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Supplemental Material

Rice consumption and squamous cell carcinoma of the skin in a United States population

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Table S4: Associations between rice consumption (any frequency or rice variety compared to no rice consumption) and urinary arsenic (As) metabolites among study participants from the New Hampshire Skin Cancer Study, July 2007-2009, stratified by water arsenic concentration [a] <1 or ≥1 μg/L. Crude and adjusted parameter estimates (95% confidence intervals) for the percent change in the expected geometric means of urinary As concentrations (if As outcome was $\log_e$-transformed), or the difference in As concentrations (if As outcome was not transformed), between those without rice consumption [b] compared to those with rice consumption of any variety.

Supplemental Figure S1: Food frequency questionnaire - rice questions

YOUR DIET LAST YEAR

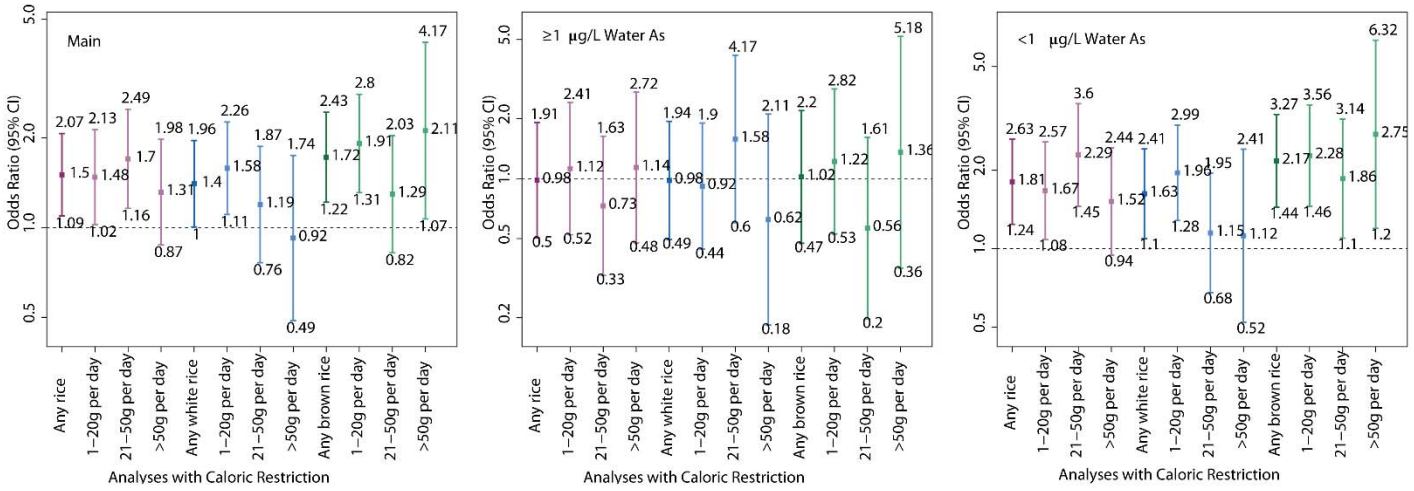
For each food there is an amount shown, either a "medium serving" or a common household unit such as a slice or teaspoon. Please put a tick (✓) in the box to indicate how often, **on average**, you have eaten the specified amount of each food **during the past year**.

Please estimate your average food use as best as you can, and please answer every question – do not leave ANY lines blank. PLEASE PUT A (✓) TICK ON EVERY LINE

