Published in final edited form as:

Cancer Causes Control. 2020 December ; 31(12): 1129–1140. doi:10.1007/s10552-020-01350-9.

Association of rice consumption with risk of cancer incidence in the California Teachers Study

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Abstract

Purpose: We evaluated the contribution of rice intake, a source of dietary arsenic, to cancer risk in a population of women with likely low arsenic exposure from drinking water and variable rice intake who participated in the California Teachers Study.

Methods: Rice consumption was categorized into quartiles (<9.6, 9.7-15.6, 15.7-42.7, and ≥42.8 g/day). Multivariable-adjusted hazard ratios and 95% confidence intervals (95%CI) for incident cancer were estimated comparing rice consumption categories with bladder, breast, kidney, lung, and pancreatic cancer, with progressive adjustment for age, total calories, BMI, race, smoking status, physical activity, and cancer-specific covariates.

Results: The number of breast, lung, pancreatic, bladder, and kidney cancer cases was 7,351; 1,100; 411; 344; and 238 respectively. The adjusted hazard ratios (95% CI) comparing the highest versus lowest rice intake quartiles were 1.07 (1.00 - 1.15); 0.87 (0.72 – 1.04); 0.95 (0.66 – 1.37); 1.11 (0.81 – 1.52) and 1.07 (0.72 – 1.59) for breast, lung, pancreatic, bladder, and kidney cancers respectively. Results were consistent when rice was modeled as a continuous variable and in analyses stratified by smoking status.

Conclusion: Rice consumption was not associated with risk of kidney, lung or pancreatic cancer, except maybe a small excess risk for breast cancer and a small non-significant excess risk for bladder cancer, comparing the highest versus lowest quartile of rice intake. Due to lower

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consumption patterns in this cohort, future studies should involve populations for which rice is a staple food and use of an arsenic biomarker.

Keywords

arsenic; rice; cancer incidence

Introduction

Inorganic arsenic is a human carcinogen for skin, liver, lung, bladder, kidney, and prostate cancers [1]: however, the evidence at low-exposure levels is limited and there is substantial uncertainty about the shape of the dose-response curve [2]. In populations exposed to low levels of arsenic in drinking water, like those in the US, diet is the primary route of arsenic exposure, via consuming foods with a high arsenic content, such as rice [3–5]. Participants who frequently consume rice have higher levels of urinary arsenic [3]. Participants in the Multi-Ethnic Study of Atherosclerosis (MESA) who consumed more than two servings of rice a week had 31% higher urinary arsenic compared to participants who never or rarely consumed rice [6]. In the National Health and Nutrition Examination Survey, participants, aged 25 to 80 years, who ate rice more than twice weekly had higher concentrations of urinary total arsenic compared to those who ate rice less than twice weekly; even after adjusting for demographic factors, seafood consumption and drinking water source, there was a statistically significant association between urinary total arsenic and rice consumption (OR (95% CI)= 1.51 (1.08 - 2.09)) [5]. Whether the consumption of foods high in arsenic, especially rice, increases the risk for some cancers, however, is unclear due to limited epidemiological data.

A qualitative risk assessment estimating cancer risk attributable to dietary arsenic found that dietary arsenic may lead to an increased risk for bladder, lung, and non-melanoma skin cancer [7]. A study to assess the relationship between rice consumption and risk for cancer development conducted in the Health Professionals Follow-up Study (HPFS), and Nurses' Health Study I and II (NHS I and NHS II), however, found no significant relationship between higher rice consumption and risk for prostate, breast, colon and rectum, bladder, kidney, and lung cancers, although few participants consumed rice daily [8].

In this study, we evaluated the contribution of rice intake, a major source of dietary arsenic, to cancer risk in a population of women with likely low arsenic exposure in drinking water and substantial variability in rice intake who participated in the California Teachers Study (CTS). Specifically, we assessed the association between rice consumption and incident bladder, breast, kidney, lung, and pancreatic cancer.

