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Rice Consumption and Squamous Cell Carcinoma of the Skin in a United States Population

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Background: Rice contains arsenic, a known skin carcinogen. Rice intake has been associated with arsenic-related skin lesions in South Asia, but its association with skin cancers is as yet unknown.

Objectives: We aimed to investigate whether rice intake contributes to urinary arsenic concentration and risk of squamous cell carcinoma (SCC) of the skin in a U.S. population.

Methods: Rice consumption was assessed using a food frequency questionnaire administered as part of a population-based case–control study of 487 SCC cases and 462 age- and gender-matched controls. Arsenic concentration in household tap water and urine samples were measured using inductively coupled mass spectrometry (ICP-MS) and high-resolution ICP-MS, respectively. Odds ratios (OR) for SCC associated with the frequency of rice consumption were estimated using logistic regression, with adjustment for age, gender, and caloric intake.

Results: Those who reported any rice consumption had higher urinary arsenic concentrations than those who did not consume rice, and the association was most pronounced among those with <1 μg/L arsenic in their household water (19.2% increase in total urinary arsenic, 95% CI: 5.0, 35.3%). Any rice consumption was associated with a 1.5-fold (95% CI: 1.1, 2.0) higher odds of SCC compared with those who reported no rice consumption, and the relation appeared to be largely among those with <1 μg/L water arsenic.

Conclusion: Rice consumption may be related to the occurrence of SCC in the United States, especially among those with relatively low drinking water arsenic exposure. https://doi.org/10.1289/EHP1065

Introduction

The potential human health risk posed by arsenic (As)-contaminated rice consumption has recently emerged as a threat to food safety (Zhu et al. 2008). Arsenic is a known human carcinogen (IARC 1987; Straif et al. 2009) that can naturally occur in groundwater used to irrigate paddy field soils supporting rice crops (Meharg and Rahman 2003). The high As content in rice is due to its uptake via a silicon transport system with an affinity for inorganic As (iAs) (Ma et al. 2008; Mitani et al. 2009). Inorganic forms of As, arsenate (As^V) and arsenite (As^{III}), are generally considered to exhibit a higher degree of acute human toxicity and carcinogenicity than organic arsenical compounds, monomethylarsonic acid (MMA) and dimethylarsinic acid (DMA) (Straif et al. 2009). However, some animal studies suggest trivalent forms of methylated arsenic species may be at least as toxic as arsenite (Styblo et al. 2000). Rice also may contain DMA, which is excreted through the kidneys (Gilbert-Diamond et al. 2011); and urinary DMA concentrations have been associated with an increased risk of skin lesions in Bangladesh (Ahsan et al. 2007; Kile et al. 2011; Lindberg et al. 2008), Taiwan (Yu et al. 2000), Mexico (Valenzuela et al. 2005), and China (Zhang et al. 2014). Arsenobetaine, an unmetabolized form of arsenic found in fish and seafood, is considered nontoxic (Francesconi et al. 2002).

Cutaneous squamous cell carcinoma (SCC) is a common keratinocyte cancer (KC), with increasing incidence rates reported in the United States (Glass and Hoover 1989; Karagas et al. 2006; Karia et al. 2013; Kwa et al. 1992), and carries considerable morbidity and health care costs (Rogers et al. 2010; Rogers et al. 2015). Ultraviolet light, fair skin pigmentation, male gender, and elderly age are primary risk factors for SCC (Karagas et al. 2006); however, environmental exposure to As through contaminated drinking water is known to manifest KCs and arsenical skin lesions (e.g., hyperpigmentation, hypopigmentation, keratosis, melanosis), even at relatively low water As concentrations (Karagas et al. 2015). Recent evidence from Bangladesh suggests that rice containing As may contribute to the occurrence of these lesions (Melkonian et al. 2013).

Rice is a staple food throughout the world, including the United States where rice consumption has increased in recent years (Batres-Marquez et al. 2009). Numerous studies have indicated that rice consumption contributes to dietary As intake and internal As dose (Cleland et al. 2009; Davis et al. 2012; Gilbert-Diamond et al. 2011). However, limited epidemiologic research exists on the potential oncogenic role of rice consumption. Therefore, as part of a U.S. population–based case–control study, we sought to investigate the association between the frequency of rice consumption in relation to urinary arsenic concentrations and incident SCC. We further assessed whether any observed association between rice consumption and SCC was modified by household tap water As concentrations.