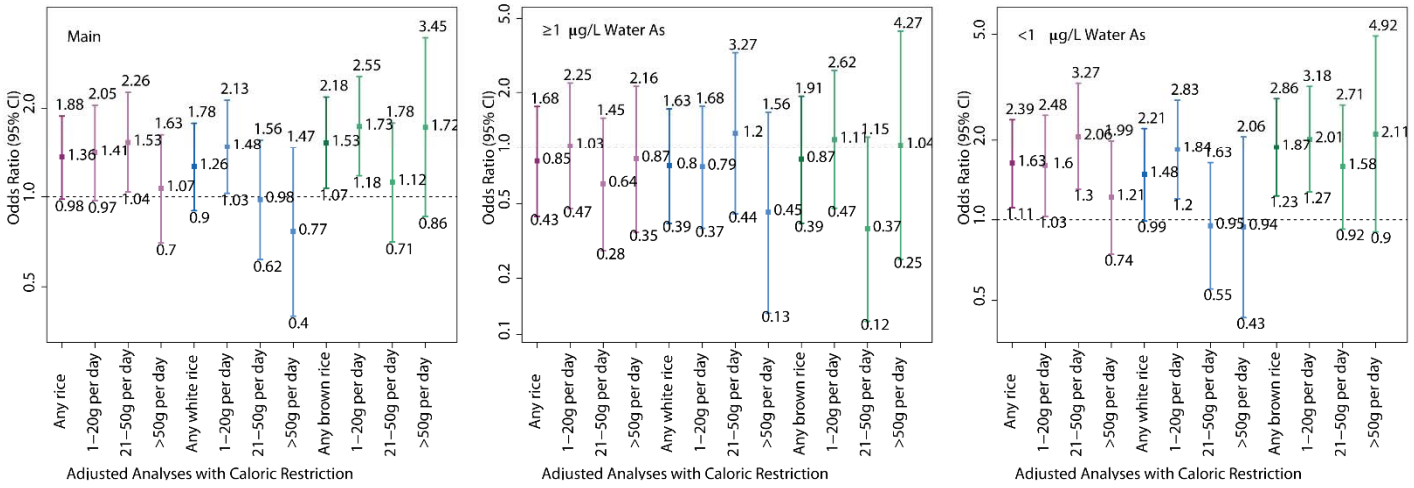
FOODS AND AMOUNTS	**AVERAGE USE LAST YEAR**								
BREADS, CEREALS, STARCHES (medium serving)									
	Never or less than once/month	1-3 per month	Once a week	2-4 per week	5-6 per week	Once a day	2-3 per day	4-5 per day	6+ per day
White rice									
Brown rice									

Supplemental Figure S 1: Rice consumption questions from the validated food frequency questionnaire used in this study.

Supplemental Figure S2: Sensitivity analysis by exclusion of extreme calories



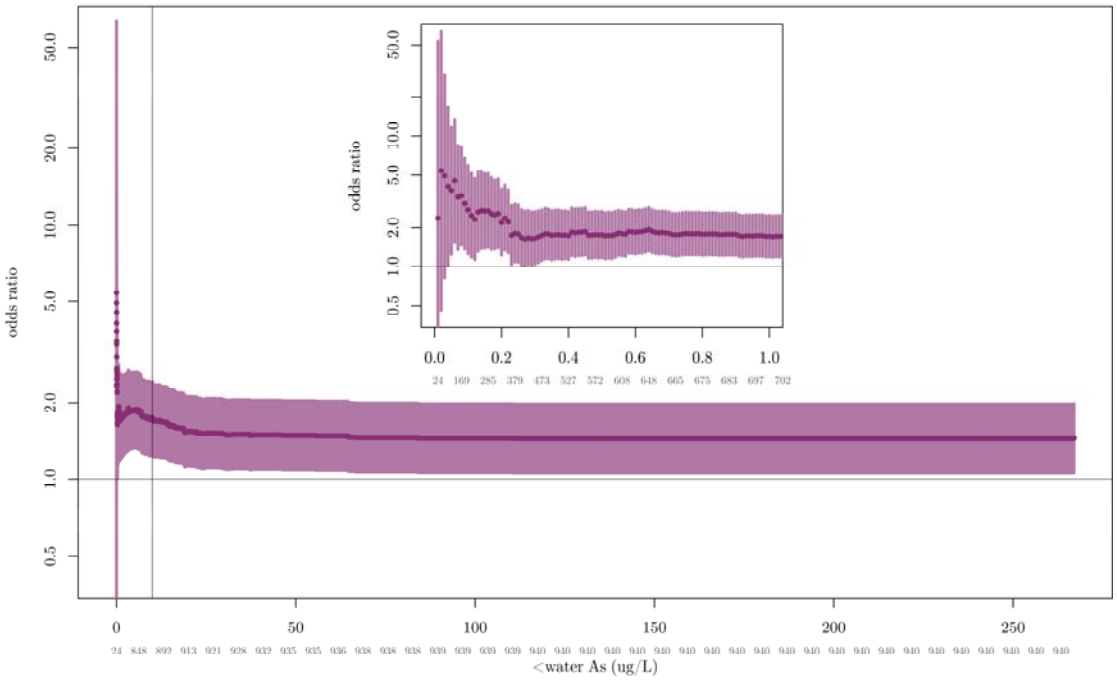
(a) Analyses were adjusted for age group, gender, and caloric consumption.



