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FOOD, HEALTH, AND THE ENVIRONMENT (K NACHMAN, SECTION EDITOR)

Rice Intake and Emerging Concerns on Arsenic in Rice: a Review of the Human Evidence and Methodologic Challenges

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Abstract

Purpose of Review Rice is a major staple food worldwide and a dietary source of arsenic. We therefore summarized the state of the epidemiologic evidence on whether rice consumption relates to health outcomes associated with arsenic exposure.

Recent Findings While epidemiologic studies have reported that higher rice consumption may increase the risk of certain chronic conditions, i.e., type 2 diabetes, most did not consider specific constituents of rice or other sources of arsenic exposure. Studies that examined rice intake stratified by water concentrations of arsenic found evidence of increasing trends in cardiovascular disease risk, skin lesions, and squamous cell skin cancers and bladder cancer associated with higher rice consumption.

Summary Further studies are needed to understand the health impacts of arsenic exposure from rice consumption taking into account all sources of rice intake and potential confounding by other dietary constituents or contaminants and arsenic exposure from sources such as water.

Keywords Rice · Arsenic · Epidemiology · Diet · Health effects

Introduction

Rice is a staple food for about half of the world's population [1]. Although the average US population consumes less rice than those from other countries, consumption has increased, with an average of ~1 cup of cooked rice per day consumed among the 25% of Americans who report rice intake [2]. Moreover, rice-derived products such as flours and syrups are widely used in processed food products [3], and baby rice cereal is often among the first solid foods introduced at infancy [4]. Rice is also a component of multiple processed foods marketed to children [3]. Rice products have recently been defined by a US Food and Drug Administration (FDA) report to include any products that contain rice [5], which may include rice-based foods such as rice syrup, often used in cereal bars [3]; rice milk; rice bran; rice-based breakfast cereals and baby cereals; and rice crackers. Daily rice consumption varies by level of education, race/ethnicity, special dietary choices, such as vegetarianism, and medical conditions like celiac disease, wheat allergy, and non-celiac gluten sensitivity. In the USA, Asians and Hispanics have the greatest per capita rice consumption because rice is a staple in their traditional diets [2].

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Rice (*Oryza sativa* L.) has the ability to accumulate arsenic, amassing concentrations ten times higher than other cereals such as wheat. In particular, rice grown under flooded conditions favors greater soil arsenic solubility and uptake into the plant. Movement of arsenic into rice is mediated by silicon transporters [6] that inadvertently transport arsenite due to its similarity to silicic acid. This makes rice a major dietary source of arsenic, especially for populations with relatively low drinking water concentrations of arsenic [7–11]. Thus, awareness of the human health risk posed by arsenic-contaminated rice consumption has become a more widely recognized threat to food safety [7, 12–15].

Studies have suggested that elevated arsenic in rice may substantially contribute to dietary arsenic intake and internal arsenic dose in the USA [2], especially among children and infants [12, 13, 16]. Indeed, exposure to arsenic from rice products may reach equivalent or greater concentrations than the US EPA maximum contaminant level for drinking water (10 μg/L) [3]. This is a particular concern given that even low levels of prenatal and early-life arsenic exposure may have effects on long-term health and disease [4, 16].

The potential for adverse health impacts of arsenic exposure through rice consumption has prompted regulatory agencies to consider limiting the arsenic content of rice and rice products. The European Commission (EC) proposed a 0.1-mg/kg limit for inorganic arsenic in rice for foods for infants and young children, a 0.20-mg/kg limit for non-parboiled milled rice (polished or white rice), 0.25-mg/kg limit for parboiled rice and husked rice, and a 0.30-mg/kg limit for rice waffles, wafers, crackers, and cakes [17]. In 2016, the US FDA proposed a limit, or "action level," of 100 ppb for inorganic arsenic in infant rice cereal and found that less than half of the products it tests were below this limit [18]. Regulatory limits on arsenic in rice have yet to be established in many parts of the world, including the Indian subcontinent, where dietary arsenic intake may contribute significantly to overall arsenic exposure. In light of possible human health risks, we convened a group of experts as part of the Collaborative on Food with Arsenic and Associated Risk and Regulation (C-FARR) to review the body of evidence about the possible health risks posed by rice consumption and arsenic exposure through rice consumption. We sought to capture the current state of the available literature with the goal of identifying key gaps in our knowledge, challenges to addressing this potential health concern, and areas for future research pursuit.

