IJC
International Journal of Cancer

Cancer Epidemiology

Rice consumption and cancer incidence in US men and women

Ran Zhang[1,2]*, Xuehong Zhang[3]*, Kana Wu[1], Hongyu Wu[1], Qi Sun[1,3], Frank B. Hu[1,2,3], Jiali Han[2,3,4], Walter C. Willett[1,2,3] and Edward L. Giovannucci[1,2,3]

[1] Department of Nutrition, Harvard T. H. Chan School of Public Health, Boston, MA
[2] Department of Epidemiology, Harvard T. H. Chan School of Public Health, Boston, MA
[3] Department of Medicine, Channing Division of Network Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA
[4] Department of Public Health, Indiana University School of Medicine, Indianapolis, IN

While both the 2012 and 2014 Consumer Reports concerned arsenic levels in US rice, no previous study has evaluated long-term consumption of total rice, white rice and brown rice in relation to risk of developing cancers. We investigated this in the female Nurses' Health Study (1984–2010), and Nurses' Health Study II (1989–2009), and the male Health Professionals Follow-up Study (1986–2008), which included a total of 45,231 men and 160,408 women, free of cancer at baseline. Validated food frequency questionnaires were used to measure rice consumption at baseline and repeated almost every 4 years thereafter. We employed Cox proportional hazards regression model to estimate multivariable relative risks (RRs) and 95% confidence intervals (95% CIs). During up to 26 years of follow-up, we documented 31,655 incident cancer cases (10,833 in men and 20,822 in women). Age-adjusted results were similar to multivariable-adjusted results. Compared to participants with less than one serving per week, the multivariable RRs of overall cancer for individuals who ate at least five servings per week were 0.97 for total rice (95% CI: 0.85–1.07), 0.87 for white rice (95% CI: 0.75–1.01), and 1.17 for brown rice (95% CI: 0.90–1.26). Similar non-significant associations were observed for specific sites of cancers including prostate, breast, colon and rectum, melanoma, bladder, kidney, and lung. Additionally, the null associations were observed among European Americans and non-smokers, and were not modified by BMI. Long-term consumption of total rice, white rice or brown rice was not associated with risk of developing cancer in US men and women.

Paddy rice is a major component of the global food supply, serving as a staple for over 50% of the world population.[1] Compared to Asian countries, per capita rice consumption in the US is much lower with substantial variation across ethnic groups.[2] White rice, as milled grain with husk, bran and germ removed, has a finer texture and longer shelf life. In contrast, brown rice is a whole grain, produced by only removing the outermost layer (husk) and thus contains more dietary fiber, minerals, and biologically active substances.[3–6]

The 2012 Consumer Reports claimed that "samples of white rice, brown rice and rice breakfast cereals that many U.S. adults and children eat may contain worrisome levels of arsenic."[7] A positive association between rice consumption and arsenic level in human body has been observed in previous studies in US.[8,9] While arsenic is a naturally occurring element found in air, soil, water, and foods, inorganic arsenic has been associated with various types of cancers, including those of the lung, liver, bladder, kidney and skin.[10–14]

Key words: rice, arsenic, prostate cancer, breast cancer, colorectal cancer, melanoma, bladder cancer, kidney cancer, and lung cancer
Additional Supporting Information may be found in the online version of this article.
Drs. Ran Zhang and Xuehong Zhang had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Zhang, Zhang, Wu, Wu, Sun, Hu, Han, Willett and Giovannucci. Acquisition of data: Willett and Giovannucci. Analysis and interpretation of data: Zhang, Zhang, Wu, Wu, Sun, Hu, Han, Willett and Giovannucci. Drafting of the manuscript: Ran Zhang and Xuehong Zhang. Statistical analysis: Ran Zhang and Xuehong Zhang. Obtained funding: Willett and Giovannucci. Administrative, technical, or material support: Willett and Giovannucci. Study supervision: Willett and Giovannucci. Critical revision of the manuscript for important intellectual content: Zhang, Zhang, Wu, Wu, Sun, Hu, Han, Willett and Giovannucci
*R.Z. and X.Z. contributed equally to this work
Grant sponsor: National Institutes of Health (NIH); **Grant numbers:** CA87969, CA55075 and K07 CA188126
DOI: 10.1002/ijc.29704
History: Received 1 June 2015; Accepted 20 July 2015; Online 28 July 2015
Correspondence to: Xuehong Zhang, Brigham and Women's Hospital and Harvard Medical School, 181 Longwood Avenue, Room 355, Boston, MA 02115, USA, Tel.: 617-525-0342, Fax.: 617-525-2008, E-mail: xuehong.zhang@channing.harvard.eduor Edward Giovannucci, Harvard School of Public Health, Harvard Medical School, 665 Huntington Avenue, Bldg. 2, Room 371, Boston, MA 02115, USA, E-mail: egiovann@hsph.harvard.edu

What's new?
Although rice consumption per capita in the United States is low compared to Asian countries, the various types of rice eaten in the United States may contain elevated levels of arsenic, raising health concerns. This report explores possible relationships between rice consumption and cancer development. Analyses of data from the Nurses' Health Study, Nurses' Health Study II, and Health Professionals Follow-Up Study show that among U.S. men and women, neither total rice consumption nor white rice or brown rice consumption are associated with cancer. Measures of arsenic should be assessed in the context of rice consumption in future research.

Nonetheless, it remains unclear whether arsenic intakes at the levels found in rice are related to risk of human cancer.

Hence, we conducted this first study to comprehensively evaluate whether individuals with relatively high amounts of rice consumption over decades have a higher risk of developing cancers. Specifically, we utilized unique data from three well-established on-going prospective cohorts, the female Nurses' Health Study and Nurses' Health Study II, and the male Health Professionals Follow-up Study. In each cohort we have collected detailed information on consumption of white rice and brown rice every 4 years for up to 26 years.