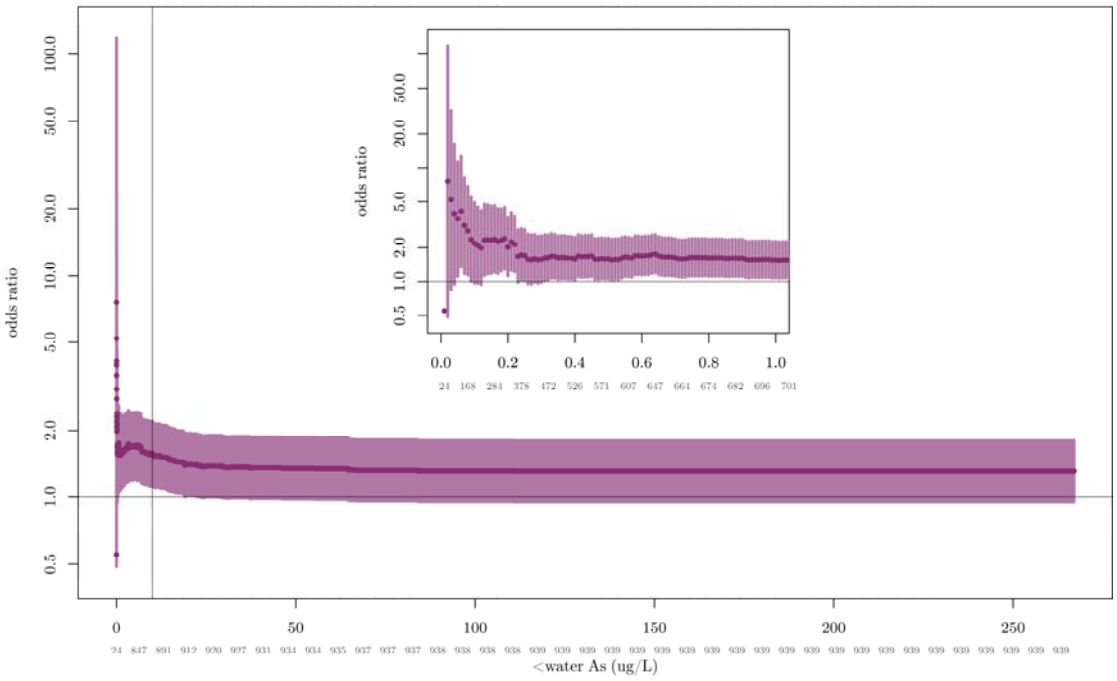
(b) Analyses were adjusted for age group, gender, caloric consumption, and education.

Supplemental Figure S 2: Odds ratios (OR) and 95% confidence intervals (CI) as whiskers for cutaneous squamous cell carcinoma (SCC) by any (purple lines), white (blue lines), or brown (green lines) rice consumption among 918 study participants from the New Hampshire Skin Cancer Study, July 2007-July 2009, following the exclusion of those participants who reported an extreme caloric intake (n=31), also stratified by </≥1 μg/L water arsenic (As) concentration (n=8 missing). The referent group of no rice consumption includes no rice consumption of either white or brown rice varieties.

Supplemental Figure S3: Association between any rice consumption and SCC risk, restricting by water arsenic



(a) Analyses were adjusted for age group, gender, and caloric consumption.



(b) Analyses were adjusted for age group, gender, caloric consumption, and education.

Supplemental Figure S 3: Association between any (white or brown) rice consumption and odds of squamous cell carcinoma (SCC) among study participants from the New Hampshire Skin Cancer Study, July 2007-2009, restricting to just those participants with water arsenic (As) concentrations below the value specified along the x-axis. The referent group of no rice consumption includes no rice consumption of either white or brown rice varieties. The resulting crude and adjusted odds ratios (dots) and 95% confidence intervals (whiskers) for SCC are shown along the y-axis. The sample sizes are presented in gray along the x-axis. The inset zooms in on the odds ratio estimates when restricting analyses to those participants with <1 μg/L water As.