Methods

We conducted a literature search in PubMed for original research studies evaluating rice consumption and human health outcomes known to be caused by arsenic exposure largely from studies of drinking water contamination including cancers (e.g., of the skin, bladder, and lung) and cardiovascular diseases and their precursors or risk factors such as skin lesions, hypertension, and diabetes [19–21]. We further included data on outcomes for which there is evidence that arsenic may be causally related [19–21] if literature on rice consumption existed (e.g., respiratory conditions). For certain outcomes with either known or suspected relationships with arsenic, we were not able to identify any studies that evaluated rice consumption (e.g., for adverse pregnancy outcomes). Our search terms included "rice" with exposure-related terms: "diet," "intake," "consumption," or "serving," and health-related terms: "health," "epidemiology," "outcome," "disease", "cardiovascular disease," "hypertension," "diabetes," "glucose metabolism," "respiratory conditions," "atopic conditions," "cancer," "neoplasms," or "lesions." We used filters for human studies and studies written in English. Members of our working group with knowledge of the literature identified additional studies in publication at the time of our search. We further supplemented our search with a manual search of references in selected articles. Studies were considered for inclusion if they met each of the following a priori eligibility criteria: original observational research conducted on humans with any cross-sectional, case-control, cohort, or meta-analysis design; presented data on individual-level rice exposure; and reported on individual-level health outcomes. We excluded review articles, experimental studies, ecologic studies, case reports, case studies, and risk assessments. We further excluded studies in which rice itself could not be distinguished from other grains, broader dietary patterns, or other ingredients. Studies on the association of rice oil contaminated by polychlorinated biphenyls and related health effects (e.g., Yushō disease) and studies of rice as a dietary strategy for the management of diarrhea were also not included in this review. We extracted the study authors, year of publication, study location (country), sample size, outcome(s), exposure measures (i.e., rice consumption, type consumption), effect estimates with 95% confidence intervals (CI, where available), adjusted covariates, and whether arsenic exposure via other sources (e.g., drinking water) was accounted for in the analysis. Health outcomes were broadly classified using the 10th edition of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) categories.

Results

Overall, studies of rice consumption and human health outcomes varied in their study design, exposure metrics, health endpoints, and control of confounders (Online Resource 1). Geographically, the majority of research on rice and human health has been conducted in Asia. Studies of rice consumption have usually used food frequency questionnaires (FFQs), common in epidemiologic studies due to their ease, cost effectiveness, and ability to estimate food intake over time [22].

A variety of exposure metrics have been used, including volume-based and mass-based serving sizes, or as a proportion of total energy consumed. Others have simply assessed servings of rice without providing serving sizes or rice exposure dichotomized by consumption status or consumption frequency. Frequency has typically been characterized daily; however, some studies have assessed weekly and yearly consumption. Health endpoints of interest have varied, with most studies focusing on cardiovascular disease, hypertension, diabetes, and neoplasms (i.e., precancerous and cancerous) (Table 1). At present, few studies described below have considered arsenic exposure. To date, none of the epidemiologic studies directly measured the arsenic content of the rice consumed, so exposure assessment has been solely based on reported rice consumption which is subject to misclassification due to varied concentrations of arsenic in rice. Moreover, self-reported intake is subject to recall bias. Given these potential sources of misclassification, it may be difficult to detect an association with rice consumption in populations already exposed to arsenic through drinking water. Alternatively, if the effects of drinking water and arsenic in rice are additive, you might find associations largely among those with higher drinking water arsenic concentrations.

Cardiovascular Diseases and Hypertension

Studies of rice consumption and cardiovascular disease have produced mixed results. In a case-control study of adults from China, cases of ischemic stroke had higher weekly consumption of white rice compared with controls ($n = 838$) [33]. Large cohort studies from Japan and China (samples sizes of 35,064 to 48,688 adults) have generally found no association [28, 30–32] with cerebrovascular, ischemic heart disease, and total cardiovascular mortality. One of these cohorts initially found an inverse association among men, but this was not confirmed in a subsequent study [28, 30]. A more recent study of ischemic stroke from the US Nurse's Health Study (NHS), a prospective study of over 70,000 married women and the US Health Professionals Follow-Up Study of over 40,000 men [34] was conducted. Those who consumed more than one serving of brown rice per week (versus less than once per month) had a 15% higher incidence of ischemic stroke (95% CI = 0.99–1.33) after adjustment for multiple dietary and other risk factors. While, a reduction in coronary heart disease risk was initially observed with brown rice consumption in the NHS [33, 35], a subsequent study combining NHS, NHS II, and the Health Professionals Follow-Up Study [36] found a positive linear trend between white rice consumption and cardiovascular disease risk within low arsenic areas (32,705 participants with groundwater levels of < 3.0 μg/L) and no association was observed within moderate to high arsenic areas (61,520 participants with groundwater levels of 3.0–9.9 μg/L or > 10 μg/L). Brown rice consumption, albeit with less statistical power, was not clearly related to the development of cardiovascular disease, and the trend in risk by overall rice consumption was of borderline statistical significance [36].