Methods

Study Population

The California Teachers Study, established in 1995-1996, is a prospective study of female public-school teachers or administrators who participated in the California State Teachers Retirement System [9]. The primary goal of the CTS was to examine the possible risk

factors related to breast and other cancers among female teachers in California [10]. At the time of enrollment, the participants were active in the school system, were retired or had left the school system within the past 6 years [10]. A total of 133,477 females completed and returned the questionnaires. Within the population of 133,477, women were excluded if they resided outside of California at baseline (n = 8,851), if they had a history of cancer at baseline (n = 13,663), only consented to participate in breast cancer research (n = 18), or had unusable data (n = 4), bringing the total number of eligible participants to 110,941.

Although arsenic is not a known breast cancer carcinogen, we included breast cancer in our analysis as it is the most commonly diagnosed cancer in the CTS. As information on non-melanoma skin cancer was not reported in cancer registries, we limited our investigation to bladder, kidney, lung, prostate, and breast cancers.

Exclusions

Out of the 110,941 eligible participants, we further excluded participants missing data on rice consumption (n = 8,643), body mass index (BMI) (n = 3,649), total caloric intake (n = 1,734), race/ethnicity (n = 695), physical activity (n = 377) and smoking status (n = 99), bringing the total number of included participants to 95,744 (Figure 1). For our cancer-specific adjustment analysis (model 3), we further excluded participants if they had missing data on the additional adjustment variables. For breast cancer, participants with missing data on pregnancy history (n = 938) or missing total years of oral contraceptive use (n = 4,086) were excluded; (n = 5,024, 391 breast cancer cases excluded). For bladder cancer, participants with missing data on smoking pack-years (n = 2,612) or nonsteroidal anti-inflammatory drugs (NSAIDs) use (n = 1,590) were excluded; (n = 4,202, 16 bladder cancer cases excluded). For kidney, lung, and pancreatic cancer, participants with missing data on smoking pack-years were excluded; (n = 2,612 with missing pack-year data excluded, including 6 kidney cancer cases, 40 lung cancer cases; 10 pancreatic cancer cases and 6 pancreatic adenocarcinomas cases excluded).

Exposure Assessment

Rice consumption data was assessed at baseline by food frequency questionnaire using an early version of the food-item Block95 questionnaire [11] with the addition of a few phytoestrogen-rich foods, for a total of 113 food and beverage items/groups [12]. Participants were asked “in the past year, how often do you eat rice or rice dishes?”. Frequency of consumption (never or <l/month, 1/month, 2-3/month, 1/week, 2/week, 3-4/week, 5-6/week, every day, or 2+/day) and usual portion size (small, medium, large, or extra-large relative to a given standard medium (0.75 cup cooked rice) portion) were recorded [12]. The USDA defines the standard serving size for cooked rice is 0.5 cup or 79g [13] and in this population, we estimated rice consumption in g cooked rice/day based on frequency of consumption and portion size. Rice consumption was examined both as a continuous variable (per 10 g/day of rice increase) and by quartiles: <9.6 g/day, 9.7-15.6 g/day, 15.7-42.7 g/day, and ≥42.8 g/day.

Outcome Assessment

CTS investigators have been continuously conducting follow-up and collecting data on cancer and other health outcomes of all the participants, as previously described [10, 14, 15]. Briefly, incident cancer cases are identified via linkage with the California Cancer Registry and mortality outcomes are identified via linkage with the California Automated Mortality Linkage System, the Social Security Administration Death Master File, and the National Death Index [14]. CTS receives additional data on updated addresses, health status, non-cancer outcomes and surgical procedures from the California Office of Statewide Health Planning and Development (OSF1PD) [14, 15]. The California Cancer Registry is a population-based statewide cancer registration system that is modeled after the Surveillance, Epidemiology, and End Results (SEER) program [9] and incident cancer cases are identified through SEER and ICD-O codes. Information is also obtained regarding the characteristics of the tumor, including site and stage, in-situ or invasive, and estrogen receptor status for breast cancer [9, 16, 17]. The SEER/ICD-O codes for cause of death are as follows: bladder cancer (29010, C670-C679); breast cancer (2600/C500-C509); kidney cancer (29020/C649, C659); lung cancer (22030/C340-C349); and pancreatic cancer (21100/C250-C259). Among pancreatic cancer cases, we used the ICD-O-3 histology codes 8140–8149, 8160–8169, 8180–8229, 8250–8509, 8520–8560, and 8570–8579 to classify pancreatic adenocarcinomas.