Supplemental Table S1. Selected characteristics of cutaneous squamous cell carcinoma (SCC) cases and matched controls from the New Hampshire Skin Cancer Study, July 2007-July 2009 (n=873).[a]

Characteristic	<Median total urinary Arsenic concentration [b] (n=436), No. (%)	≥Median total urinary Arsenic concentration [b] (n=437), No. (%)
Gender		
Male	240 (55.0)	280 (64.1)**
Female	196 (45.0)	157 (35.9)
Reference age (years)		
25-40	3 (0.7)	4 (0.9)**
41-50	11 (2.5)	19 (4.3)
51-60	83 (19.0)	116 (26.5)
61-67	140 (32.1)	145 (33.2)
68-70	82 (18.8)	52 (11.9)
71+	117 (26.8)	101 (23.1)
Education		
High school	148 (33.9)	127 (29.1)
College	167 (38.3)	170 (38.9)
Graduate or professional	120 (27.5)	140 (32.0)
Cigarette smoking [c]		
Never smoked	169 (38.8)	182 (41.6)
Former smoker	203 (46.6)	207 (47.4)
Current smoker	64 (14.7)	48 (11.0)
Body mass index at 18 years old (kg/m^2)		
Underweight <18.5	45 (10.3)	45 (10.3)
Normal 18.5-24.9	317 (72.7)	313 (71.6)
Overweight 25.0-29.9	56 (12.8)	72 (16.5)
Obese >30.0	18 (4.1)	7 (1.6)
Caloric intake (kcal/day) [d]		
Quartile 1: ≤ 1412	114 (26.1)	79 (18.1)**
Quartile 2: 1412-1831	119 (27.3)	107 (24.5)
Quartile 3: 1831-2328	104 (23.9)	118 (27.0)
Quartile 4: >2328	99 (22.7)	133 (30.4)
Water Arsenic (μg/L), median [standard deviation] [d]	0.27 [3.2]	0.45 [16.5]
Urinary Arsenobetaine (μg/L), median [standard deviation] [e]	6.47 [125.7]	7.02 [106.5]
SCC body site [f]		
Head or neck	128 (29.4)	110 (25.2)
Limbs and trunk	106 (24.3)	140 (32.0)
Skin reaction to initial sun exposure [g]		
Tan	56 (12.8)	68 (15.6)
Mild burn then tan	204 (46.8)	224 (51.3)
Burn then Peel	145 (33.3)	113 (25.9)
Blister	30 (6.9)	30 (6.9)
No. of blistering sunburns		

Supplemental Table S2. Median (interquartile range) of urinary arsenic (As) metabolites and creatinine among all study participants (with total sample size n), those with rice consumption of any variety, and those without rice consumption [a] separately from the New Hampshire Skin Cancer Study, July 2007-2009.

Urinary Arsenic Variable (units) [b]	**Total n (%)** [c]	**Total Median (IQR)**	**Without rice consumption,** [a,d] **Median (IQR)**	**With any (white or brown) rice consumption,** [d] **Median (IQR)**	***P*** [e]
Total arsenic (μg/L) [f]	875 (92.0)	5.01 (3.29-8.44)	4.41 (2.72-7.24)	5.24 (3.40-8.70)	0.00094
iAs (μg/L)	851 (89.7)	0.33 (0.12-0.58)	0.30 (0.12-0.50)	0.34 (0.12-0.61)	0.069
MMA (μg/L)	872 (91.9)	0.50 (0.30-0.82)	0.44 (0.27-0.75)	0.52 (0.31-0.85)	0.025
DMA (μg/L)	875 (92.2)	4.06 (2.60-6.98)	3.55 (2.16-5.84)	4.25 (2.79-7.14)	0.00065
% iAs (%)	851 (89.7)	7.10 (4.42-10.25)	7.46 (5.09-10.87)	6.94 (4.26-10.21)	0.13
% MMA (%)	872 (91.9)	10.24 (7.42-13.43)	10.66 (7.64-14.03)	10.16 (7.36-13.28)	0.26
% DMA (%)	873 (92.0)	82.01 (76.02-87.10)	81.24 (75.80-86.51)	82.26 (76.11-87.38)	0.15
Creatinine (mg/dL)	949 (100)	97.90 (81.03-118.00)	97.90 (82.15-117.70)	97.90 (80.37-118.00)	0.89

IQR=interquartile range, As=arsenic, iAs=inorganic arsenic, MMA=monomethylarsonic acid, and DMA=dimethylarsinic acid.