Cohort studies also have examined blood pressure, the major risk factor for stroke. In NHS ($n = 41{,}541$ women) in the USA, both white and brown rice were associated with decreased blood pressure [23]. Similarly, a smaller Chinese cohort study ($n = 683$) found eating more rice was inversely related to hypertension incidence [26]. In contrast, cross-sectional studies of rice consumption and blood pressure have found either no ($n = 2209$, from Korea) [25] or positive associations ($n = 1879$, from Costa Rica) [24]. However, none of these studies considered exposure from arsenic. In a large Hispanic/Latino study ($n = 12{,}609$), among high rice consumers (top decile) who did not smoke, reduced arsenic metabolism (higher inorganic arsenic (iAs) % and monomethylarsonic acid (MMA) %, and lower dimethylarsinic acid (DMA) %) was associated with increased diastolic and systolic blood pressure, suggesting the association with rice may be due to arsenic [27].

Diabetes

Greater consumption of white rice appears to increase the risk of developing type 2 diabetes, as evidenced in two recent meta-analyses [60, 61]; however, the associations are thought to be due to its higher glycemic index than for other grains, and none of these studies considered arsenic exposure from drinking water or water used for cooking, or arsenic levels in rice. The one study that examined arsenic metabolism found no association among high rice consumers in a Latino cohort [27]. The positive association between white rice intake and incident diabetes was stronger among Japanese ($n = 59{,}288$) [42] and Chinese cohorts ($n = 64{,}227$) [45], who tend to consume more rice, than in US NHS I, NHS II, and Health Professional Follow-up Study cohorts of largely Caucasians ($n = 197{,}228$) [44]. However, not all studies in Asian populations have consistently observed positive associations between rice consumption and diabetes. Notably, a prospective cohort of 690 Chinese adults found no association between the total amount of rice (white or brown) eaten per week and type 2 diabetes [46], and one cross-sectional study of 7628 Chinese adults found that the association between energy derived from white rice intake and type 2 diabetes differed by geographic region [39]. Similarly, multiple studies conducted outside of East Asia, including a nested case-control study of 2658 participants in the USA [38], a cross-sectional study of 3006 participants in Iran [37], a cohort study of 36,787 participants in Australia [40], and a cohort study of 605 participants in Spain [43] observed either no association, or an inverse association with rice consumption and diabetes. In the largest cohort study of rice consumption and incident diabetes in the USA ($n = 197{,}228$), elevated risk ratios were only observed for the highest frequency consumers (i.e., participants eating ≥ 5

Table 1 Summary of epidemiology studies on rice consumption and human health outcomes