Follow-up extended from the date of the baseline examination until the date of cancer diagnosis, the date of death, the date moved out of California, or December 31, 2015, whichever occurred first. For breast cancer models, women who underwent bilateral mastectomy were also censored at time of mastectomy (50 bilateral mastectomy cases were performed on participants from 1991 to 2015).

Other variables

Self-reported information on age, race/ethnicity, smoking history (smoking status and smoking pack-years), menopausal status, height, weight, alcohol intake, physical activity levels (strenuous, moderate or other physical activity), total daily caloric intake, total calories from fat, pregnancy status, number of years of oral contraceptive use, and hormone therapy use was obtained from a baseline questionnaire. Bilateral mastectomy surgeries were identified through annual linkages with the California Office of Statewide Health Planning and Development.

Statistical Analysis

Descriptive statistics were used to describe characteristics of the study population by quartiles of rice intake. Multivariable-adjusted hazard ratios and 95% confidence intervals for incident cancer were estimated using Cox-proportional hazard models comparing rice consumption quartiles for bladder, breast, kidney, lung and pancreatic (only adenocarcinomas) cancer. Three different models were run for each cancer type. Model 1, the minimally adjusted model, was adjusted for age (years, continuous) and total caloric intake (kcal, continuous). Model 2, was further adjusted for variables that are commonly associated with increased cancer risk including BMI (kg/m^2, continuous), race/ethnicity, smoking status (never, former, current) and physical activity levels (hrs/wk, continuous).

Model 3 was different for each cancer type as this model further adjusted for cancer-specific variables. Covariates chosen for Model 3 analyses were based on strong evidence of risk factors for these cancers [18]. For bladder cancer, model 3 was further adjusted for smoking pack-years and NSAIDs use (intermittent to <1yr, 1-2yrs, 3-4 yrs, 5-9 yrs, 10+ yrs) [19, 20]. For breast cancer, model 3 was further adjusted for alcohol use (never, <20g/day, ≥20 g/day), height (in, continuous), pregnancy history (parous, nulliparous), years of oral contraceptive use (no use, <1, 1-2, 2-4, 5-9, 10-14, 15-19, 20-24, 25+), estrogen receptor (ER) status (ER +, ER−), and a combination of menopause and menopausal hormone therapy (MHT) (pre-menopausal, post-menopausal and no MHT, post- menopausal and past MHT, post-menopausal and current estrogen, post-menopausal and current estrogen & progestin, other) [21]. For kidney cancer, model 3 was further adjusted for smoking pack-years (continuous), height (in, continuous), and percent of calories from fat (continuous) [22]. For lung cancer, model 3 was further adjusted for smoking pack-years (continuous) and alcohol use (never, <20 g/day, ≥20 g/day never, <20 g/day, ≥20 g/day) [23, 24]. Lastly, for pancreatic cancer, model 3 was further adjusted for smoking pack-years (continuous), height (in, continuous), percent of calories from fat (continuous) and alcohol use (never, <20 g/day, ≥20 g/day) [25]. A p-trend analysis was conducted to test for significant differences in the outcomes of interest amongst groups of rice consumers by modeling quartiles of rice intake as a continuous variable and assessing the Wald test.

In sensitivity analyses, we conducted analyses for each of the 5 cancers studied stratified by smoking status using model 3 adjustments. For lung cancer and breast cancer, we stratified by age (<50, ≥50 years). For breast cancer, we further stratified by pregnancy status (never, ever) and menopausal status (pre, post). To test for multiplicative interaction, terms for rice intake, the stratification variable and their cross-product term, were included in the model. The coefficient for the cross-product term was evaluated for statistical significance by the Wald test. For breast cancer, we ran separate analyses for hormone receptor status (ER+, ER −), among cases with known ER status. To test whether the exposure-disease associations differed by ER status, we used the contrast test method. For pancreatic cancer, we ran analyses restricted to pancreatic adenocarcinomas. SAS software (Version 9.4) was used for all analyses. All statistical tests were based on a two-sided p-value. Tests with p-values <0.05 were considered statistically significant.