[a] The group of no rice consumption includes no rice consumption of either white or brown rice varieties as collected from the Harvard Food Frequency Questionnaire.

[b] Urinary As metabolites were measured using high-performance liquid chromatography, and urinary creatinine was measured using Cayman's creatinine assay kit.

[c] Sample sizes <949 due to missingness in the biomarkers of As exposure data. Missing creatinine values (n=315 (33.2%)) were imputed with the median value, 97.90 mg/dL.

[d] Rice consumption derived from the Harvard Food Frequency Questionnaire section on "Breads, Cereals, Starches" using items "Brown rice" and "White rice".

[e] *P* values obtained from the Wilcoxon rank-sum test comparing continuous urinary concentrations, ratios, or percentages of different As variables in those without rice consumption compared to those with rice consumption of any variety.

[f] Total urinary As is the sum of iAs, MMA, and DMA; arsenobetaine was not included in this total.

Supplemental Table S3. Associations between rice consumption (any frequency or rice variety compared to no rice consumption) and urinary arsenic (As) metabolites among study participants from the New Hampshire Skin Cancer Study, July 2007-2009. Crude and adjusted parameter estimates (95% confidence intervals) for the percent change in the expected geometric means of urinary As concentrations (if As outcome was $\log_e$-transformed), or the difference in As concentrations (if As outcome was not transformed), between those without rice consumption [a] compared to those with rice consumption of any variety.

Urinary Arsenic Outcome [b]	Any rice (any frequency) [d]			White rice (any frequency) [d]			Brown rice (any frequency) [d]		
	Adjusted [e] Estimate (95% CI)	*P*	$P_{interaction}$ [f]	Adjusted [e] Estimate (95% CI)	*P*	$P_{interaction}$ [f]	Adjusted [e] Estimate (95% CI)	*P*	$P_{inter\ action}$ [f]
$\log_e$-Total arsenic [c]	16.5 (4.04-30.46)	0.0083	0.0057	19.4 (5.87-34.65)	0.0040	0.0034	17.18 (4.39-31.53)	0.0074	0.11
$\log_e$-iAs	3.66 (-9.18-18.31)	0.59	0.063	6.1 (-7.76-22.04)	0.41	0.038	1.76 (-11.6-17.13)	0.81	0.99
$\log_e$-MMA	9.84 (-2.51-23.76)	0.12	0.000030	12.31 (-1.25-27.73)	0.077	0.000023	10.15 (-2.88-24.93)	0.13	0.03
$\log_e$-DMA	18.18 (5.02-32.99)	0.0057	0.016	21.17 (6.91-37.32)	0.0027	0.0097	19.03 (5.5-34.3)	0.0048	0.17
% iAs	-0.78 (-1.66-0.1)	0.082	0.55	-0.76 (-1.67-0.15)	0.10	0.49	-1.01 (-1.95--0.07)	0.035	0.64
% MMA	-0.61 (-1.39-0.17)	0.12	0.0076	-0.52 (-1.36-0.31)	0.22	0.0086	-0.65 (-1.52-0.21)	0.14	0.16
% DMA	1.26 (-0.13-2.66)	0.075	0.24	1.11 (-0.35-2.57)	0.14	0.25	1.51 (-0.01-3.03)	0.053	0.60

CI=confidence interval, As=arsenic, iAs=inorganic arsenic, MMA=monomethylarsonic acid, and DMA=dimethylarsinic acid.

[a] 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.

[b] Urinary As metabolites were measured using high-performance liquid chromatography, and urinary creatinine was measured using Cayman's creatinine assay kit.

[c] Total urinary As is the sum of iAs, MMA, and DMA; arsenobetaine was not included in this total.

[d] Rice consumption derived from the Harvard Food Frequency Questionnaire section on "Breads, Cereals, Starches" using items "Brown rice" and "White rice".

[e] Analyses were adjusted for age group, gender, caloric consumption, and creatinine concentration.