Methods

Study Population

The New Hampshire Skin Cancer Study population and methods have been described in detail elsewhere (Karagas et al. 1998; Karagas et al. 1999; Karagas et al. 2006; Karagas et al. 2010). Briefly, histologically confirmed, incident SCC cases were identified through active surveillance of dermatology and pathology laboratories throughout the state of New Hampshire, United States. We selected SCC cases diagnosed between July 2007 and

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July 2009. Controls were chosen from lists of New Hampshire residents obtained from the New Hampshire Department of Transportation (<65 y of age) and Medicare enrollment lists (≥65 y of age), and frequency-matched to the age (25–34, 35–44, 45–54, 55–64, 65–69, and 70–74 y) and gender distribution of cases. To be eligible, participants were required to be residents of New Hampshire, 25–74 y of age at the time of diagnosis, speak English, and have a listed telephone number. Personal interviews were conducted upon enrollment to obtain sociodemographic information (e.g., level of education), lifestyle factors (e.g., cigarette smoking), body mass index (BMI), and sunlight-related characteristics (e.g., skin response to sun exposure, number of blistering sunburns, tanning lamp use, and pigmentation). All participants provided informed consent in accordance with the Committee for the Protection of Human Subjects at Dartmouth College.

Estimation of Rice Consumption

Dietary information was collected from study participants upon enrollment using a validated 121-item semiquantitative food frequency questionnaire (FFQ) developed at Harvard (Salvini et al. 1989). Participants were asked about their usual dietary intake for the previous 12-mo period, including two questions on white and brown rice consumption (see Figure S1). Responses ranged from "never consumed" to "consumed six or more times a day." The average intake of rice in grams per day was calculated by multiplying frequency of consumption by the grams of rice content (assuming 250 g per cup of rice) for the specified portion size (Michaud et al. 1999). In addition, estimates of total energy intake were based primarily on data from the U.S. Department of Agriculture, and were calculated by the Channing Laboratory for Nutritional Health in the Department of Nutrition at Harvard School of Public Health (Watt and Merrill 1993). Brown and white rice consumption were combined to evaluate total rice intake.

Water Arsenic Analysis

Household tap water samples were collected for analysis of total As concentration as described previously (Gruber et al. 2012; Karagas et al. 2000). Briefly, samples were analyzed at the Dartmouth Trace Element Analysis Core using inductively coupled mass spectrometry (ICP-MS). The minimum detection limit for As in the water was 0.01 μg/L. For undetectable water As levels ($n=4$), a value of one-half the limit of detection was used (0.005 μg/L) (Gilbert-Diamond et al. 2013).

Urinary Arsenic Metabolites Analysis

Participants were provided a urine collection kit to collect a first-morning-void urine sample as described previously (Gilbert-Diamond et al. 2011; Gilbert-Diamond et al. 2013). Briefly, urine samples were analyzed at the University of Arizona using a high-performance liquid chromatography (HPLC) inductively coupled plasma mass spectrometry (ICP-MS) system to quantify the concentration of inorganic and organic As metabolites, and arsenobetaine (AsB). The minimum detection limits for urinary As were: 0.15 μg/L for As^{III}, 0.10 μg/L for As^{V}, 0.14 μg/L for MMA, and 0.11 μg/L for DMA. No study participant on whom we measured urinary arsenic had all undetectable urinary As metabolite concentrations. Urinary creatinine levels were also measured (Barr et al. 2005; Gamble and Liu 2005; Nermell et al. 2008) using Cayman's creatinine assay kit according to the manufacturer's protocol (Cayman Chemical, Ann Arbor, MI). Missing creatinine values ($n=315$) were imputed using the median value (97.90 mg/dL) (Gossai et al. 2015).

We computed the total urinary As concentration by summing iAs, MMA, and DMA concentrations (excluding arsenobetaine) (Francesconi et al. 2002). Inorganic arsenic was considered the sum of As^{III} and As^{V}. We further calculated the percentages of each As metabolite (%iAs, %MMA, %DMA) by dividing the concentration of each metabolite by the concentration of total As.

Statistical Analysis

All statistical tests were two-sided, and significance was assessed at the $\alpha=0.05$ level. Statistical analyses were performed in R (version 3.1.0; R Core Team).

Individual characteristics of SCC cases and controls, participants without and with any reported rice consumption, and participants with <1 and ≥1 μg/L water As concentration, were compared using the χ^2 test (for categorical variables, i.e., gender, education, cigarette smoking, BMI, quartile of caloric intake, skin reaction to initial sun exposure in summer, number of blistering sunburns, tanning lamp use, skin color) or Fisher's exact test (for categorical variables with strata containing <10 participants, i.e., age group), and Wilcoxon rank sum test (for continuous variables, i.e., water and urinary As concentrations).

