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Short communication

Considerations when using longitudinal cohort studies to assess dietary exposure to inorganic arsenic and chronic health outcomes

Carolyn G. Scrafford [a, *], Leila M. Barraj [a], Joyce S. Tsuji [b]

[a] Center for Chemical Regulation and Food Safety, Exponent, Inc., 1150 Connecticut Avenue, NW, Washington DC, 20036, USA
[b] Toxicology and Mechanistic Biology, Exponent, Inc., 15375 SE 30th Place, Suite 250, Bellevue, WA, 98007, USA

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ABSTRACT

Dietary arsenic exposure and chronic health outcomes are of interest, due in part to increased awareness and data available on inorganic arsenic levels in some foods. Recent concerns regarding levels of inorganic arsenic, the primary form of arsenic of human health concern, in foods are based on extrapolation from adverse health effects observed at high levels of inorganic arsenic exposure; the potential for the occurrence of these health effects from lower levels of dietary inorganic arsenic exposure has not been established. In this review, longitudinal cohort studies are evaluated for their utility in estimating dietary inorganic arsenic exposure and quantifying statistically reliable associations with health outcomes. The primary limiting factor in longitudinal studies is incomplete data on inorganic arsenic levels in foods combined with the aggregation of consumption of foods with varying arsenic levels into a single category, resulting in exposure misclassification. Longitudinal cohort studies could provide some evidence to evaluate associations of dietary patterns related to inorganic arsenic exposure with risk of arsenic-related diseases. However, currently available data from longitudinal cohort studies limit causal analyses regarding the association between inorganic arsenic exposure and health outcomes. Any conclusions should therefore be viewed with knowledge of the analytical and methodological limitations.

1. Introduction

The level of arsenic in food and chronic health outcomes associated with dietary exposure is currently a topic of considerable interest for the public, U.S. and international regulatory agencies, scientific researchers, and public health professionals. Publication of arsenic monitoring results in apple juice and rice and rice-based products by the U.S. Food and Drug Administration (FDA) (U.S. FDA, 2011,2013) and fruit juices and rice-based products by the Consumer Reports Magazine (Consumers Union, 2012a,b) followed by a quantitative assessment of inorganic arsenic in apple juice conducted by the U.S. FDA (Carrington et al., 2013) has increased the consumers' awareness of the presence of arsenic in their food supply.

Inorganic arsenic is the primary form of arsenic that has been associated with human health effects. Recent concerns regarding background levels of inorganic arsenic in foods have been based on extrapolation from adverse health effects observed at much higher inorganic arsenic doses. Further, often only total arsenic levels are reported for foods and therefore, arsenic exposure estimated from such data will include inorganic arsenic along with organic forms, which are much less toxic (Cohen et al., 2013). These risk estimates are typically based on high exposures in populations drinking inorganic arsenic in groundwater from outside of the U.S. linked to cancers of the skin, lung, and bladder (IARC, 2012) as well as ischemic heart disease, hypertension and stroke (NRC, 2013). Health risks in populations have not been documented at considerably lower levels of inorganic arsenic from background dietary exposures (e.g., dose levels over 100 times lower than in the more highly exposed populations, Cohen et al., 2013; Xue et al., 2010), and some recent research has indicated that such low exposures would be associated with negligible risk of health effects (Cohen et al., 2013). A meta-analysis of observational epidemiological studies of nutritionally-sufficient populations indicates that low levels of exposure to inorganic arsenic, based on populations primarily exposed to lower levels of arsenic in water (e.g., <100 μg/L), does not increase risk of bladder cancer incidence (Tsuji et al., 2014). Cross-sectional evaluations to estimate dietary exposure to inorganic arsenic using national survey data have been conducted

* Corresponding author.
E-mail address: cscrafford@exponent.com (C.G. Scrafford).

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(Xue et al., 2010; Davis et al., 2012); however, association of such data with incidence of health outcomes are complicated by limitations in the available inorganic arsenic data in foods and accurate estimations of consumption of these foods along with the cross-sectional study design in which no information is available to assess whether the exposure preceded the disease in question. Databases from longitudinal studies could provide an improved basis to understand whether the dietary patterns may be associated with health outcomes.