Material and Methods

Study population

We used the data from three on-going prospective US cohorts: the Nurses' Health Study (NHS, $n = 121{,}700$ registered female nurses, aged 30 to 55 years at baseline in 1976), the Nurses' Health Study II (NHS II, $n = 116{,}609$ registered female nurses, aged 25 to 42 at baseline in 1989), and the Health Professionals Follow-up Study (HPFS, $n = 51{,}529$ male professionals, aged 40 to 75 years at baseline in 1986). Details of these three cohorts have been described elsewhere.[15–17] In all three cohorts, participants at enrollment completed baseline questionnaires regarding demographic, lifestyle, medication, and newly diagnosed diseases. During the follow-up questionnaires were administered every 2 years to update medical, lifestyle and other health-related information. The follow-up rate has been >90% for each cohort.

In the current analysis, we excluded participants with diagnosis of cancer at baseline (except for the non-melanoma skin cancer) and those with missing date of cancer diagnosis. In addition, we excluded participants with missing information on rice consumption at baseline, those with unusual self-reported total energy intake (*i.e.,* <500 or >3,500 kcal/day for NHS and NHS II; <800 or >4,200 kcal/day for HPFS). After exclusion, data from 70,603 NHS participants, 90,264 NHS II participants, and 45,382 HPFS participants were available for the analysis.

These cohorts have been approved by the institutional review boards at the Harvard T. H. Chan School of Pubic Heath and Brigham and Women's Hospital, Boston, Massachusetts. The completion of the self-administered questionnaire was considered to imply informed consent.

Assessment of rice consumption

Information on rice consumption was first assessed in 1980 in NHS participants using a validated semi-quantitative food frequency questionnaire (SFFQ), and repeated in 1984, 1986, and every 4 years thereafter. Similar SFFQs were administered every 4 years for NHS II participants during 1991 through 2009 and for HPFS participants during 1986 through 2008. In each SFFQ, we asked the participants how often, on average over the past year, they consumed a specified portion size of each food, with nine possible frequency choices ranging from "almost never" to "six or more times per day." For white rice and brown rice, we used one cup as the serving unit. The total rice intake was calculated as the sum of white rice and brown rice. In the current study, we categorized participants' rice intake into four categories (<1 serving per week, 1 serving per week, 2–4 servings per week and ≥5 servings per week). The reproducibility and validity of these SFFQs have been evaluated in detail elsewhere.[18–21] Assessments of white rice and brown rice consumption were moderately correlated with diet record assessments. For example, the corrected Pearson correlation coefficients between these two assessments were 0.53 for white rice and 0.41 for brown rice in the HPFS.[18]

Assessment of other covariates

Other dietary factors such as consumption of red meat, fish, alcohol, fruit and vegetables, whole grain, nuts were also collected from the baseline and subsequent SFFQs. Nutrient intakes were calculated as the frequency of intake multiplied by the nutrient composition of the specified portion size; the composition values were obtained mainly from U.S. Department of Agriculture sources, supplemented with other data. In addition, we also collected and updated information on medical, lifestyle and other health-related factors, such as body weight, physical activity, smoking status, family history of cancer, multivitamin use, and history of diabetes, hypertension and hypercholesterolemia. In NHS and NHS II, we also queried postmenopausal hormone use.

Ascertainment of incident cancer cases

In each cohort, participants reported cancer and other disease endpoints in biennial questionnaires. Researchers obtained permission from the study participants to obtain their medical records and pathological reports and abstracted the

Table 1. Baseline age-standardized characteristics according to white rice and brown rice intake

	White Rice Intake				Brown Rice Intake			
	<1/wk	1/wk	2–4/wk	≥5/wk	<1/wk	1/wk	2-4/wk	≥5/wk
NHS								
Participants (no.)	47,461	18,376	5,126	640	65,653	4,461	1,291	198
Age (yr)	50.8	49.5	49.5	50.2	50.3	50.5	51.1	51.6
Rice intake (servings/d)	0.047	0.14	0.43	1.04	0.013	0.14	0.43	0.99
Physical activity (MET-h/wk)	13.8	14.2	15.1	15.7	13.5	19	22.1	25
BMI (kg/m^2)	25.1	25	24.9	24.4	25.1	24.6	24.3	23.7
Race (%)								
European Americans	98.8	98.1	93.7	50.9	97.9	98.1	96.4	92.6
Asian	0.16	0.25	1.6	41.9	0.7	0.3	1	2.6
African-American	0.33	0.62	1.6	1.6	1	0.9	1.9	2.5
Other	0.72	1.08	3.1	5.7	0.5	0.7	0.8	2.3
Never smoking (%)	43.9	43.1	44.5	56.3	43.8	43.6	45.2	53.4
Type 2 diabetes (%)	3.2	3.1	3.3	4.9	3.2	2.9	3	3.6
Current multivitamin use, %)	36.9	36.2	37.4	37.2	35.8	46.3	52.2	48.1
Dietary intake								
Alcohol (g/d)	6.5	7.5	8.1	3.9	6.8	7.5	6.8	5.1
Fruit (servings/d)	2	2.2	2.3	2.5	2.1	2.6	2.9	3
Vegetables (servings/d)	2.4	2.7	3	2.9	2.4	3.1	3.5	4
Red meat (servings/d)	1.2	1.3	1.3	1.4	1.3	1.1	1	0.7
Fish (servings/d)	0.2	0.2	0.3	0.3	0.2	0.3	0.3	0.3
Whole grain (g/d)	14.4	13.3	13.1	10.4	12.9	22.2	37	66.7
Total saturated fat (g/d)	22.5	21.8	20.7	18.5	22.3	20.4	18.6	15.7
NHS II								
Participants (no.)	50,134	26,436	11,727	1,967	74,030	11,406	4,201	627
Age (yr)	35.9	36.3	36.4	36.3	36.1	36	36.2	36.6
Rice intake (servings/d)	0.045	0.14	0.43	1.14	0.019	0.14	0.43	0.93
Physical activity, MET (h/wk)	20.6	20.6	22.1	21.3	19.4	26	28.9	38.6
BMI (kg/m^2)	24.7	24.6	24.6	24	24.7	24.1	24	24
Race (%)								
European Americans	94.5	94.1	89.2	50.9	92.5	94.6	92.8	85.8
Asian	0.4	0.8	2.5	37	1.7	0.8	0.9	4.2
African-American	1.2	1.3	2.5	4.1	1.6	0.9	1.2	4
Other	3.9	3.9	5.8	8	4.2	3.7	5.1	6
Never smoking (%)	65.7	65.3	65.1	74.5	66.2	63.9	61.5	61.6
Type 2 diabetes (%)	1	1	0.9	1	1	0.8	0.9	1.2
Current multivitamin use, %	43.8	43.3	44.9	43.7	42.5	48.9	51	52.5
Dietary intake								
Alcohol (g/d)	2.9	3.3	3.5	2.4	3	3.7	3.8	3.1
Fruit (servings/d)	1.1	1.3	1.4	1.4	1.1	1.5	1.7	2
Vegetables (servings/d)	3	3.5	4	4.3	3.1	4	4.8	6.1
Red meat (servings/d)	0.8	0.8	0.8	0.8	0.8	0.7	0.6	0.5
Fish (servings/d)	0.2	0.3	0.3	0.4	0.3	0.3	0.4	0.4
Whole grain (g/d)	20.8	20.1	20.2	16.4	17.7	27.3	43.4	66.8
Total saturated fat (g/d)	23	22.3	20.9	18.8	22.9	21.1	19.1	16.3