Results

After exclusions, 95,744 women were included in our analyses (Figure 1). Overall, 7,353 participants developed breast cancer, 1,100 developed lung cancer, 411 pancreatic cancer, 344 bladder cancer and 238 developed kidney cancer (Table 1). Of the 411 pancreatic cancer cases, 264 were adenocarcinomas. Table 1 provides characteristics of the study population per quartile of rice consumption. The median rice consumption was 15.7 g/day. Participants with higher rice intake were more likely to be younger, have a higher total caloric intake and higher BMI, were more likely to be physically activity and less likely to be white (Table 1). Height, smoking status, pack-years, alcohol intake, pregnancy history, and years of oral contraceptive use were similar across rice consumption categories.

Table 2 shows the results for the hazard ratios and 95% confidence intervals for rice intake and risk of five cancers. For bladder cancer, all models found a higher, albeit non-significant, cancer risk among participants with rice intake ≥42.8 g/day compared to those eating <9.6 g/day; (hazard ratio (95% CI) for model 3 was 1.11 (0.81, 1.52)). For breast cancer, there was a small excess significant cancer risk observed among participants who consumed ≥42.8 g/day compared to those consumed <9.6 g/day; (hazard ratio (95% CI) for model 3 was 1.07 (1.00, 1.15)). For other cancers, the associations were null or towards a weak non-statistically significant inverse association. The model 3 hazard ratios (95% CI) comparing participants with rice intake ≥42.8 vs. <9.6 g/day were 1.07 (0.72, 1.59) for kidney cancer, 0.87 (0.72, 1.04) for lung cancer, and 0.88 (0.65, 1.18) for pancreatic cancer (0.95 (0.66, 1.37) for pancreatic adenocarcinomas). A similar null association was found for all cancers when rice intake was modeled as continuous variable instead of as quartiles.

There was no evidence of effect modification by smoking status for any of the cancers evaluated except for kidney cancer (Table 3). A significant interaction was found between smoking status and kidney cancer, with never smokers showing a positive association between rice intake and kidney cancer and ever smokers showing an inverse association (p-interaction = 0.04) (Table 3). Similarly, there was no evidence of effect modification by age for the association between rice consumption and lung cancer (data not shown). Finally, for breast cancer there was no evidence of effect modification by prior pregnancy status, menopausal status, age, or estrogen receptor status (Table 4).

In a post-hoc power calculation, with 80% power and an alpha of 0.05 and a median survival time among participants in the lowest quartile of rice intake (<9.2 g/day) of 19.9 years, the minimum detectable difference comparing participants in the highest quartile of rice intake (≥42.8 g/day) to the lowest quartile of rice intake (<9.6 g/day) was 0.967 or 1.035.

Discussion

In this longitudinal study of female teachers in California, we found no association between rice intake, a marker of dietary arsenic exposure and lung, kidney, or pancreatic cancer risk. For breast cancer and bladder cancer, there was a small increased risk, which was statistically significant for breast cancer. To our knowledge, very few epidemiologic studies have examined the relationship between rice consumption and risk of site specific or total cancer. In the New Hampshire Skin Cancer Study, a case-control study among 487 skin cancer cases and 462 controls, participants who reported any rice consumption had higher urinary arsenic concentrations and also had higher odds of squamous cell carcinoma compared to those who did not consume rice, OR (95% CI) = 1.5 (1.1, 2.0) [3]. Alternatively, a previous study in the Health Professionals Follow-up Study and Nurses' Health Study similarly found no significant relationship between consumption of rice and risk for melanoma, and cancers of the prostate, breast, colon, and rectum, consistent with our results [8]. These consistent non-significant results could indicate that there is truly no association between rice intake and cancer, or results could be attributed to the inclusion of similar US populations, characterized by predominantly white participants and relatively low rice intake.