To evaluate the feasibility and appropriateness of quantifying the association between dietary inorganic arsenic exposure and associated chronic health outcomes, we reviewed 11 publically available epidemiological cohorts with underlying data that would allow for a longitudinal evaluation of consumption of foods known to contribute to dietary inorganic arsenic and select health outcomes. This article summarizes our findings based on reviews of existing study populations and cohorts that represent the data that are available in the U.S. with a focus on the methodological and analytical considerations. These considerations are particularly relevant to an assessment of health outcomes associated with dietary consumption patterns with higher potential inorganic arsenic exposure. Specifically, this review focuses on the dietary assessment methods available in longitudinal studies to quantify, or surrogate for, exposure; the correlation with, and availability of, inorganic arsenic levels in dietary sources; and the feasibility of quantifying statistically reliable associations with chronic health outcomes as it relates to dietary inorganic arsenic exposure.

2. Methods

We reviewed the National Health and Nutrition Examination Surveys (NHANES) 1988–1994 (NHANES III) to determine if the dietary information collected in the food frequency questionnaire (FFQ) can be used to identify dietary patterns for use in an evaluation of the association with mortality from long-term health outcomes in the U.S. population as collected in the NHANES III Mortality Follow-up survey. We also researched and evaluated a selection of longitudinal cohort studies conducted in the U.S. for assessment of health outcomes associated with consumption of foods assumed to have higher inorganic arsenic levels. Table 1 presents a summary of the criteria used to evaluate the components and characteristics of selected individual studies and cohorts. The health outcomes evaluated included incidence of, or mortality from cancer, cardiovascular disease, and diabetes based on previous scientific research in populations with higher inorganic arsenic exposures (IARC, 2012; USDHHS/ATSDR, 2011; NRC, 2013).

3. Results of review of longitudinal studies

The individual study/cohorts included in the review are summarized in Table 2. A summary of the methodological and analytical considerations in using these studies to evaluate the association between dietary inorganic arsenic exposure and health outcomes follows.

3.1. Dietary assessment

The primary method of dietary assessment in the studies included in this review was an FFQ aimed at estimating usual or longer-term consumption patterns. These questionnaires are primarily administered at baseline only (i.e., enrollment). For example, the NHANES III FFQ was collected once at enrollment and included 60 food categories. Study participants were asked to report their frequency of consumption of each category over the past month. The implementation of the FFQ in NHANES III was intended to collect qualitative dietary data that allows for the assessment of general trends in the subject's diet (NCHS, 1994). NHANES III also collected 24-dietary recalls from the participants; however, this represents short-term intake and would not necessarily be representative of the participant's typical diet. Use of the FFQ as the method of measuring usual, long-term dietary patterns and the association with mortality from chronic diseases such as cardiovascular disease, diabetes, and/or cancer is more appropriate than relying on short-term consumption patterns based on 24-h dietary recalls (Willett, 1998).

The FFQs included in the studies reviewed contained food categories ranging from approximately 60 to 131 items. Table 3 provides an example of the food categories collected in the NHANES III FFQ that may be of interest in an evaluation of dietary patterns associated with potentially higher dietary inorganic arsenic exposure based on previously published research (Xue et al., 2010; Schoof et al., 1999). Specifically, Xue et al. (2010) reported that the major food contributors to inorganic arsenic exposure were vegetables (24%), fruit juices and fruits (18%), rice (17%), beer and wine (12%), and flour, corn and wheat (11%).

Many of the categories of food included in the FFQ include a broad grouping of products. Some of the foods that are combined into one question within an FFQ may be high contributors to arsenic exposure while others were not. This aggregation of individual foods into broader categories would lead to potential exposure misclassification. For example, the NHANES III FFQ combines green beans, corn, peas, mushrooms, and zucchini under the "Other vegetables category", while Schoof et al. (1999) sampled and analyzed green beans, corn, and peas, but not mushrooms and zucchini. Additionally, grapes, which have higher inorganic arsenic levels (Schoof et al., 1999), are often combined into a category with a number of other fruits, including those with low inorganic arsenic levels (e.g., bananas). Therefore, if an individual responds to the FFQ as a high consumer of "Other fruits" but is primarily a banana consumer, they may be incorrectly classified as having high exposure to inorganic arsenic-containing foods when in reality, they do not consume fruits known to have high levels.

Table 1
Criteria used to select and evaluate studies.

Component/characteristic	Criteria
Dietary assessment method	Food frequency questionnaire with appropriate grouping of foods and food groups with higher inorganic arsenic levels, including: a Rice b Beer/wine c Cereal products and breakfast cereal d Fruits and fruit juices e Fish/shellfish f Vegetables g Other grains including corn and flour
Sample size	Large population size to produce sufficient number of cases/deaths to allow for detection of statistically significant associations.
Population age	Study population ages 40 years and up to allow opportunity for incident cases to develop.