Table 1. Baseline age-standardized characteristics according to white rice and brown rice intake (Continued)

	White Rice Intake				Brown Rice Intake			
	<1/wk	1/wk	2–4/wk	≥5/wk	<1/wk	1/wk	2-4/wk	≥5/wk
HPFS								
Participants (no.)	28,432	11,295	4,748	907	36,917	5,966	2,131	368
Age (yr)	54.6	52.2	52.1	51.7	54.1	51.7	52.3	52.5
Rice intake (servings/d)	0.04	0.14	0.43	1.06	0.02	0.41	0.43	0.98
Physical activity, MET-h/wk	20.8	21.6	21	20.3	20	24.4	26.8	33.3
BMI (kg/m^2)	25	25	24.8	24.2	25	24.8	24.5	23.7
Race (%)								
European Americans	96.7	96	91	48.5	95	96.1	94.3	83.4
Asian	0.3	0.5	3.9	46.1	1.7	0.6	1.6	12.9
African-American	0.7	1	2.6	2.2	1	0.9	1.6	1.1
Other	2.2	2.5	2.5	3.2	2.3	2.4	2.5	2.6
Never smoking (%)	44.7	45.6	43.9	45	44.1	47.9	48.8	49.2
Type 2 diabetes (%)	3	3.2	3.4	4.3	3.1	3.1	3.2	2.8
Current multivitamin use (%)	42.3	40.3	40.5	45.2	40.4	45.6	50.4	52.2
Dietary intake								
Alcohol (g/d)	11.3	11.6	11.5	8.4	11.3	11.5	11	8.3
Fruit (servings/d)	2.3	2.5	2.6	2.5	2.2	2.8	3.1	3.6
Vegetables (servings/d)	2.9	3.3	3.7	3.4	2.9	3.7	4.3	5.1
Red meat, servings/d	1.1	1.2	1.2	1.2	1.2	1	0.9	0.5
Fish (servings/d)	0.3	0.4	0.4	0.4	0.3	0.4	0.5	0.6
Whole grain (g/d)	22.3	21.8	21.9	18.2	19.1	28.5	45.2	76.9
Total saturated fat (g/d)	25	23.9	22.6	21.2	25.1	22.6	20	15.9

Values are means or percentages and are standardized to the age distribution of the study population except for the age variable; MET-h hours of metabolic equivalent tasks; BMI = body mass index.

information on anatomic location, stage, and histological type of the cancer. For deceased study participants with a known or suspected cancer, we contacted next of kin for permission to review their medical records and pathology report. For those deceased participants we were unable to obtain medical records, the state tumor registries were contacted to confirm the cancer. The confirmed cancers were defined according to the International Classification of Diseases, Ninth Revision [ICD-9].[22]

Statistical analysis

We computed person-time of follow-up for each participant from the return date of the baseline questionnaire to the date of cancer diagnosis, death from any cause, or the end of follow-up (May 31st, 2010 in NHS, May 31st, 2009 in NHS II, and January 31st, 2008 in HPFS), whichever came first. Relative risks (RRs) and 95% confidence intervals (CI's) of total and site-specific cancers were estimated using time-dependent Cox proportional hazards regression models.[23] All models were stratified by age in months and calendar time. In multivariable analysis, we simultaneously controlled for ethnicity and other factors that may influence cancer risk (see Table 2 footnote for these variables and their categorizations). In NHS and NHS II, we further adjusted for postmenopausal hormone use (never, past, current). To better represent long-term diet and minimize the effect of within-person variation, we used the cumulative average intake method.[24] Specifically we calculated the cumulative average from all SFFQs until the diagnosis of cancer, death, or the end of follow-up. Cumulative average intake can better reflects long term dietary intake and minimize the influence of random measurement errors by using dietary assessments.[24] Taking HPFS as an example, total rice intake in 1986 was used for analyses of colorectal cancer diagnosed from 1986 through 1990, and the average total rice intake in 1986 and 1990 was used for analyses of colorectal cancer diagnosed from 1990 through 1994, and so on. To address the missing dietary information in repeated SFFQs, we replaced the missing values of dietary variables with those from the previous SFFQ.