[f] In the adjusted analyses, the *P* for interactions between continuous water arsenic levels and Any, White, and Brown rice are shown for each model, respectively.

Supplemental Table S4. Associations between rice consumption (any frequency or rice variety compared to no rice consumption) and urinary arsenic (As) metabolites among study participants from the New Hampshire Skin Cancer Study, July 2007-2009, stratified by water arsenic concentration [a] <1 or ≥1 μg/L. Crude and adjusted parameter estimates (95% confidence intervals) for the percent change in the expected geometric means of urinary As concentrations (if As outcome was $\log_e$-transformed), or the difference in As concentrations (if As outcome was not transformed), between those without rice consumption [b] compared to those with rice consumption of any variety.

Urinary Arsenic Outcome [c]	Any rice (any frequency) [e]		White rice (any frequency) [e]		Brown rice (any frequency) [e]	
	Adjusted [f] Estimate (95% CI)	*P*	Adjusted [f] Estimate (95% CI)	*P*	Adjusted [f] Estimate (95% CI)	*P*
≥1 μG/L WATER ARSENIC						
$\log_e$-Total arsenic [d]	7.36 (-14.68-35.09)	0.54	7.77 (-15.75-37.86)	0.55	6.87 (-14.63-33.8)	0.56
$\log_e$-iAs	-0.3 (-25.13-32.75)	0.98	5.33 (-22.33-42.84)	0.74	-11.86 (-33.71-17.18)	0.39
$\log_e$-MMA	6.87 (-16.78-37.24)	0.60	8.84 (-17.37-43.35)	0.55	-0.88 (-22.46-26.7)	0.94
$\log_e$-DMA	8.08 (-14.7-36.95)	0.52	7.49 (-16.44-38.28)	0.57	9.93 (-13.14-39.12)	0.43
% iAs	-0.41 (-2.21-1.39)	0.66	0.05 (-1.82-1.92)	0.96	-1.33 (-3.07-0.41)	0.14
% MMA	-0.17 (-1.74-1.4)	0.83	-0.03 (-1.68-1.63)	0.98	-0.87 (-2.61-0.87)	0.33
% DMA	0.28 (-2.63-3.18)	0.85	-0.41 (-3.42-2.6)	0.79	1.98 (-1.16-5.12)	0.22
<1 μG/L WATER ARSENIC						
$\log_e$-Total arsenic [d]	19.19 (5.02-35.28)	0.0067	24.33 (8.66-42.25)	0.0016	20.29 (5.43-37.24)	0.0063
$\log_e$-iAs	5.38 (-8.63-21.53)	0.47	7.23 (-7.69-24.57)	0.36	8.52 (-7.44-27.24)	0.31
$\log_e$-MMA	10.95 (-2.35-26.05)	0.11	14.35 (-0.29-31.15)	0.056	14.23 (-0.76-31.49)	0.064
$\log_e$-DMA	20.97 (5.81-38.3)	0.0055	26.76 (9.91-46.19)	0.0012	21.11 (5.47-39.07)	0.0069
% iAs	-0.83 (-1.86-0.19)	0.11	-1.01 (-2.07-0.04)	0.060	-0.65 (-1.77-0.48)	0.26
% MMA	-0.67 (-1.57-0.23)	0.15	-0.64 (-1.62-0.33)	0.20	-0.49 (-1.5-0.53)	0.35
% DMA	1.42 (-0.16-3)	0.078	1.54 (-0.11-3.19)	0.068	1.01 (-0.73-2.76)	0.26

CI=confidence interval, As=arsenic, iAs=inorganic arsenic, MMA=monomethylarsonic acid, and DMA=dimethylarsinic acid.

[a] 8 Study participants were missing water arsenic concentrations.

[b] 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.

[c] Urinary As metabolites were measured using high-performance liquid chromatography, and urinary creatinine was measured using Cayman's creatinine assay kit.

[d] Total urinary As is the sum of iAs, MMA, and DMA; arsenobetaine was not included in this total.

[e] Rice consumption derived from the Harvard Food Frequency Questionnaire section on "Breads, Cereals, Starches" using items "Brown rice" and "White rice".

[f] Analyses were adjusted for age group, gender, caloric consumption, and creatinine concentration.