We first used multivariable linear regression models to assess the relation between any, white, or brown rice consumption and no consumption of any rice variety (reference group) and urinary As concentrations (natural log ($\log_e$)-transformed outcome). All models were adjusted for age group and gender (as used in the frequency matching), as well as quartile of caloric intake and creatinine concentration to control for urinary dilution (Barr et al. 2005; Gamble and Liu 2005; Nermell et al. 2008). In addition, we assessed the potentially confounding effects of SCC case–control status, education, smoking status, BMI, drinking water As concentration, urinary AsB concentration, skin reaction to initial sun exposure, number of blistering sunburns, tanning lamp use, and skin color (Cleland et al. 2009; Gilbert-Diamond et al. 2011; Gruber et al. 2012; Melkonian et al. 2013) (see Table S1); however, only those factors that resulted in a >10% change in estimate (Maldonado and Greenland 1993) were ultimately included as covariates in our models. For interpretability, the linear relationship between the $\log_e$-transformed urinary As outcome and the binary rice predictor was presented as the $(e^{\beta}-1)\times 100$ percent change in the expected geometric mean of the As concentration for those with rice consumption compared with those without rice consumption. The modifying effect of drinking water As on the relation between rice consumption and urinary As was assessed in analyses stratified by <1 μg/L versus ≥1 μg/L water As, and the interaction between continuous water As concentration and any, brown, and white rice consumption for urinary As measures was also formally tested by the inclusion of an interaction term in our models, using the likelihood ratio test of the addition of a cross-product term in the linear regression models.

We then used unconditional logistic regression to calculate the odds ratios (ORs) and 95% confidence intervals (CI) for SCC by any, white, or brown rice consumption compared with no consumption of any rice variety (reference group), while adjusting for age group and gender (the frequency matching factors), as well as quartile of caloric intake. We computed the ORs according to frequency of rice consumption per day (1–20 g, 21–50 g, >50 g, compared with no consumption of any rice variety), and calculated a p for trend based on these categories by including an ordinal variable in the logistic model. Of the potentially confounding factors that were associated with both SCC and rice consumption (i.e., urinary AsB, education and tanning lamp use; Table 1), only education and AsB produced a >10% change (Maldonado and Greenland 1993) in our OR estimate for SCC, but only with brown rice consumption. Therefore, our OR estimates were adjusted for age group, gender, and quartiles of

Table 1. Selected characteristics of cutaneous squamous cell carcinoma (SCC) cases and matched controls from the New Hampshire Skin Cancer Study, July 2007–July 2009 ($n = 949$) [n (%) or median ± SD unless otherwise indicated].

Characteristic	SCC cases	Controls	No rice[a]	Any rice[a]	<1 μg/L water As[b]	≥1 μg/L water As[b]
Total no.	487	462	224	725	699	242
Gender						
Male	293 (60.2)	269 (58.2)	147 (65.6)	415 (57.2)*	409 (58.5)	152 (62.8)
Female	194 (39.8)	193 (41.8)	77 (34.4)	310 (42.8)	290 (41.5)	90 (37.2)
Reference age (years)						
25–40	4 (0.8)	3 (0.6)	1 (0.4)	6 (0.8)*	5 (0.7)	2 (0.8)
41–50	20 (4.1)	20 (4.3)	4 (1.8)	36 (5.0)	30 (4.3)	9 (3.7)
51–60	107 (22.0)	121 (26.2)	47 (21.0)	181 (25.0)	160 (22.9)	66 (27.3)
61–67	164 (33.7)	137 (29.7)	65 (29.0)	236 (32.6)	225 (32.2)	74 (30.6)
68–70	66 (13.6)	75 (16.2)	39 (17.4)	102 (14.1)	100 (14.3)	40 (16.5)
>71	126 (25.9)	126 (27.3)	68 (30.4)	164 (22.6)	179 (25.6)	51 (21.1)
Education						
High school	114 (23.4)	178 (38.5)***	97 (43.3)	195 (26.9)***	224 (32.0)	67 (27.7)
College	199 (40.9)	170 (36.8)	82 (36.6)	287 (39.6)	270 (38.6)	95 (39.3)
Graduate or professional	173 (35.5)	114 (24.7)	45 (20.1)	242 (33.4)	204 (29.2)	80 (33.1)
Cigarette smoking[c]						
Never smoked	215 (44.1)	174 (37.7)	84 (37.5)	305 (42.1)	292 (41.8)	94 (38.8)
Former smoker	215 (44.1)	223 (48.3)	103 (46.0)	335 (46.2)	321 (45.9)	113 (46.7)
Current smoker	57 (11.7)	65 (14.1)	37 (16.5)	85 (11.7)	86 (12.3)	35 (14.5)
Body mass index at 18 y old (kg/m^2)						
Underweight <18.5	49 (10.1)	52 (11.3)	18 (8.0)	83 (11.4)	71 (10.2)	29 (12.0)
Normal 18.5–24.9	348 (71.5)	332 (71.9)	152 (67.9)	528 (72.8)	501 (71.7)	173 (71.5)
Overweight 25.0–29.9	77 (15.8)	62 (13.4)	44 (19.6)	95 (13.1)	104 (14.9)	35 (14.5)
Obese >30.0	13 (2.7)	15 (3.2)	10 (4.5)	18 (2.5)	23 (3.3)	5 (2.1)
Caloric intake (kcal/d)[d]						
Quartile 1: ≤1,412	96 (19.7)	116 (25.1)	76 (33.9)	136 (18.8)***	153 (21.9)	55 (22.7)
Quartile 2: 1,412–1,831	133 (27.3)	115 (24.9)	70 (31.2)	178 (24.6)	189 (27.0)	59 (24.4)
Quartile 3: 1,831–2,328	126 (25.9)	115 (24.9)	44 (19.6)	197 (27.2)	179 (25.6)	59 (24.4)
Quartile 4: >2,328	132 (27.1)	116 (25.1)	34 (15.2)	214 (29.5)	178 (25.5)	69 (28.5)
Water Arsenic (μg/L)[b]	0.33 ± 13.7	0.30 ± 9.0	0.33 ± 6.8	0.31 ± 12.8	0.21 ± 0.22	3.82 ± 21.44
Urinary Arsenobetaine (μg/L)[e]	7.55 ± 136.9	5.30 ± 87.5*	6.51 ± 119.2	6.67 ± 115.1	6.90 ± 131.4	6.04 ± 51.8
SCC body site[f]						
Head or neck	241 (49.5)	—	53 (23.7)	188 (27.7)	178 (25.5)	60 (24.8)
Limbs and trunk	246 (50.5)	—	45 (20.1)	201 (25.9)	177 (25.3)	69 (28.5)
Skin reaction to initial sun exposure[g]						
Tan	36 (7.4)	95 (20.6)***	31 (13.8)	100 (13.8)	85 (12.2)	45 (18.6)
Mild burn then tan	242 (49.7)	230 (49.8)	109 (48.7)	363 (50.1)	349 (49.9)	120 (49.6)
Burn then peel	173 (35.5)	108 (23.4)	67 (29.9)	214 (29.5)	216 (30.9)	61 (25.2)
Blister	33 (6.8)	29 (6.3)	16 (7.1)	46 (6.3)	47 (6.7)	15 (6.2)
No. of blistering sunburns						
None	237 (48.7)	255 (55.2)***	116 (51.8)	376 (51.9)	366 (52.4)	125 (51.7)
1	63 (12.9)	60 (13.0)	30 (13.4)	93 (12.8)	93 (13.3)	28 (11.6)
2	27 (5.5)	16 (3.5)	16 (7.1)	27 (3.7)	32 (4.6)	11 (4.5)
≥3	118 (24.2)	58 (12.6)	37 (16.5)	139 (19.2)	124 (17.7)	50 (20.7)
Tanning lamp use						
Yes	151 (31.0)	112 (24.2)*	46 (20.5)	217 (29.9)**	193 (27.6)	67 (27.7)
No	336 (69.0)	350 (75.8)	178 (79.5)	508 (70.1)	506 (72.4)	175 (72.3)
Skin color[h]						
Light	437 (89.7)	353 (76.4)***	193 (86.2)	597 (82.3)	586 (83.8)	200 (82.6)
Medium	50 (10.3)	108 (23.4)	31 (13.8)	127 (17.5)	113 (16.2)	42 (17.4)