In addition to overall cancer, we further investigated the risk of common site-specific cancers, including prostate cancer, breast cancer, lung cancer, colorectal cancer, bladder cancer, kidney cancer and melanoma. In NHS II, only breast

Table 2. Risk of overall cancer according to total rice intake in the HPFS, NHS I, and NHS II

Total rice intake, no. of servings	<1/week	1/week	2–4/week	≥5/week	*p* (trend)
NHS					
No. cases	6,931	3,442	4,776	524	
RR (95% CI)					
Model 1[1]	1 (ref)	1.00 (0.96–1.04)	0.98 (0.94–1.01)	0.94 (0.86–1.02)	0.08
Model 2[2]	1 (ref)	1.01 (0.97–1.05)	1.00 (0.96–1.04)	1.02 (0.93–1.12)	0.81
Model 3[3]	1 (ref)	1.01 (0.97–1.05)	1.00 (0.96–1.04)	1.02 (0.93–1.12)	0.72
NHS II					
No. cases	1,693	1,165	1,904	387	
RR (95% CI)					
Model 1[1]	1 (ref)	0.94 (0.87–1.01)	0.95 (0.89–1.02)	0.82 (0.73–0.92)	0.001
Model 2[2]	1 (ref)	0.92 (0.86–1.00)	0.92 (0.86–0.98)	0.82 (0.73–0.92)	0.001
Model 3[3]	1 (ref)	0.93 (0.86–1.00)	0.93 (0.86–0.99)	0.83 (0.73–0.94)	0.003
HPFS					
No. cases	3,920	2,290	3,751	872	
RR (95% CI)					
Model 1[1]	1 (ref)	0.98 (0.93–1.03)	0.99 (0.95–1.04)	0.94 (0.87–1.01)	0.14
Model 2[2]	1 (ref)	0.99 (0.94–1.04)	1.00 (0.95–1.04)	1.00 (0.92–1.08)	0.99
Model 3[3]	1 (ref)	0.99 (0.94–1.04)	1.00 (0.95–1.05)	1.00 (0.93–1.10)	0.85
Pooled results					
RR (95% CI)	1 (ref)	0.98 (0.93–1.03)	0.98 (0.94–1.02)	0.97 (0.85–1.07)	0.37
p heterogeneity		0.07	0.1	0.02	0.02

[1]Age-adjusted.
[2]Adjusted for age (years), ethnicity (European Americans, Asian, African American, other), body mass index (calculated as weight in kilograms divided by height in meters squared; <21.0, 21.0–22.9, 23.0–24.9, 25.0–26.9, 27.0–29.9, 30.0–32.9, 33.0–34.9, or ≥35.0), smoking status (never smoked, past smokers, current smokers 1 to 14 cigarettes/day, 15 to 24 cigarettes/day, or ≥25 cigarettes/day), physical activity (MET-hours/week, in quintiles), family history of cancer (yes or no), multivitamin supplementation (yes or no), and total energy intake (kilocalories/day, in quintiles). For women, postmenopausal hormone use (yes or no) was further adjusted for.
[3]In addition to model 2, model 3 was further adjusted for intake of alcohol, fruit, vegetables, red meat, fish, nuts, whole grain (except brown rice), sugar-sweetened beverage (all in quartiles).
Abbreviations: CI, confidence interval; HPFS, Health Professionals Follow-up Study; NHS, Nurses' Health Study.

cancer and melanoma were included in the site-specific analysis due to the small number of cases for other cancers. We also conducted several sensitivity analyses: (*i*) for total rice consumption, we examined intake of at least 1 serving/day; (*ii*) in men, we also excluded the cases of organ-confined prostate cancer, as those were usually detected from PSA screening test and had high incidence but good prognosis; (*iii*) we applied 4 to 8 years lag due to concern of reverse causation because participants with subclinical malignancy may change their diet due to the illness; (*iv*) we further examined whether the associations were modified by ethnicity, smoking status, and body mass index (BMI). In our three cohorts, the majority of participants are European Americans, and we were unable to have stable estimate in other ethnicity due to small sample size. Therefore, we restricted the stratified analysis to European Americans . Similarly we conducted analyses stratified by smoking status (never, past, and current) and by BMI (<25, 25-30, and ≥30 kg/m^2).

Tests for trend were conducted by assigning the median value to each category and using this variable as a continuous variable in the models. We used the meta-analysis assuming fixed-effects to pool the RRs from multivariable models across the three cohorts. *p* values for heterogeneity between cohorts were calculated by Cochran *Q* test.[25] All *p* values were two-sided and all statistical procedures were performed using SAS release 9.2 (SAS Institute, Cary, NC).

Results

We identified 15,673 incident cancer cases during 26 years of follow-up in the NHS, 5,149 cases during 18 years in the NHS II, and 10,833 cases during 22 years in the HPFS. In NHS, breast cancer was the most common cancer (n = 5,714; 36.8%), followed by colorectal cancer (n = 1,352; 8.7%) and lung cancer (n = 1,205; 7.7%). In NHS II, breast cancer was the most common cancer (n = 2,401; 47.0%) and melanoma was the next common cancer (n = 538; 10.4%). In HPFS,

Table 3. Risk of overall cancer according to white rice intake in the HPFS, NHS I, and NHS II

White rice intake, no. servings	<1/week	1/week	2–4/week	≥5/week	*p* (trend)
NHS					
No. cases	9,588	3,093	2,815	177	
RR (95% CI)					
Model 1[1]	1 (ref)	1.00 (0.96–1.05)	1.01 (0.96–1.05)	0.85 (0.74–0.99)	0.2
Model 2[2]	1 (ref)	1.01 (0.97–1.05)	1.02 (0.98–1.06)	0.96 (0.81–1.14)	0.74
Model 3[3]	1 (ref)	1.01 (0.96–1.05)	1.02 (0.97–1.06)	0.96 (0.81–1.14)	0.8
NHS II					
No. cases	2,636	1,210	1,196	107	
RR (95% CI)					
Model 1[1]	1 (ref)	0.96 (0.90–1.03)	0.98 (0.92–1.05)	0.70 (0.58–0.85)	0.002
Model 2[2]	1 (ref)	0.96 (0.89–1.02)	0.96 (0.89–1.02)	0.72 (0.58–0.89)	0.004
Model 3[3]	1 (ref)	0.96 (0.89–1.03)	0.96 (0.90–1.03)	0.73 (0.59–0.90)	0.01
HPFS					
No. cases	6,391	2,102	2,087	253	
RR (95% CI)					
Model 1[1]	1 (ref)	1.01 (0.96–1.06)	1.03 (0.98–1.08)	0.84 (0.74–0.95)	0.09
Model 2[2]	1 (ref)	1.02 (0.97–1.07)	1.03 (0.98–1.08)	0.92 (0.79–1.06)	0.76
Model 3[3]	1 (ref)	1.02 (0.97–1.07)	1.03 (0.98–1.08)	0.91 (0.79–1.05)	0.7
Pooled results					
RR (95% CI)	1 (ref)	1.00 (0.97–1.03)	1.01 (0.97–1.04)	0.87 (0.75–1.01)	0.17
p heterogeneity		0.32	0.24	0.28	0.07