In a study of 229 pregnant women in the US , consumption of 0.56 cups of cooked rice per day was comparable to drinking 1 L/day of 10 μg arsenic/L water [26] based on measurement of total arsenic; given the median intake of rice among rice consumers in this study was about 0.5 cups/day (or 79g) of cooked rice, 50% of women had levels of arsenic exposure at the current US maximum contaminant limit [27]. In our study population, the median rice intake was 15.7 g cooked rice/day and our highest quartile of exposure (rice intake ≥42.8 g/day) was approximately half of the standard serving size of 79g, indicating that both rice intake and arsenic exposure in our study population are likely very low compared to other ethnic groups.

In our study population, Asians/Pacific Islanders consumed a median of 62.3 g of rice/day, suggesting that certain ethnic groups in the United States population are likely exposed to high levels of arsenic through rice consumption [26]. In the Multiethnic Cohort study based in Hawaii and Los Angeles, Native Hawaiians, Japanese Americans and Latino Mexicans consumed up to 37% more rice compared to Caucasians [28]. Data from the 2001-2002 National Health and Nutrition Examination Survey (ISTHANES) showed that only 14% of the total population who consumed ≥0.25 cup of white or brown rice per day were non-Hispanic White [29]. Similarly, NHANES data from 2003-2006 indicated that while only 17.7% of non-Hispanic Whites consumed rice more than twice weekly, 63.5% of Hispanics, non-Hispanic Blacks and adults of other races/ethnicities consumed rice more than twice weekly [5]. In our data, consumers of higher amounts of rice were more likely to be Asians/Pacific Islanders, however, Asians/Pacific Islanders only represented 3.4% of CTS participants at the time of enrollment (Table 1). While the demographics of our study sample adequately reflects the demographics of California teachers in the mid-1990s, due to the smaller numbers of individuals who are in race/ethnic groups besides non-Hispanic Whites, we were unable to assess differences by race/ethnic groups.

The only cancers for which we found a possible increased risk were bladder cancer and breast cancer. A systematic review and meta-analysis of the 28 published studies on the association between water arsenic and bladder cancer risk found that arsenic, even at low levels (10μg/L) almost doubles the risk of bladder cancer [30]. Furthermore, a recent study from a case-control study on bladder cancer found that in the presence of elevated levels of arsenic in water, brown rice consumption may increase the risk of bladder cancer [31]. The study found a significant interaction between water arsenic and brown rice consumption, concluding that while there was no clear evidence that rice contributes to overall bladder cancer incidence, the interaction between rice consumption and elevated water arsenic should be further studied [31].

For breast cancer, we found a small, significant increased risk in both the main analysis and in stratified analyses. The evidence on the relationship between arsenic and breast cancer is ambiguous. In the Strong Heart Study, which measured baseline urinary arsenic [32], in the Sisters Study, which measured toenail arsenic in disease-discordant sister pairs [33], and in the Nurses' Health Study, which measured baseline toenail arsenic in a nested case-control design [34], arsenic biomarkers were not associated with breast cancer risk. Our findings on rice and breast cancer risk, together with these null findings for arsenic biomarkers and breast cancer, are inconsistent with a previous study conducted in Northern Chile that found

extremely high exposure to arsenic in drinking water between 1958 and 1970 was associated with lower breast cancer mortality rates; women who were exposed to high levels of arsenic in drinking water (>200 μg/L) experienced around a 70% reduction in breast cancer mortality compared to women from areas of Chile with low water arsenic [35]. Our findings on rice and breast cancer risk, however, are consistent with a case-control study in Mexico [36] and a longitudinal cohort study in Poland [37] which found that participants with higher urinary and blood arsenic levels, respectively, was associated with increased breast cancer risk. In another study from the California Teachers Study, ambient inorganic arsenic exposure was marginally associated with elevated risks for hormone receptor-negative breast tumors [38]. While the mechanism through which arsenic increases the risk of breast cancer is unknown, arsenic may influence the development of cancer by disrupting estrogen receptor function or through oxidative DNA damaged induced by arsenic exposure [39].

