risk at arsenic levels below about 150–200 μg/liter. If the dose-response curve is linear or close to linear, well-designed cohort or case-control studies of cancer of the bladder, lung, or kidney should be able to detect excess risk at exposure levels near the former US limit of 50 μg/liter or lower, as suggested by the Chiu et al. study (20).

What does the future hold for research in this area? Limited evidence suggests that genetic variants of enzymes involved in arsenic detoxification, such as glutathione S-transferases M1 and T1 and 5,10-methylenetetrahydrofolate reductase, influence susceptibility to carcinogenic effects of arsenic (26, 27). Incorporation in future study designs of polymorphic variation in these and other enzymes should enhance our ability to detect carcinogenic effects, if present, at relatively low levels of exposure. Features of arsenic biotransformation and of the genetic factors that contribute to variability in patterns of cancer risk and patterns of excreted arsenic metabolites deserve continuing attention and incorporation into epidemiologic evaluations of this well-known poison.

REFERENCES