[1]Age-adjusted.
[2,3]Adjusted for the same sets of covariates as for model 2 and model 3 in Table 2.
Abbreviations: CI, confidence interval; HPFS, Health Professionals Follow-up Study; NHS, Nurses' Health Study.

prostate cancer was the most common cancer ($n = 5{,}060$; 46.7%), followed by colorectal cancer ($n = 1{,}042$; 9.6%) and lung cancer ($n = 742$; 6.8%). There were 110 incident liver cancer cases (48 in the NHS, 5 in the NHS II, and 57 in the HPFS).

Baseline characteristics of the study participants according to the intake of white rice and brown rice are shown in Table 1. In men and women, Asian participants were more likely to have higher white rice intake. Ethnicity was not strongly associated with brown rice intake. Participants with higher intake of white rice and brown rice were less likely to consume total saturated fats. However, higher brown rice consumption in general was expectedly associated with more health-conscious diet and lifestyles, including greater level of physical activity, less cigarette smoking, more use of multivitamin supplement, and higher intake of fruit, vegetables and whole grain.

As shown in Table 2, long-term total rice intake was not associated with risk of overall cancer incidence. Specifically, participants who ate at least five servings of total rice per week had a relative risk of 0.97 (95% CI 0.85–1.07; *p* for trend 0.37). Similarly, neither white rice intake (Table 3) nor brown rice intake (Table 4) was associated with overall cancer risk. For the same comparison, the multivariable RRs of overall cancer risk were 0.87 for white rice (95% CI 0.75–1.01; *p* for trend 0.17) and 1.07 for brown rice (95% CI 0.90–1.26; *p* for trend 0.97).

In terms of the specific cancer sites, total rice consumption was not associated with risk of prostate, colorectal, lung, kidney cancer in any of these cohorts separately or pooled analyses (Table 5). For bladder cancer, borderline significant positive associations were seen with intake of total rice in both NHS and HPFS (pooled RR = 1.32, 95% CI 0.99–1.76; *p* for trend 0.09). For prostate cancer, the results did not change materially after excluding participants diagnosed with organ-confined tumor (RR for total rice consumption ≥ 5 *vs.* <1 servings/wk: 1.06; 95% CI: 0.79–1.42; *p* for trend 0.76).

In the sensitivity analyses, we found similar results after restricting our analyses within European Americans, never smokers, applying 4 to 8 years lag in updating dietary intakes, or stratified analyses according to BMI (Supporting Information Table 1). In addition, rice consumption was not associated with risk of bladder cancer by smoking status or

Table 4. Risk of overall cancer according to brown rice intake in the HPFS, NHS I, and NHS II

Brown rice intake, no. of servings	< 1/week	1/week	2-4/week	≥ 5/week	*p* (trend)
NHS					
No. cases	14,107	798	707	61	
RR (95% CI)					
Model 1[1]	1 (ref)	0.99 (0.92–1.06)	0.95 (0.88–1.03)	0.98 (0.76–1.25)	0.25
Model 2[2]	1 (ref)	1.01 (0.94–1.09)	0.99 (0.92–1.07)	1.05 (0.82–1.36)	0.88
Model 3[3]	1 (ref)	1.02 (0.95–1.10)	1.00 (0.93–1.09)	1.07 (0.84–1.38)	0.69
NHS II					
No. cases	4,233	478	388	50	
RR (95% CI)					
Model 1[1]	1 (ref)	1.01 (0.92–1.11)	0.95 (0.85–1.05)	1.20 (0.91–1.59)	0.95
Model 2[2]	1 (ref)	1.01 (0.92–1.11)	0.93 (0.84–1.03)	1.22 (0.92–1.62)	0.88
Model 3[3]	1 (ref)	1.02 (0.93–1.13)	0.95 (0.85–1.06)	1.28 (0.96–1.70)	0.66
HPFS					
No. cases	8,886	999	856	92	
RR (95% CI)					
Model 1[1]	1 (ref)	0.98 (0.92–1.05)	0.95 (0.88–1.01)	0.86 (0.70–1.06)	0.04
Model 2[2]	1 (ref)	1.00 (0.93–1.06)	0.95 (0.89–1.04)	0.93 (0.75–1.14)	0.18
Model 3[3]	1 (ref)	1.00 (0.94–1.07)	0.96 (0.91–1.05)	0.95 (0.77–1.17)	0.36
Pooled results					
RR (95% CI)	1 (ref)	1.01 (0.97–1.06)	0.98 (0.94–1.03)	1.07 (0.90–1.26)	0.97
p heterogeneity		0.91	0.74	0.25	0.59

[1]Age-adjusted.
[2,3]Adjusted for the same sets of covariates as for model 2 and model 3 in Table 2.
Abbreviations: CI, confidence interval; HPFS, Health Professionals Follow-up Study; NHS, Nurses' Health Study.

breast cancer by menopausal status (Supporting Information Table 2). Moreover, the proportions of Asian population were 0.7% for the NHS, 1.6% for the NHS II, and 1.7% for the HPFS. Rice intake was not associated risk of cancer among Asians. Comparing participants who ate at least five servings/week with those of <1/week, the age-adjusted relative risk were 0.84 (95% CI 0.48–1.46) for total rice intake, 0.73 (95% CI 0.46–1.16) for white rice intake, and 1.35 (95% CI 0.50–3.60) for brown rice intake (all *p* values for heterogeneity by cohort >0.05). Lastly, results were essentially the same when we further adjusted for intake of total seafood, poultry, total saturated fat, and diabetes status (data not shown).