Note: Numbers may not sum to the overall total due to missing data. They were excluded from complete-case analyses. p -Values obtained from χ^2, Fisher's exact, or Wilcoxon rank sum test (as appropriate) comparing sociodemographic and skin cancer risk factors between SCC cases and controls.
[a]Rice consumption derived from the Harvard Food Frequency Questionnaire section on "Breads, Cereals, Starches" using items "Brown rice" and "White rice."
[b]Eight study participants were missing water arsenic concentrations.
[c]Cigarette smoking status at 1 y prior to the reference or diagnosis date.
[d]Caloric intake quartiles determined from the control subject distribution.
[e]Seventy-six study participants were missing urinary arsenobetaine concentrations.
[f]Among SCC cases only. Numbers will not sum to the overall total due to lack of inclusion of controls.
[g]Sun sensitivity was defined as the reaction to 1 h of sun exposure the first time in the summer.
[h]Self-reported coloring. Natural skin color on areas never exposed to the sun.
*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

caloric intake, and then further adjusted for level of education and urinary AsB in additional models. As sensitivity analyses, we excluded participants with extremes in the reported caloric intake as suggested by Willett (1998) ($n = 20$ men who reported a caloric intake of <800 or >4,000 kcal/d, and $n = 11$ women who reported a caloric intake <500 or >3,500 kcal/d) (Willett 1998). No appreciable change in results was detected (see Figure S2), and thus these individuals remained in our analyses. Finally, we assessed the potential modifying effect of drinking water As concentration on the association between rice consumption and SCC risk in stratified analyses, classifying participants as having <1 μg/L and ≥1 μg/L water As, and excluding those who did not have a water As sample ($n = 8$). The modifying effect of drinking water As on the relation between rice consumption and urinary As was assessed in analyses stratified by <1 μg/L versus ≥1 μg/L water As. We formally tested the interaction between continuous water As concentration and any, brown, and white rice consumption for risk of SCC by the likelihood ratio test of

Table 2. Odds ratios (95% confidence intervals) for cutaneous squamous cell carcinoma (SCC) by rice consumption among 949 study participants from the New Hampshire Skin Cancer Study, July 2007–July 2009.