End points	No. of studies	Sample sizes	Exposure	Consideration of water arsenic	Direction of association	Summary of findings[a]	References
Cardiovascular disease and hypertension							
Blood pressure	5	$N = 41{,}541$; $N = 1879$; $N = 2209$ (1164 boys, 1045 girls in Song et al. 2015); $N = 683$; $N = 12{,}609$	White rice, brown rice, rice	Yes for one study	Inconsistent	Two prospective studies (US and China) suggest inverse relationship; one found a positive association between arsenic metabolism efficiency among high rice consumers, cross-sectional studies suggest either no or positive associations.	Ascherio et al. 1996 [23]; Mattei et al. 2011 [24]; Song et al. 2015 [25]; Shi et al. 2012 [26]; Scannell Bryan (2019) [27]
Cardiovascular disease mortality	5	$N = 48{,}688$; $N = 61{,}491$; $N = 91{,}223$; $N = 27{,}862$ (15,301 women + 12,561 men in Oba et al. 2010); $N = 53{,}469$ (29,968 women, 23,501 men in Rebelo et al. 2014)	Rice	No	Inconsistent	Generally no association	Eshak et al. 2011 [28]; Iso et al. 2007 [29]; Eshak et al. 2014 [30]; Oba et al. 2010 [31]; Rebello et al. 2014 [32]
Stroke	3	$N = 27{,}862$ (15,301 women + 12,561 men in Oba et al. 2010); $N = 838$; $N = 106{,}194$ (44,703 men, 61,491 women in Iso et al. 2007); $N = 114{,}573$ (71,750 women, 42,823 men in Juan et al.)	White rice, brown rice, rice	No	Inconsistent	Positive association in one small case-control study from China, but cohort studies suggest no association	Oba et al. 2010 [31]; Liang et al. 2010 [33]; Iso et al. 2007 [29]; Juan et al. (2017) [34]
Coronary heart disease	3	$N = 61{,}491$; $N = 53{,}469$ (29,968 women, 23,501 men in Rebello et al. 2014); $N = 106{,}194$ (44,703 men, 61,491 women in Iso et al. 2007)	Rice, brown rice	No	Decreased risk	Large US prospective cohort of women inverse association with brown rice consumption, without consideration of water arsenic	Iso et al. 2007 [29]; Rebello et al. 2014 [32]; Liu et al. 1999 [35]
Cardiovascular disease incidence	1	$N = 94{,}225$	White rice	Yes	Increased risk	One large prospective study from the US found no overall association, but an increased risk among those with low water arsenic concentrations	Muraki et al. 2015 [36]
Diabetes, diabetes-related outcomes							
Diabetes (type 1 or 2)	10	$N = 3006$; $N = 2658$; $N = 7628$ (1529 North region, 2719 Central region, 3380 South region in Dong et al. 2015); $N = 36{,}787$; $N = 75{,}521$; $N = 59{,}288$ (33,622 women, 25,666 men in Nanri et al. 2010); $N = 605$; $N = 197{,}228$; $N = 64{,}227$; $N = 690$	White rice, rice, brown rice	No	Increased risk	Positively associations based on 2 meta-analyses, but not consistent so. Large cohorts outside of Asia observed no association, and 2 large prospective cohorts observed inverse associations with brown rice which was attributed to eating whole grains.	Khosravi-Boroujeni et al. 2013 [37]; Shimakawa et al. 1993 [38]; Dong et al. 2015 [39]; Hodge et al. 2004 [40]; Liu et al. 2000 [41]; Nanri et al. 2010 [42]; Soriguer et al. 2013 [43]; Sun et al. 2010 [44]; Villegas et al. 2007 [45]; Yu et al. 2011 [46]
Diabetes-related endpoints	5	$N = 1879$; $N = 2209$ (1164 boys, 1045 girls in Song et al. 2015); $N = 2728$; $N = 3006$; $N = 1025$; $N = 12{,}609$	White rice, rice	Yes for one study	Increased risk	Positive associations with glucose levels, glycated hemoglobin (HbA1c) levels, insulin levels, hyperglycemia, insulin resistance, and β-cell function in prospective and cross-sectional studies. Positive associations of systolic and diastolic blood with iAs% and MMA% increase and negative association with DMA% increase. No association with HbA1c% or HOMA-IR and arsenic metabolism efficiency among high rice consumers.	Mattei et al. 2011 [24]; Song et al. 2015 [25]; Zuniga et al. 2014 [47]; Khosravi-Boroujeni et al. 2013 [37]; Shi et al. 2012 [26]; Scannell Bryan et al. [27]

Table 1 (continued)