Discussion

During 18 to 26 years follow-up for over 280,000 US men and women, results from three prospective cohorts suggested the intakes of total rice, white rice or brown rice were not significantly associated with the risk of overall cancers. The null association remained among Asian and European American participants, never smokers, and after stratifying by BMI.

While arsenic and inorganic arsenic are carcinogenic to humans, it remains unknown whether arsenic associated with rice consumption increases risks of developing cancers. Hence, we conducted this first study to specifically address the question whether amounts of arsenic in rice are sufficient to see a detectable increase in cancer risk. Our study found no association between long-term rice consumption and overall cancer risk. To our knowledge, this study is the only analysis to date to assess the associations between the rice consumption and the risk of overall cancers. The age-adjusted null results were essentially similar to multivariable results. Additionally, the null results were observed in both genders and even among individuals with regular intake for decades. The highest category of rice intake in our study was at least five servings per week, which is approximately equivalent to 9.5 μg/day inorganic arsenic from white rice, or 20.1 μg/day from brown rice (1 serving = 1 cup ≈158 g cooked white rice or 195 g cooked brown rice[26]). These amounts of arsenic in our study were comparable with those based on the Consumer Reports, which have shown that the average inorganic arsenic level is 13.3 μg/cup in white rice and 28.2 μg/cup in brown rice[7]).

Compared with white rice, brown rice has low glycemic index and high contents of multiple nutrients, such as fiber, minerals, and vitamins. Hence, brown rice may favorably

Cancer Epidemiology

Table 5. Risk of specific sites of cancer according to total rice intake in the HPFS, NHS I, and NHS II

Total rice intake, no. of servings						
	No. cases	<1/week	1/week	2–4/week	≥5/week	*p* (trend)
Prostate						
HPFS	5,060	1 (ref)	1.03 (0.96–1.11)	1.00 (0.93–1.07)	1.02 (0.91–1.15)	0.86
Breast						
NHS	5,714	1 (ref)	0.97 (0.91–1.04)	1.00 (0.94–1.07)	1.03 (0.89–1.20)	0.64
NHS II	2,401	1 (ref)	0.91 (0.81–1.02)	0.95 (0.85,1.05)	0.80 (0.67–0.96)	0.04
Pooled		1 (ref)	0.95 (0.88–1.03)	0.99 (0.93–1.04)	0.90 (0.70–1.16)	0.48
Colorectal						
NHS	1,352	1 (ref)	1.02 (0.89–1.18)	1.02 (0.88–1.16)	0.99 (0.71–1.38)	0.96
HPFS	1,042	1 (ref)	0.98 (0.83–1.16)	1.09 (0.93–1.27)	0.88 (0.66–1.16)	0.51
Pooled		1 (ref)	1.01 (0.91–1.13)	1.04 (0.93–1.15)	0.91 (0.74–1.13)	0.57
Melanoma						
NHS	870	1 (ref)	1.14 (0.97–1.36)	1.00 (0.84–1.18)	0.92 (0.60–1.40)	0.63
NHS II	538	1 (ref)	0.94 (0.74–1.18)	0.90 (0.72–1.12)	0.93 (0.65–1.33)	0.59
HPFS	695	1 (ref)	0.88 (0.71–1.09)	1.00 (0.83–1.21)	0.71 (0.51–1.00)	0.1
Pooled		1 (ref)	0.99 (0.82–1.19)	0.96 (0.86–1.07)	0.81 (0.65–0.99)	0.06
Lung						
NHS	1,205	1 (ref)	1.00 (0.86–1.16)	0.92 (0.79–1.07)	0.87 (0.58–1.30)	0.26
HPFS	742	1 (ref)	0.88 (0.72–1.07)	0.90 (0.75–1.09)	0.87 (0.63–1.21)	0.35
Pooled		1 (ref)	0.96 (0.85–1.08)	0.91 (0.81–1.03)	0.87 (0.67–1.11)	0.15
Bladder						
NHS	357	1 (ref)	0.95 (0.70–1.26)	0.96 (0.74–1.25)	1.33 (0.74–2.37)	0.54
HPFS	592	1 (ref)	1.06 (0.85–1.32)	1.07 (0.87–1.32)	1.31 (0.94–1.83)	0.12
Pooled		1 (ref)	1.00 (0.84–1.19)	1.02 (0.87–1.20)	1.32 (0.99–1.76)	0.09
Kidney						
NHS	268	1 (ref)	1.37 (1.00–1.87)	1.15 (0.84–1.56)	1.20 (0.58–2.48)	0.52
HPFS	272	1 (ref)	0.95 (0.69–1.30)	0.87 (0.64–1.18)	0.73 (0.42–1.27)	0.24
Pooled		1 (ref)	1.15 (0.77–1.71)	1.02 (0.75–1.39)	0.90 (0.57–1.41)	0.85

All the models were adjusted for age (years), ethnicity (European Americans, Asian, African American, other), body mass index (calculated as weight in kilograms divided by height in meters squared; <21.0, 21.0–22.9, 23.0–24.9, 25.0–26.9, 27.0–29.9, 30.0–32.9, 33.0–34.9, or ≥35.0), smoking status (never smoked, past smokers, current smokers 1–14 cigarettes/day, 15–24 cigarettes/day, or ≥25 cigarettes/day), physical activity (MET-hours/week, in quintiles), family history of cancer (yes or no), multivitamin supplementation (yes or no), total energy intake (kilocalories/day, in quintiles), consumption of fruit, vegetables, red meat, fish, nuts, whole grain (except brown rice), sugar-sweetened beverage (all in quintiles). For women, postmenopausal hormone use (yes or no) was further adjusted for.
Abbreviations: CI, confidence interval; HPFS, Health Professionals Follow-up Study; NHS, Nurses' Health Study.

influence cancer risk *via* its antioxidant, anti-inflammatory and antimutagenic properties.[3–6] However, in contrast to our hypothesis, in the NHS II, we observed significant inverse associations between consumption of total rice and white rice (but not brown rice) and total cancer risk. These results appeared to be primarily driven by the inverse associations with breast cancer (47% of overall cancer) in this cohort. However, the only study on rice consumption and breast cancer we identified reported positive associations with white rice consumption and inverse associations with brown rice among postmenopausal women.[27] Nonetheless, these unexpected results may be due to chance, unmeasured confounding, or reflect unknown biology, which requires further investigation.