Rice consumption	Controls, *n* (%)	SCC cases, *n* (%)	Adjusted OR_1 (95% CI)[a]	Adjusted OR_2 (95% CI)[b]	Adjusted OR_3 (95% CI)[c]
Total no.	462	487	487	487	487
None[d]	126 (27.3)	98 (20.1)	1.00 (referent)	1.00 (referent)	1.00 (referent)
Any rice (any frequency)	336 (72.7)	389 (79.9)	1.47 (1.08, 2.01)	1.34 (0.98, 1.84)	1.60 (1.15, 2.22)
1–20 g/d[e]	129 (27.9)	150 (30.8)	1.48 (1.03, 2.12)	1.42 (0.99, 2.05)	1.69 (1.16, 2.45)
21–50 g/d	108 (23.4)	138 (28.3)	1.63 (1.12, 2.37)	1.48 (1.01, 2.17)	1.71 (1.15, 2.53)
>50 g/d	99 (21.4)	101 (20.7)	1.27 (0.85, 1.90)	1.04 (0.69, 1.58)	1.34 (0.88, 2.04)
p-Trend			0.19	0.75	0.92
White rice (any frequency)	260 (67.4)	281 (74.1)	1.36 (0.98, 1.89)	1.23 (0.88, 1.72)	1.46 (1.03, 2.05)
1–20 g/d[e]	157 (40.7)	192 (50.7)	1.54 (1.09, 2.19)	1.45 (1.01, 2.07)	1.66 (1.15, 2.39)
21–50 g/d	73 (18.9)	66 (17.4)	1.11 (0.72, 1.73)	0.92 (0.59, 1.46)	1.11 (0.70, 1.78)
>50 g/d	30 (7.8)	23 (6.1)	0.95 (0.51, 1.76)	0.80 (0.42, 1.50)	1.14 (0.60, 2.17)
p-Trend			0.35	0.13	0.79
Brown rice (any frequency)	201 (61.5)	261 (72.7)	1.68 (1.20, 2.37)	1.50 (1.06, 2.13)	1.82 (1.27, 2.60)
1–20 g/d[e]	110 (33.6)	164 (45.7)	1.91 (1.31, 2.77)	1.74 (1.19, 2.54)	2.05 (1.39, 3.03)
21–50 g/d	72 (22.0)	68 (18.9)	1.21 (0.78, 1.89)	1.05 (0.67, 1.66)	1.32 (0.82, 2.11)
>50 g/d	19 (5.8)	29 (8.1)	2.06 (1.06, 4.00)	1.71 (0.87, 3.35)	2.08 (1.05, 4.13)
p-Trend			0.04	0.23	0.99

Abbreviations: OR, odds ratio; CI, confidence interval.
[a]OR_1 were adjusted for age group, gender, and caloric consumption.
[b]OR_2 were adjusted for age group, gender, caloric consumption, and education.
[c]OR_3 were adjusted for age group, gender, caloric consumption, and arsenobetaine.
[d]The referent group of no rice consumption includes no rice consumption of either white or brown rice varieties. This referent group is used in common for all types of rice consumption collected from the Harvard Food Frequency Questionnaire.
[e]The grams of rice consumption per day were derived from the Harvard Food Frequency Questionnaire categories of rice intake during a year.

the addition of a cross-product term in the logistic regression models.

Results

We estimated rice consumption from 487 (83.2%) of the 549 interviewed SCC cases, and 462 (86.4%) of the 535 interviewed matched controls. Compared with controls, SCC cases tended to have a higher level of education, skin that burned rather than tanned following sun exposure, a history of a greater number of sunburns in their lifetime, used a tanning lamp, and lighter pigmentation (Table 1). Approximately half of the SCC tumors occurred on the head or neck, and roughly half on the limbs and trunk. Compared with those who reported no rice consumption of either white or brown rice varieties (23.6%), those who reported any rice consumption were generally more likely to be female, younger, more educated, have a higher caloric intake, and less likely to use a tanning lamp (Table 1). Drinking water As concentration ranged from 0 to 266.98 μg/L (median = 0.32, IQR: 0.13–1.07 μg/L), and 59 (6.2%) study participants had household water As concentrations above the current U.S. Environmental Protection Agency standard and World Health Organization drinking water guideline of 10 μg/L (WHO 2017).