End points	No. of studies	Sample sizes	Exposure	Consideration of water arsenic	Direction of association	Summary of findings[a]	References
Respiratory conditions							
Respiratory endpoints and diseases	3	$N = 20{,}106$; $N = 1466$; $N = 13{,}503$; $N = 6814$	Rice	Yes for one study	Inconsistent	Generally no associations, with one cross-sectional study finding an inverse relationship with bronchial hyperactivity,. Decreased lung capacity, forced expiratory volume and forced vital capacity and increased cardiac-based HAA with similar findings for urinary arsenic concentrations.	Garcia-Marcos et al. 2007 [48]; Woods et al. 2003 [49]; Suárez-Varela et al. 2010 [50]; Sanchez et al. (2019) [51••]
Neoplasms and preneoplastic lesions							
Kidney cancer	1	$N = 106{,}194$ (44,703 men, 61,491 women)	Rice	No	Inconsistent	Increased risk of kidney cancer for women but not men.	Iso et al. (2007) [29]
Liver cancer mortality	1	$N = 106{,}194$ (44,703 men, 61,491 women)	Rice	No	Decreased risk	Observed decreased risk of liver cancer mortality for those with high rice consumption.	Iso et al. (2007) [29]
Lung cancer mortality	2	$N = 106{,}194$ (44,703 men, 61,491 women in Iso et al.); $N = 98{,}248$ (42,940 men, 55,308 women in Ozasa et al.)	Rice	No	Inconsistent	Generally no association between lung cancer mortality and rice consumption, with some weakly positive.	Iso et al. (2007) [29]; Ozasa et al. (2001) [52]
Pancreatic cancer and pancreatic cancer mortality	3	$N = 2233$; $N = 1050$ (890 men, 160 women in Falk et al.); N = 106,194 (44,703 men, 61,491 women in Iso et al. 2007)	Rice	No	Null	No clear association between pancreatic cancer or pancreatic cancer mortality and rice consumption.	Chan et al. (2007) [53]; Falk et al. (1988) [54]; Iso et al. (2007) [29]
Prostate cancer mortality	2	$N = 7999$; $N = 44{,}703$	Rice	No	Null	No association with prostate cancer mortality and rice consumption.	Severson et al. (1989) [55]; Iso et al. (2007) [29]
Bladder and urothelial tract cancer	3	N = 106,194 (44,703 men, 61,491 women in Iso et al. 2007); $N = 546$; $N = 205{,}639$ (45,231 men and 160,408 women in Zhang et al.)	Rice, white rice, brown rice	Yes for one study	Inconsistent	No association was found between urothelial tract cancer mortality.Weakly increased risk of bladder cancer in US cohort and case-control studies.	Iso et al. 2007 [29]; Signes-Pastor et al. (2019) [56]; Zhang et al. 2016 [57]
Skin lesions (cancer and precancerous Lesions)	1	$N = 18{,}470$; $N = 487$ squamous cell skin cancer cases and $N = 462$ controls (in Gossai et al. 2017)	Rice	Yes	Increased risk	Increased risk with rice consumption among those with lower drinking water arsenic concentrations.	Melkonian et al. 2013 Gossai et al., 2017 [58••, 59••]

[a] Summary of specific estimates can be found in Online Resource 1

servings of white rice in a week) [44]. Studies examining diabetes-related endpoints such as glucose levels, glycated hemoglobin (HbA1c) levels, insulin levels, hyperglycemia, insulin resistance, and β-cell function have likewise found positive cross-sectional and prospective associations with rice intake among East Asian populations [24–26, 47], but not among Iranians [37]. In contrast, for brown rice, studies suggest that it may reduce the risk of type 2 diabetes, with two prospective analyses of US cohorts, including the NHS I and II and the Health Professionals Follow-up Study totaling more than 75,000 participants observing reduced risks [41, 44]. However, these associations were attributed to eating whole grains and could be due to other factors relating to "healthier" diet or lifestyles among those who eat brown rice.

Respiratory Conditions

Several cross-sectional studies have assessed rice consumption with respiratory conditions. A study of 20,106 Spanish school children found no relationship between servings of rice consumed weekly and asthma or rhinoconjunctivitis [48]. Similarly, an Australian study of young adults observed no association with asthma ($n = 1466$), but found eating rice daily was associated with a 49% (95% CI: 0.31–0.84) decrease in the odds of bronchial hyperactivity compared with non-daily rice consumption ($n = 1073$) [49]. In an analysis of the Multi-Ethnic Study of Athersclerosis (MESA), consuming greater than one serving of rice a day (versus < 1 serving/week) was associated with a decreased in forced vital capacity of 102 mL/s (95% CI − 198, − 7) and forced expiratory volume of 90 mL/s (95% CI − 170, − 11) ($n = 2250$) [51••]. Additionally, higher rice consumption related to a lowering of total lung capacity (1.33%; 95% CI − 4.29, 1.72; $n = 5710$) and was increased by 3.66% (95% CI 1.22, 6.15) for cardiac-based high attenuated areas (HAA) [51••].