While primary exposure route of arsenic is from foods especially for people with limited exposure through drinking water,[28,29] we do not have information on contaminated areas. Nonetheless, in some regions with contamination, the ground water is the main source of inorganic arsenic.[30–32] In the southwestern region of Taiwan, with arsenic concentration in well water up to 1,000 μg/L, positive associations were reported for urinary tract cancer, skin cancer and lung cancer.[11,12,33] However, studies conducted in US where the level of arsenic in water is much lower (<100–200 μg/L), generally reported null results.[34–37]

With regard to cancer sites, our study did not observe a statistically significant association between rice consumption and risk of any each specific cancer. However, it worthwhile noting that we observed a borderline significant increased risk of bladder cancer comparing ≥5/week *vs.* <1 week of total rice intake (RR = 1.32, 95% CI: 0.99–1.76). While we did not directly measure arsenic in this study, bladder cancer is arguably the most susceptible cancer site to arsenic exposure although studies on bladder cancer and arsenic in low concentrations have been inconsistent.[38,39] Clearly, our observation of borderline significant associations between rice intake and bladder cancer risk warrants further investigation.

Strengths of our study include the large population, prospective design with decades of follow-up, repeated assessments of rice consumption, parallel analyses among men and women, and control for many risk factors for cancers. Limitations of this study merit consideration. First, our study did not directly measure arsenic levels in rice or other foods. Instead, this study addressed the specific question of whether the amounts of arsenic in rice are sufficient to see a detectable increase in cancer risk. We acknowledge that studies of arsenic are clearly desirable, but possibly require a biomarker. Considering growing evidence suggests that toenails provide an integration of arsenic exposure over time,[40–42] future studies measuring directly arsenic levels using toenail samples to study the relation with cancers will be informative. Second, measurement errors using SFFQs to assess rice intake exist. However, the correlations ($r \sim 0.5$) between the SFFQs and multiple 1-week dietary records suggested that rice consumption was reasonably assessed in current study. Thirdly, our results should be generalized to other population with caution because most of our study participants are of European origin. The rice products consumed by our European-American participants were much less than those eaten by Asian, Hispanic and Indian populations. In addition, we have no information on where the rice was produced in the US, and arsenic levels in rice may vary by place of production, rice cooking methods, and the quality of water used to cook rice. Fourthly, as with all observational studies, residual confounding by other factors cannot be totally excluded; however, the consistently observed null results in both men and women argued against missing strong associations. Lastly, while our sample sizes are large overall, we had limited power to examine the potential effect of rice consumption on certain cancer sites such as liver cancer with relatively low incidence in the US.

In summary, we did not find statistically significant associations between rice consumption and overall cancer risk in adult men or women. Future research to combine measuring levels of arsenic with amounts of rice consumption is warranted to better evaluate the effect of arsenic ingested from food on cancer risk.

Acknowledgements

The authors thank the participants and staff of the Nurses' Health Study and Nurses' Health Study II, and Health Professionals Follow-up Study, for their valuable contributions as well as the following state cancer registries for their help: AL, AZ, AR, CA, CO, CT, DE, FL, GA, ID, IL, IN, IA, KY, LA, ME, MD, MA, MI, NE, NH, NJ, NY, NC, ND, OH, OK, OR, PA, RI, SC, TN, TX, VA, WA, WY. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

References

1. World rice statistics. International Rice Research Institute, 1994. Available at: http://www.scribd.com/doc/119860372/RT-Vol-12-No-1-Rice-facts#fullscreen=1.
2. Batres-Marquez SP, Jensen HH, Upton J. Rice consumption in the United States: recent evidence from food consumption surveys. *J Am Diet Assoc* 2009; 109:1719–27.
3. Ardiansyah, Shirakawa H, Koseki T, et al. Rice bran fractions improve blood pressure, lipid profile, and glucose metabolism in stroke-prone spontaneously hypertensive rats. *J Agric Food Chem* 2006; 54:1914–20.
4. Hagiwara H, Seki T, Ariga T. The effect of pregerminated brown rice intake on blood glucose and PAI-1 levels in streptozotocin-induced diabetic rats. *Biosci Biotechnol Biochem* 2004; 68: 444–7.
5. Norhaizan ME, Ng SK, Norashareena MS, et al. Antioxidant and cytotoxicity effect of rice bran phytic acid as an anticancer agent on ovarian, breast and liver cancer cell lines. *Malaysian J Nutr* 2011; 17:367–75.
6. Verschoyle RD, Greaves P, Cai H, et al. Evaluation of the cancer chemopreventive efficacy of rice bran in genetic mouse models of breast, prostate and intestinal carcinogenesis. *Br J Cancer* 2007; 96:248–54.
7. Arsenic in your food. Consumer Reports Magazine, 2012. Available at: http://www.consumerreports.org/cro/magazine/2012/11/arsenic-in-your-food/index.htm.
8. Davis MA, Mackenzie TA, Cottingham KL, et al. Rice consumption and urinary arsenic concentrations in U.S. children. *Environ Health Perspect* 2012; 120:1418–24.
9. Gilbert-Diamond D, Cottingham KL, et al. Rice consumption contributes to arsenic exposure in US women. *Proc Natl Acad Sci USA* 2011; 108: 20656–60.
10. Cebrian ME, Albores A, Aguilar M, et al. Chronic arsenic poisoning in the north of Mexico. *Hum Toxicol* 1983; 2:121–33.
11. Chen CJ, Chen CW, Wu MM, et al. Cancer potential in liver, lung, bladder and kidney due to ingested inorganic arsenic in drinking water. *Br J Cancer* 1992; 66:888–92.
12. Chen CL, Chiou HY, Hsu LI, et al. Arsenic in drinking water and risk of urinary tract cancer: a follow-up study from northeastern Taiwan. *Cancer Epidemiol Biomarkers Prev* 2010; 19:101–10.
13. Hopenhayn-Rich C, Biggs ML Smith AH. Lung kidney cancer mortality associated with arsenic in drinking water in Cordoba, Argentina. *Int J Epidemiol* 1998; 27:561–9.
14. Tseng WP, Chu HM, How SW, et al. Prevalence of skin cancer in an endemic area of chronic arsenicism in Taiwan. *J Natl Cancer Inst* 1968; 40:453–63.
15. Belanger CF, Hennekens CH, Rosner B, et al. The nurses' health study. *Am J Nurs* 1978; 78: 1039–40.
16. Rimm EB, Stampfer MJ, Colditz GA, et al. Effectiveness of various mailing strategies among nonrespondents in a prospective cohort study. *Am J Epidemiol* 1990; 131:1068–71.
17. Wolf AM, Hunter DJ, Colditz GA, et al. Reproducibility and validity of a self-administered physical activity questionnaire. *Int J Epidemiol* 1994; 23:991–9.
18. Feskanich D, Rimm EB, Giovannucci EL, et al. Reproducibility and validity of food intake measurements from a semiquantitative food frequency questionnaire. *J Am Diet Assoc* 1993; 93: 790–6.
19. Rimm EB, Giovannucci EL, Stampfer MJ, et al. Reproducibility and validity of an expanded self-administered semiquantitative food frequency questionnaire among male health professionals. *Am J Epidemiol* 1992; 135:1114–26; discussion 27-36.
20. Salvini S, Hunter DJ, Sampson L, et al. Food-based validation of a dietary questionnaire: the