Rice Consumption and Urinary Arsenic

Urinary arsenic concentrations were available on 875 (92%) of the 949 participants. The median total urinary As concentration was 0.8 μg/L higher among those who reported any rice consumption (5.24 μg/L) compared with those who reported no consumption (4.41 μg/L) of either white or brown rice ($p = 0.0009$) (see Table S2). Any-rice–consumers also had a 0.04-μg/L higher median iAs concentration ($p = 0.07$), 0.08-μg/L higher median MMA concentration ($p = 0.02$), and 0.7-μg/L higher median DMA concentration ($p = 0.0006$), than non-rice–consumers (see Table S2). Urinary As concentration generally increased with rice consumption (see Table S3). In linear models, consumers of either white or brown rice had a 16.5% (95% CI: 4.0, 30.5%), 3.7% (95% CI: −9.2, 18.3%), 9.8% (95% CI: −2.5, 23.8%), and 18.2% (95% CI: 5.0, 33.0%) increase in total urinary As, iAs, MMA, and DMA, respectively, compared with non-rice–consumers (see Table S3). Associations between rice intake and urinary As were stronger among those with lower household tap water As concentrations (see Table S4). There was a 19.2% (95% CI: 5.0, 35.3%) increase in total urinary As, and a 21.0% (95% CI: 5.8, 38.3%) increase in DMA, with any rice consumption among those with <1 μg/L water As. In contrast, the increase in total urinary As and DMA with rice consumption was only 7.4% (95% CI: −14.7, 35, p for interaction = 0.006) and 8.1% (95% CI: −14.7, 36.9%, p for interaction = 0.02) among those with ≥1 μg/L water As concentration, respectively (see Tables S3 and S4).

Rice Consumption and Cutaneous Squamous Cell Carcinoma

Overall, 79.9% of cases and 72.7% of controls reported rice consumption, and there was an increased odds of SCC with any [OR = 1.5 (95% CI: 1.1, 2.0)], white [OR = 1.4 (95% CI: 1.0, 1.9)], and brown [OR = 1.7 (95% CI: 1.2, 2.8)] rice consumption in logistic models (Table 2). A positive trend in SCC risk was associated with increasing grams of brown rice consumption (p for trend = 0.04), and this was only slightly attenuated after adjustment for level of education (Table 2); SCC risk increased after adjustment for urinary AsB.

Odds ratios for SCC associated with rice consumption were stronger among those with lower As concentrations in the drinking water than those with higher As concentrations (Table 3). Although no clear association was observed between rice consumption and SCC among those with ≥1 μg/L As in their household tap water, an increased risk of SCC with any [OR = 1.7 (95% CI: 1.2, 2.5)], white [OR = 1.5 (95% CI: 1.0, 2.3)], and brown [OR = 2.1 (95% CI: 1.4, 3.1)] rice consumption was found among those with water As concentrations <1 μg/L (Table 3). A positive trend in SCC risk was associated with increasing frequency of any (p for trend = 0.06) and brown (p for trend = 0.005) rice consumption among those with <1 μg/L As concentration (Table 3). Such trends were not observed in the ≥1 μg/L water As concentration strata (Table 3). The increased odds of SCC associated with any rice consumption among those with low water As concentrations appeared insensitive to cut-point of water As used for stratification (see Figure S3). The interactions between tap water

Table 3. Odds ratios (95% confidence intervals) for cutaneous squamous cell carcinoma (SCC) by rice consumption among 949 study participants from the New Hampshire Skin Cancer Study, July 2007–July 2009, stratified by water arsenic concentration <1 or ≥1 μg/L.