Neoplasms and Preneoplastic Lesions

A scant literature exists on cancers or preneoplastic lesions that are known to be related to arsenic exposure that have investigated rice intake. In a study of rice and skin conditions, including preneoplastic and neoplastic lesions, Melkonian et al. assessed the amount of steamed rice consumed daily and skin lesions at baseline and prospectively [58••]. Dietary analyses derived from food frequency questionnaires of 18,470 Bangladeshis yielded statistically significant linear associations for steamed rice intake and prevalent skin lesions among individuals with well water arsenic concentrations < 100 μg/L (p-for-trend = 0.007), but not among individuals with well water arsenic concentrations > 100 μg/L. A similar trend was observed between steamed rice consumption and incident skin lesions at lower well water arsenic concentrations. A population-based case-control study from New Hampshire, similarly found an increased risk of squamous cell carcinoma of the skin in relation to rice consumption, among those with low drinking water arsenic concentrations, with an overall odds ratio of 1.5 (95% CI 1.1, 2.0) [59••].

Studies that have evaluated the role of rice intake on other cancers, include a study of prostate, kidney, urothelial tract, liver, lung, and pancreas cancer mortality from a Japanese cohort ($n = 106{,}194$ total and 44,703 men) [29]. Relative risk estimates were largely either close to or below 1.0, with exceptions within subgroups by gender for the highest exposure category, including an increased risk of kidney cancer mortality (RR = 4.85 (95% CI 1.35, 17.4)), lung cancer mortality (RR = 1.40 (95% CI 0.95, 2.04)) and, with limited statistical precision, urothelial cancers (RR = 1.48 (95% CI 0.54, 4.02)) among women. Two studies specifically focused on bladder cancer incidence. One, published by Zhang and colleagues [62] based on the NHS and HPFS found no overall association with cancer incidence; those with 5 or more servings of rice per week, the RR was 0.97 (95% CI 0.85, 1.07), for white rice 0.87 (95% CI 0.75, 1.01) and for brown rice 1.17 (95% CI 0.90, 1.26). For bladder cancer, the pooled RR was 1.32 (0.99, 1.76) and the trend by categories of servings was of borderline statistical significance (p-for-trend = 0.09). No other associations were observed for specific cancers [57]. A more recent analysis of a population-based case-control study found a similarly increased odds ratio with rice consumption (OR = 1.3, 95% CI 0.4, 3.5), particularly brown rice (OR = 2.3; 95% CI 0.6, 9.3) among those with higher drinking water arsenic concentrations, however with wide confidence intervals. The interaction between grams of brown rice consumed and drinking water arsenic (less than versus equal to or greater than 1 μg/L arsenic) in water was statistically significant [56] Lastly, two additional case-control studies of pancreatic cancer incidence from the USA found limited evidence of associations. In one study, odds ratios were slightly elevated in men and women but lacked statistical precision (OR for > 30 servings/month versus < 4 servings/month = 1.46 among men ($n = 890$) and 1.16 among women ($n = 160$)). The other, large study ($n = 2233$) reported no association (OR for > twice/week versus < once /month = 0.72 (95% CI 0.44, 1.20)). Thus, epidemiologic studies are sparse and many used cancer mortality as the endpoint and these mostly observed no associations. More recent studies, especially of skin and bladder neoplasms, suggest possible associations especially when water arsenic is considered.

Discussion

In our review of the epidemiologic literature on rice intake and health outcomes, we found inconsistencies across outcomes with studies finding no association, inverse associations, and positive associations depending on the outcome and also substantial differences in results within outcomes. In general, studies observed that higher rice consumption was associated with chronic disease outcomes such as ischemic stroke and type 2 diabetes. While large prospective investigations exist, for many outcomes there were too few studies to determine whether the findings were consistent. Studies were particularly lacking among pregnant women, infants, and children, and for some health outcomes hypothesized to be related to arsenic exposure based on studies of drinking water, i.e., immune-related endpoints. Moreover, the vast majority of the literature did not consider specific constituents of rice, did not measure arsenic biomarkers, or take into account other sources of arsenic exposure such as drinking water. In the three studies that examined rice intake stratified by water arsenic concentrations of arsenic, one found evidence of an increased risk of cardiovascular disease in a combined analysis of large US cohorts [36], another found an increased risk of skin lesions in a large cohort from Bangladesh [58••], and another found an increased risk of squamous cell carcinoma of the skin [59••]. An additional study of bladder cancer only found an increased risk among those with higher water concentrations [56]. One study that measured arsenic metabolites found higher percentages of iAs and MMA associated with higher blood pressure and percentage of DMA associated with lower blood pressure among high rice consumers [27]. Methodologic challenges to evaluating health impacts of arsenic exposure via rice consumption are discussed below and summarized in Table 2.