effects of week-to-week variation in food consumption. *Int J Epidemiol* 1989; 18:858–67.
21. Willett WC, Sampson L, Stampfer MJ, et al. Reproducibility and validity of a semiquantitative food frequency questionnaire. *Am J Epidemiol* 1985; 122:51–65.
22. WHO. International classification of diseases, 9th revision. Geneva: WHO, 1980.
23. Cox DR, Oakes D. Analysis of survival data, vol. viii. London: Chapman and Hall, 1984. 201 p.
24. Hu FB, Stampfer MJ, Rimm E, et al. Dietary fat and coronary heart disease: a comparison of approaches for adjusting for total energy intake and modeling repeated dietary measurements. *Am J Epidemiol* 1999; 149:531–40.
25. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002; 21:1539–58.
26. USDA National Nutrient Database for Standard Reference. U.S. Department of Agriculture, 2012. Available at: http://ndb.nal.usda.gov/ndb/foods/show/6456.
27. Yun SH, Kim K, Nam SJ, et al. The association of carbohydrate intake, glycemic load, glycemic index, and selected rice foods with breast cancer risk: a case-control study in South Korea. *Asia Pac J Clin Nutr* 2010; 19:383–92.
28. Jones FT. A broad view of arsenic. *Poult Sci* 2007; 86:2–14.
29. Petroczi A, Naughton DP. Mercury, cadmium and lead contamination in seafood: a comparative study to evaluate the usefulness of target hazard quotients. *Food Chem Toxicol* 2009; 47:298–302.
30. Chetia M, Chatterjee S, Banerjee S, et al. Groundwater arsenic contamination in Brahmaputra river basin: a water quality assessment in Golaghat (Assam), India. *Environ Monitor Assess* 2011; 173:371–85.
31. Liu CW, Wang SW, Jang CS, et al. Occurrence of arsenic in ground water in the Choushui River alluvial fan, Taiwan. *J Environ Qual* 2006; 35:68–75.
32. Paoloni JD, Sequeira ME, Esposito ME, et al. Arsenic in water resources of the southern Pampa Plains, Argentina. *J Environ Public Health* 2009; 2009:216470. doi: 10.1155/2009/216470.
33. Tseng WP. Effects and dose–response relationships of skin cancer and blackfoot disease with arsenic. *Environ Health Perspect* 1977; 19:109.
34. Berg JW, Burbank F. Correlations between carcinogenic trace metals in water supplies and cancer mortality. *Ann NY Acad Sci* 1972; 199:249–64.
35. Meliker JR, Slotnick MJ, AvRuskin GA, et al. Lifetime exposure to arsenic in drinking water and bladder cancer: a population-based case-control study in Michigan, USA. *Cancer Causes Control* 2010; 21:745–57.
36. Morton W, Starr G, Pohl D, et al. Skin cancer and water arsenic in Lane County, Oregon. *Cancer* 1976; 37:2523–32.
37. Mink PJ, Alexander DD, Barraj LM, et al. Low-level arsenic exposure in drinking water and bladder cancer: a review and meta-analysis. *Regul Toxicol Pharmacol* 2008; 52:299–310.
38. Steinmaus C, Yuan Y, Bates MN, et al. Case-control study of bladder cancer and drinking water arsenic in the western United States. *Am J Epidemiol* 2003; 158:1193–201.
39. Bates MN, Smith AH, Cantor KP. Case-control study of bladder cancer and arsenic in drinking water. *Am J Epidemiol* 1995; 141:523–30.
40. Davis MA, Li Z, Gilbert-Diamond D, et al. Infant toenails as a biomarker of in utero arsenic exposure. *J Expo Sci Environ Epidemiol* 2014; 24:467–73.
41. Schmitt MT, Schreinemachers D, Wu K, et al. Human nails as a biomarker of arsenic exposure from well water in Inner Mongolia: comparing atomic fluorescence spectrometry and neutron activation analysis. *Biomarkers* 2005; 10:95–104.
42. Adair BM, Hudgens EE, Schmitt MT, et al. Total arsenic concentrations in toenails quantified by two techniques provide a useful biomarker of chronic arsenic exposure in drinking water. *Environ Res* 2006; 101:213–20.