Following a 2009 report by the European Food Safety Authority (EFSA), in 2016 the European Commission started to enforce maximum limits for inorganic arsenic in rice and some rice products [40, 41]. The implementation of this regulation, however, is challenging, as more food consumption data from different European countries are needed to further decrease uncertainties associated with dietary arsenic exposure estimates [42]. Further, increasing evidence suggests that differing maximum levels for different rice-based products, such as parboiled rice versus polished rice, may need to be reassessed [41]. Alternatively in the US, agencies only have regulations for arsenic in drinking water, but not for rice [43]. Since there are no standard regulations in the US, rice that is contaminated with high levels of arsenic may find its way into the US market [43]. An analysis measuring arsenic levels in different types of rice found that inorganic arsenic content ranged from 1.2 to 11 μg per serving (based on 45 g dry weight per serving) [44]. A study from the USFDA reported in 165 rice products arsenic concentrations ranged from <4 μg arsenic/kg to 723 μg arsenic/kg. Thus, if rice is frequently consumed, it is possible that rice intake may be a substantial source of arsenic exposure [43]. In this study, we are unable to account for this variation in arsenic exposure in different types of rice.

A major limitation of this analysis is that we did not have a direct measurement of arsenic levels and arsenic species in consumed rice. Using rice as a marker of overall arsenic exposure does not allow us to consider the different species in rice and how an individual's ability to metabolize arsenic affects toxicity. Further, the cooking method [45, 46], rice variety [47, 48], and rice origin [48], are major determinants of the final arsenic level in cooked rice, with all three influencing inorganic and organic arsenicals (including methylarsonate and dimethylarsinate) levels in cooked rice. Using the frequency of intake without measuring arsenic levels in rice or in biomarkers may have led to non-differential exposure misclassification in our study, biasing the associations towards the null. A positive association between rice consumption and urinary arsenic has been noted in several other studies in the US [3, 6, 26, 49–51] and elsewhere [52, 53], strongly indicating that rice consumption contributes to arsenic exposure.

We were also unable to measure urinary arsenic and we did not have information on arsenic levels in drinking water. While arsenic naturally occurs at higher levels in groundwater in

some parts of California, women drinking from EPA-compliant public drinking water sources would be exposed to low levels of water arsenic [54].

The null findings between rice intake and cancer outcomes in this study could reflect measurement error and that a single food frequency questionnaire may not capture chronic rice intake over time, as well as overall low-level dietary arsenic exposure. The FFQ did not ask about rice consumption over the lifecourse, nor were questions asked about potential rice-based products. Arsenic biomarkers, like urinary arsenic, should be used in populations with low-level dietary arsenic exposure. Future studies should include measures of both water arsenic and multiple sources of dietary arsenic to fully capture arsenic exposure. Further, studies in populations where rice is a staple food are also warranted. Rice is a staple food for billions of people all over the world, with the highest consumers in the most populous geographic regions, such as China, India, Indonesia and Bangladesh [55]. Furthermore, for populations with drinking water arsenic levels below 10 μg/L, dietary exposure contributed 54% to 85% of inorganic arsenic exposure, while for populations with higher exposure to arsenic via drinking water, dietary exposure still contributed 30% [56], suggesting that rice consumption may be an important source of exposure to inorganic arsenic for many populations.

Conclusions

We found no association between rice consumption and risk of lung, kidney, and pancreatic cancer, although we cannot exclude an excess risk for bladder cancer and breast cancer. The number of cancer cases in the highest rice consumption category (4th quartile of rice consumption) was small and may have limited our ability to assess the long-term cancer impact of frequent rice consumption. Studies in populations with more variability in rice consumption, including larger sample sizes among frequent rice consumers are warranted.

Acknowledgements

The California Teachers Study and the research reported in this publication were supported by the National Cancer Institute of the National Institutes of Health under award number U01-CA199277; P30-CA033572; P30-CA023100; UM1-CA164917; and. R01-CA077398. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Cancer Institute or the National Institutes of Health. Drs. Sanchez, Klu, Genkinger, and Navas-Acien were supported by grant award number P42-ES010349; P30-ES009089; and R01-ES028758.