Arsenic Concentrations Vary in Rice

Rice cultivars have 3 to 37-fold variation in their ability to accumulate arsenic [63] and the proportion of inorganic arsenic in the grain also differs according to variety [64–66]. As a consequence, arsenic concentrations within commercial rice samples vary widely—influenced by the cultivar and region of growth. Rice grown in the USA [66] and in Europe had higher total arsenic concentrations than those varieties from India, Egypt, Bangladesh, and Asia [1, 65, 67]. US grown rice contained higher amounts of total arsenic and a lower proportion of inorganic arsenic (and higher organic arsenic in the form of DMA) than rice from either India or Bangladesh [1, 68]. Brown rice contains more arsenic than white rice because of the accumulation of inorganic arsenic in the bran layers [69]. However, arsenic concentrations within the brown rice grain varies, with one study in India finding arsenic accumulation in the grain increases with decreasing grain size [70]. Moreover, processing (e.g., polishing and parboiling) and cooking practices (e.g., the ratio of cooking water to rice and rinsing in large volumes of water) change the concentration and bioavailability of arsenic in rice [71, 72]. As discussed below, the levels of arsenic in cooking water also influence arsenic levels in cooked rice. While, an association between rice intake and arsenic exposure using biomarkers such as urinary arsenic has been demonstrated in two experimental studies where participants followed a controlled rice diet [7], the actual bioavailability of arsenic in rice may vary. In vitro gastrointestinal digestion simulation studies estimate that between 53 and 102% of the total arsenic in rice is bioavailable [7, 71, 73]. These factors present challenges to estimating the amount of arsenic consumed via rice consumption for epidemiologic inquiry on the health impacts.

Table 2 Methodological challenges to evaluating arsenic exposure

A limited number of studies or sample sizes for many of the outcomes
Dearth of studies of pregnant women, infants, and young children
Heterogeneity of arsenic concentrations in rice
Incomplete understanding of the bioavailability of rice
Other rice containing foods make it difficult to fully capture rice exposure
Lack of consideration of water arsenic and other non-rice arsenic-containing foods
Potential for effect modification by other dietary or other factors
Absence of adjustment for total calories, other dietary factors, or other constituents of rice as potential confounders

Other Foods Contain Rice and Rice Products

Rice and rice products are a pervasive and increasingly used ingredient in our food. These products can be formulated from various parts of the grain, and range from flours and oils to emulsifiers and sweeteners, used in a wide and rapidly growing range of baked goods [74], infant snacks, and powdered milk formulas not otherwise perceived to contain rice. Organic brown rice syrup (OBRS) used as a sweetener in a toddler formula exemplifies the potential for rice ingredients to be a substantial source of arsenic exposure [75]. Additionally, new products on the market such as rice snacks geared toward infants may contain appreciable arsenic concentrations [4, 76]. Thus, questionnaires seeking to assess the health impacts of arsenic exposure from rice in Western populations will not only need to consider the type of rice, and where it was grown, but emerging rice products and rice ingredients in processed foods as well.

Consideration of Water Concentrations of Arsenic

Arsenic exposure through drinking and cooking water could be either a confounder or effect modifier in the analyses of rice intake and health outcomes. Rice cooked with arsenic-contaminated water increases inorganic arsenic content from the absorption of water by rice grains during cooking [71, 77–79]. Conversely, cooking practices with water low in arsenic may decrease the arsenic content of rice [80]. Cooking, such as par boiling may also increase the bioaccessibility of arsenic [71]. Moreover, in regions with high drinking water contamination, water arsenic is a known causal factor for a variety of health outcomes. Thus, the ability to detect adverse effects with rice may be masked at higher drinking concentrations. To separate out the effects of arsenic in water from that of rice, a few studies have examined relationships stratified by drinking water concentrations. A priori one would expect a stronger magnitude of exposure to arsenic from rice among those who are not primarily exposed via water. This was indeed observed in the three studies, two prospective studies of large cohorts and another population-based case-control study. Thus, further studies that take into account water arsenic are needed.