Rice consumption	Controls, *n* (%)	SCC cases, *n* (%)	Adjusted OR (95% CI)[a]	Adjusted OR_1 (95% CI)[b]	Adjusted OR_2 (95% CI)[c]
<1 μg/L Water arsenic					
Total no.	344	355	355	355	355
None[d]	97 (28.2)	69 (19.4)	1.00 (referent)	1.00 (referent)	1.00 (referent)
Any rice (any frequency)[e]	247 (71.8)	286 (80.6)	1.72 (1.19, 2.49)	1.56 (1.07, 2.27)	1.87 (1.27, 2.76)
1–20 g/d[f]	95 (27.6)	105 (29.6)	1.63 (1.07, 2.49)	1.57 (1.02, 2.41)	1.86 (1.19, 2.90)
21–50 g/d	75 (21.8)	105 (29.6)	2.10 (1.35, 3.28)	1.90 (1.21, 2.99)	2.20 (1.38, 3.51)
>50 g/d	77 (22.4)	76 (21.4)	1.45 (0.91, 2.30)	1.17 (0.72, 1.89)	1.52 (0.93, 2.48)
p-Trend			0.06	0.36	0.07
White rice (any frequency)[e]	193 (66.6)	205 (74.8)	1.54 (1.04, 2.26)	1.41 (0.95, 2.08)	1.64 (1.09, 2.47)
1–20 g/d[f]	113 (39.0)	145 (52.9)	1.85 (1.22, 2.80)	1.75 (1.15, 2.66)	1.96 (1.27, 3.03)
21–50 g/d	60 (20.7)	43 (15.7)	1.04 (0.62, 1.74)	0.87 (0.51, 1.48)	1.07 (0.62, 1.86)
>50 g/d	20 (6.9)	17 (6.2)	1.19 (0.57, 2.49)	1.01 (0.47, 2.14)	1.39 (0.64, 3.00)
p-Trend			0.39	0.17	0.39
Brown rice (any frequency)[e]	146 (60.1)	196 (74.0)	2.06 (1.37, 3.08)	1.78 (1.18, 2.70)	2.21 (1.45, 3.39)
1–20 g/d[f]	83 (34.2)	119 (44.9)	2.20 (1.42, 3.41)	1.95 (1.25, 3.06)	2.38 (1.50, 3.78)
21–50 g/d	50 (20.6)	56 (21.1)	1.68 (1.00, 2.82)	1.42 (0.84, 2.42)	1.79 (1.04, 3.10)
>50 g/d	13 (5.3)	21 (7.9)	2.64 (1.19, 5.85)	2.06 (0.92, 4.65)	2.72 (1.17, 6.28)
p-Trend			0.005	0.04	0.01
≥1 μg/L Water arsenic					
Total no.	113	129	129	129	129
None[d]	27 (20.9)	29 (22.5)	1.00 (referent)	1.00 (referent)	1.00 (referent)
Any rice (any frequency)[e]	86 (76.1)	100 (77.5)	0.97 (0.51, 1.87)	0.83 (0.43, 1.63)	1.10 (0.55, 2.19)
1–20 g/d[f]	32 (28.3)	43 (33.3)	1.15 (0.54, 2.43)	1.05 (0.49, 2.25)	1.32 (0.60, 2.92)
21–50 g/d	33 (29.2)	32 (24.8)	0.72 (0.32, 1.59)	0.62 (0.27, 1.39)	0.79 (0.34, 1.83)
>50 g/d	21 (18.6)	25 (19.4)	1.06 (0.45, 2.50)	0.80 (0.33, 1.96)	1.22 (0.50, 3.02)
p-Trend			0.78	0.36	0.98
White rice (any frequency)[e]	65 (70.7)	74 (71.8)	0.95 (0.49, 1.86)	0.76 (0.38, 1.53)	1.06 (0.52, 2.15)
1–20 g/d[f]	43 (46.7)	45 (43.7)	0.90 (0.44, 1.84)	0.76 (0.36, 1.60)	1.03 (0.48, 2.21)
21–50 g/d	12 (13.0)	23 (22.3)	1.56 (0.60, 4.06)	1.15 (0.43, 3.12)	1.47 (0.53, 4.08)
>50 g/d	10 (10.9)	6 (5.8)	0.57 (0.17, 1.87)	0.41 (0.12, 1.39)	0.72 (0.21, 2.51)
p-Trend			0.68	0.41	0.84
Brown rice (any frequency)[e]	53 (66.2)	63 (68.5)	1.02 (0.48, 2.16)	0.86 (0.40, 1.88)	1.21 (0.55, 2.66)
1–20 g/d[f]	26 (32.5)	43 (46.7)	1.25 (0.55, 2.85)	1.14 (0.49, 2.63)	1.42 (0.60, 3.37)
21–50 g/d	21 (26.2)	12 (13.0)	0.54 (0.19, 1.53)	0.35 (0.11, 1.09)	0.69 (0.23, 2.07)
>50 g/d	6 (7.5)	8 (8.7)	1.30 (0.34, 4.89)	0.98 (0.24, 3.99)	1.47 (0.38, 5.65)
p-Trend			0.83	0.51	0.94

Note: Eight study participants were missing water arsenic concentrations. Abbreviations: OR, odds ratio; CI, confidence interval.
[a]OR were adjusted for age group, gender, and caloric consumption.
[b]OR_1 were adjusted for age group, gender, caloric consumption, and education.
[c]OR_2 were adjusted for age group, gender, caloric consumption, and arsenobetaine.
[d]The referent group of no rice consumption includes no rice consumption of either white or brown rice varieties. This referent group is used in common for all types of rice consumption collected from the Harvard Food Frequency Questionnaire.
[e]In the analyses, the *p* for interactions between continuous water arsenic levels and any, white, and brown rice were $p = 0.004$, $p = 0.005$, and $p = 0.002$, respectively. Likelihood ratio test $p \leq 0.001$ for all models when comparing models with and without the interaction term.
[f]The grams of rice consumption per day were derived from the Harvard Food Frequency Questionnaire categories of rice intake during a year.

As concentrations (as a continuous variable) and any rice (p for interaction = 0.004), white rice (p for interaction = 0.005), and brown rice (p for interaction = 0.002) consumption and SCC were all statistically significant. Similar but slightly altered estimates were obtained from models further adjusted for education level (Table 3); SCC risk increased after adjustment for urinary AsB.

Discussion

In our U.S. population–based case–control study, rice intake was positively associated with urinary As concentrations and an increased odds of SCC, especially among those with low household tap water As. Rice is a major dietary source of As, especially among populations with relatively low drinking water concentrations of As (Cleland et al. 2009; Gilbert-Diamond et al. 2011; Orloff et al. 2009; Tsuji et al. 2007), and rice consumption in the United States has been increasing over time (Batres-Marquez et al. 2009). Rice cultivars have a wide (i.e., 3- to 37-fold) variation in their ability to accumulate As (Norton et al. 2012), but brown rice contains more As than white rice because inorganic As concentrates in the outer layer of the brown husks (Gundert-Remy et al. 2015). This, in theory, could explain the higher risk of SCC observed with brown rice consumption than white rice consumption in our study, although additional studies are needed.