The collection of cancer incidence data used in the California Teachers Study was supported by the California Department of Public Health pursuant to California Health and Safety Code Section 103885; Centers for Disease Control and Prevention's National Program of Cancer Registries, under cooperative agreement 5NU58DP006344; the National Cancer Institute's Surveillance, Epidemiology and End Results Program under contract HHSN261201800032I awarded to the University of California, San Francisco, contract HHSN261201800015I awarded to the University of Southern California, and contract HHSN261201800009I awarded to the Public Health Institute. The opinions, findings, and conclusions expressed herein are those of the author(s) and do not necessarily reflect the official views of the State of California, Department of Public Health, the National Cancer Institute, the National Institutes of Health, the Centers for Disease Control and Prevention or their Contractors and Subcontractors, or the Regents of the University of California, or any of its programs. The authors would like to thank the California Teachers Study Steering Committee that is responsible for the formation and maintenance of the Study within which this research was conducted. A full list of California Teachers Study team members is available at https://www.calteachersstudy.org/team.

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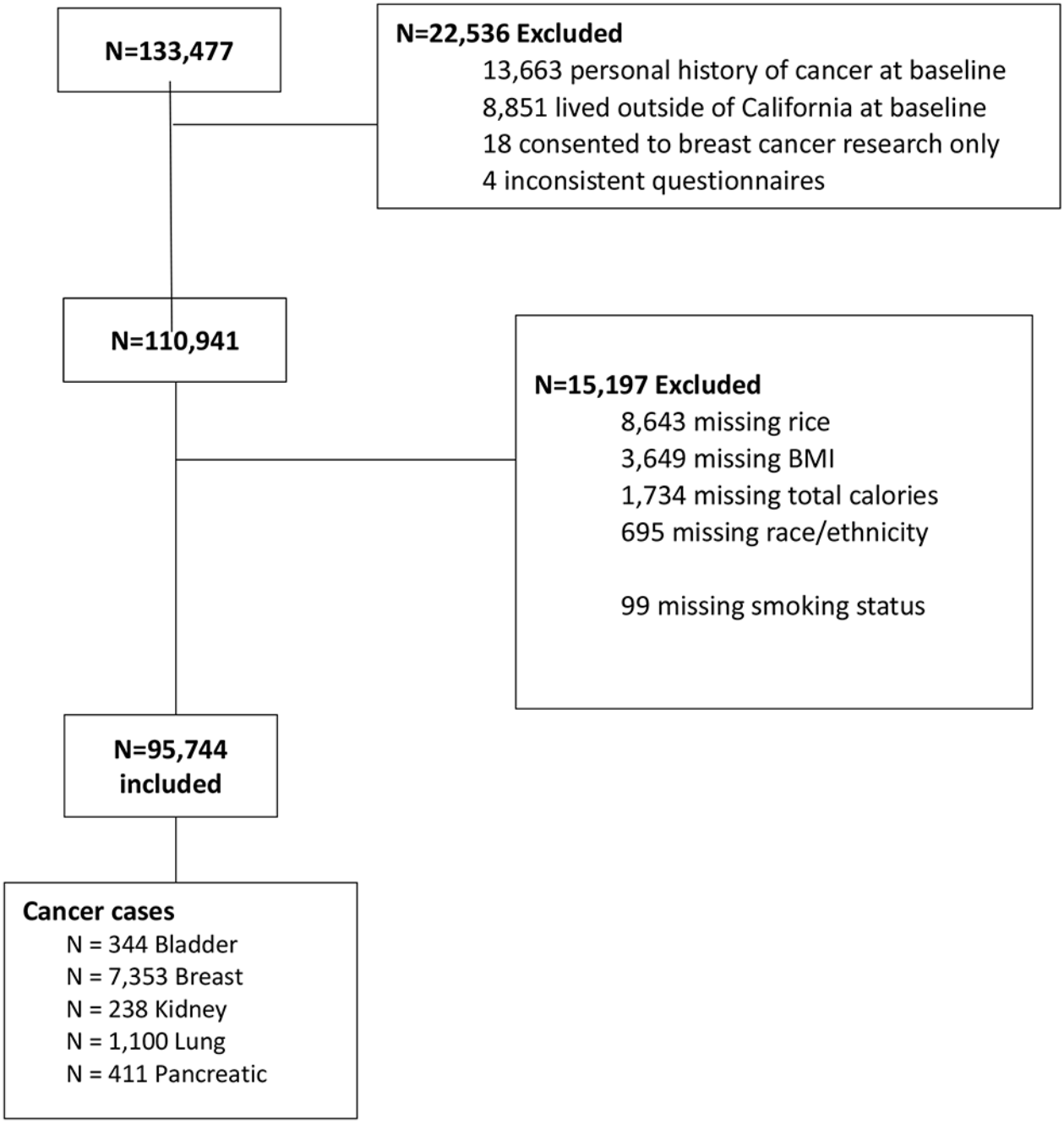

Figure 1.
Flowchart of included CTS participants

Table 1.