Potential Modifiers: Diet, Tobacco, and Genetics

Dietary factors, tobacco use, and genetic factors could potentially modify the impacts of arsenic on health outcomes. Specific nutrients participate in one-carbon metabolism, the process by which arsenic is methylated [81–87] and excreted from the body [86, 88]. Vitamins such as folate (vitamin B_9) [84, 89], B_{12} [90, 91] B_6, plus methionine [92], betaine, and choline have been associated with increased arsenic methylation. Vitamin B_{12} is a cofactor of methionine synthase, which facilitates the excretion of arsenic in some populations [84, 93]. Tobacco smoking also may influence arsenic methylation capacity and has been found to modify risks associated with arsenic exposure e.g., [62, 94–100]. Further, genetic factors potentially modify risk associated with arsenic exposure through rice as well. For example, methylation of arsenic is catalyzed by the enzyme arsenic (3+ oxidation state) methyltransferase (AS3MT), and genetic variation in *AS3MT* influences the proportion of urinary arsenic metabolites [101]. Further, the enzyme methyltetrahydrofolate reductase (MTHFR) is a critical folate-metabolizing enzyme in humans, which may also influence arsenic toxicity [102, 103]. Additionally, age and sex influence arsenic methylation capacity [104], with women and younger individuals having increased ability to methylate arsenic. As yet, no studies have evaluated potential modifying role of genetic or dietary factors on the rice—health outcome relationships. Lastly, the human gut microbiota could influence arsenic bioaccessibility and As transformation in rice bran, which illustrating the importance of food-bound As metabolism in the human body [105].

Dietary Factors as Potential Confounders

In addition to the potential for misclassification from dietary questionnaires [106], diets are complex, and thus analyses of dietary factors are subject to confounding by other dietary factors. In the National Health and Nutrition Examination Survey (NHANES), rice consumption was associated with greater nutrient intake and higher diet quality in adults [2]. Diets containing rice tended to include more fiber, grains, vegetables, and meat/poultry/fish. An early report from NHANES (1999–2004) indicated that people eating one serving per day of white or brown rice were less likely to consume fat, saturated fatty acids, and sugar and less likely to be overweight/obese or have metabolic syndrome [107]. In the Health Professionals Follow-up Study and the Nurses' Health Study I and II, consumption of brown rice was associated with greater physical activity, being leaner, being less likely to smoke, and having a higher intake of fruit, vegetables, whole grains, and a lower intake of red meat and trans fat [44]. Additionally, rice and rice products can contain other unregulated toxic metals (for example, cadmium accumulation in upland rice [108, 109] and mercury [110–113]) that may pose a health risk. Rice is also a significant source of carbohydrates, which, if replaced by certain fatty acids, may alter glucose homeostasis [114]. Thus, as mentioned, some of the observed associations between dietary arsenic and type II diabetes may conceivably be due to other dietary factors rather than arsenic.

Conclusions

Rice is a staple food. Rice is also a major dietary source of arsenic for populations with low concentrations of arsenic in the drinking water. The study of the association between rice consumption and human health outcomes is complicated by heterogeneous study designs and populations with differing rice consumption patterns relative to their total caloric intake, varying metrics for the ascertainment of rice intake that may lead to exposure misclassification, the complexity of diets, and the ability to control other components in rice itself. A randomized clinical trial to test the effects of arsenic from rice would not be ethical. A duplicate diet study would be challenging to conduct even to assess relatively short-term health outcomes associated with rice consumption. Limited data exist on the relationship between rice intake and human health outcomes from investigations that consider arsenic exposure from drinking water. High drinking water concentrations of arsenic have established health impacts [115], which are not expected to differ from food. But it will be challenging to tease out the effects of rice in areas using water high in arsenic to cook rice. In our review, the few studies that have been done raise the possibility of adverse health impacts of rice consumption among those with relatively low drinking water arsenic concentrations. Our review encompasses a number of research findings on rice consumption and a variety of health outcomes in the human population. Future research will need to address the many methodological challenges to understand the effect of arsenic ingested from food, including rice, on health risks.

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Compliance With Ethical Standards

Conflict of Interest Margaret R. Karagas, Tracy Punshon, Matt Davis, Catherine M. Bulka, Francis Slaughter, Despina Karalis, Maria Argos, and Habibul Ahsan have no potential conflicts of interests to declare.

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