A number of studies have reported that rice intake contributes to As exposure as estimated from biologic measures of internal dose. Urine is a short-term biomarker of recent As exposure (National Research Council Subcommittee on Arsenic in Drinking Water 1999); however, there is evidence that urinary As concentration is relatively consistent between 2 and 10 y (Kile et al. 2009; Navas-Acien et al. 2009). Drinking water is also a significant source of As. Thus, studies of dietary sources of exposure need to evaluate findings in the context of arsenic concentrations in water. A small study of Korean women from the state of Washington, United States, with drinking water As concentrations <2 μg/L, found a significant association between rice consumption and urinary As excretion, with rice accounting for approximately 16 μg/d of urinary iAs (Cleland et al. 2009). A study of pregnant women who drank water from private, unregulated wells in New Hampshire found that each 1-g increase in rice intake was associated with a 1% increase in urinary total As, after adjustment for As exposure from home tap water (Gilbert-Diamond et al. 2011). Among

U.S. adults from the National Health and Nutrition Examination Survey (NHANES), brown and white rice consumption was assessed using two 24-h dietary recalls; consumption of both brown and white rice were found to be related to higher total urinary As concentrations (Wu et al. 2015). In other NHANES analyses, increased MMA and DMA were associated with rice, rice cakes/crackers, and rice beverages/milk consumption (Rey deCastro et al. 2014; Wei et al. 2014). However, these NHANES analyses were unable to account for As intake from water. Further, studies have observed a positive association between the consumption of rice or rice products and total urinary As concentrations among infants and children (Davis et al. 2012; Karagas et al. 2016; Signes-Pastor et al. 2016). In our case–control study of U.S. adults, we also observed a positive association between rice intake and urinary As excretion, even after adjusting for individual As exposure through drinking water. In our analyses, we attempted to consider other foods that could contribute to arsenic exposure, such as fish and seafood, by adjusting for AsB (Mania et al. 2015; Molin et al. 2015). We found a strengthening of the association after adjustment for AsB, suggesting AsB may serve as a surrogate for other seafood arsenicals that contribute to measurement error and underestimation of the association between nonseafood arsenic (e.g., rice arsenic) with skin cancer. Organic compounds found in seafood products such as arsenosugars and arsenolipids are predominately metabolized to DMA before being excreted (Navas-Acien et al. 2011). Additionally, we did not consider dietary factors that could inhibit As accumulation and absorption, such as dietary lipids (Gruber et al. 2012). We did, however, speciate urinary As and excluded arsenobetaine, an unmetabolized form of arsenic found in fish and seafood that is not considered toxic. In addition, our findings of a stronger association between rice consumption and urinary As among those with lower household water As is consistent with the likelihood of a greater impact of dietary factors among those who are minimally exposed to As through their drinking water.

To our knowledge, the relation between SCC risk and rice consumption has not been previously investigated. One study conducted on the Indian subcontinent among populations highly exposed to As through contaminated drinking water reported associations between rice consumption and skin lesions (Melkonian et al. 2013). In this study from Bangladesh, Melkonian et al. 2013 found a positive trend in skin lesion (i.e., hyperkeratosis and melanosis) prevalence and incidence with increasing tertiles of steamed rice consumption among 18,470 participants (Melkonian et al. 2013) in the Health Effects of Arsenic Longitudinal Study (HEALS) (Ahsan et al. 2006). Similar to our study, they found greater odds of prevalent skin lesions with steamed rice intake among those with lower well water As concentration [i.e., <100 μg/L OR = 1.6 (95% CI: 1.2, 2.2) compared with ≥ 100 μg/L, OR = 1.3 (95% CI: 1.0, 1.8)] (Melkonian et al. 2013).

Strengths and Limitations

A major strength of our study was the large number of histologically confirmed cases of incident, invasive SCC identified through active population-based surveillance, along with controls derived from the general U.S. population. This reduced the opportunity for selection bias, and provided greater generalizability than clinic- or hospital-based case–control studies. Still, the possibility of selection bias and residual confounding cannot be excluded, and the generalizability to nonwhite populations is limited due to the study's location in an almost exclusively white U.S. population. There is also the potential for recall bias. However, because rice consumption is not commonly associated with skin cancer etiology, recall of dietary intake is likely to be nondifferential between cases and controls. Other potential limitations relating to measurement of dietary exposures include the possibility that preclinical disease could alter dietary intake, although this is probably less likely for SCC of the skin than internal cancers.

Conclusions

Rice consumption may be an important source of exposure to the known carcinogen, arsenic. In our population-based case–control study from the United States, we found evidence that rice consumption may be related to the occurrence of squamous cell carcinoma of the skin, and that this association may be stronger among those with low As exposure from drinking water.

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