Participant characteristics at baseline by rice consumption quartile. Data presented as n (%) or median (IQR).

	Rice Consumption			
	Q1: <9.6 g/day	**Q2: 9.7-15.6 g/day**	**Q3: 15.7-42.7 g/day**	**Q4: ≥42.8 g/day**
	N=30,450	N=18,657	N=23,273	N=23,364
Age (yrs)	53 (45, 65)	50 (43, 61)	49 (42, 58)	48 (40, 56)
Height (in)	65 (63, 66)	65 (63, 66)	65 (63, 67)	65 (63, 67)
Weight (lbs)	140 (125, 160)	140 (126, 160)	140 (127, 165)	140 (125, 165)
BMI (kg/m^2)	23.5 (21.2, 26.7)	23.5 (21.3, 26.7)	23.6 (21.3, 27.5)	23.7 (21.5, 27.5)
Race				
White	27,945 (92)	17,142 (92)	20,621(89)	18,045 (77)
Hispanic	981 (3)	633 (3)	1,1071 (5)	1,510 (7)
Black	776 (2)	366 (2)	569 (2)	744 (3)
Native American	261 (1)	124 (1)	138 (<1)	181 (1)
Others/Mixed Race	262 (1)	181 (1)	268 (1)	461 (2)
Asian/Pacific Island	225 (1)	211 (1)	606 (3)	2,423 (10)
Smoking Status				
Never	19,921 (65)	12,440 (67)	15,679 (67)	16,123 (69)
Former	8,712(29)	5,334 (29)	6,553 (28)	6,258 (27)
Current	1,817 (6)	883 (5)	1,041 (5)	983 (4)
Pack Years[a]	10 (3, 25)	8 (2, 21)	7 (2, 20)	7 (2, 18)
Total Calories (kcal)	1325 (1050, 1651)	1473 (1188, 1803)	1610 (1306, 1953)	1781 (1429, 2202)
% Calories from Fat	32 (26, 38)	32 (27, 37)	32 (27, 37)	31 (26, 36)
Alcohol Consumption				
None	10365 (34)	5612 (30)	7226 (31)	8486 (36)
<20 g/day	17361 (57)	11445 (61)	14148 (61)	13,196 (56)
>20 g/day	2724 (9)	1600 (9)	1899 (8)	1682 (7)
Ever pregnant[b]	23235 (77)	15,096 (82)	18,654 (81)	18,344 (79)
Years oral contraceptive use				
No use	10860 (38)	5286 (30)	6075 (28)	5903 (27)
< 1	2139 (7)	1444 (8)	1736 (8)	1992 (9)
1-2	2833 (10)	1911 (11)	2679 (12)	2696 (12)
3-4	3227 (11)	2376 (13)	3091 (14)	3038 (14)
5-9	5605 (20)	4066 (23)	5183 (23)	5120 (23)
10-14	2830 (10)	1877 (11)	2334 (11)	2454 (11)
15-19	918 (3)	560 (3)	727 (3)	679 (3)
20-24	318 (1)	184 (1)	263 (1)	217 (1)
25 +	101 (<1)	45 (<1)	54 (<1)	65 (<1)
Menopause/MHT				
Pre-menopausal	10589 (35)	7963 (43)	10902 (47)	12083 (52)
Post-menopausal, no MHT	4074 (13)	1894 (10)	2193 (10)	2072 (9)

	Rice Consumption			
	Q1: <9.6 g/day	**Q2: 9.7-15.6 g/day**	**Q3: 15.7-42.7 g/day**	**Q4: ≥42.8 g/day**
Post-menopausal, past MHT	2293 (8)	1130 (6)	1224 (5)	1149 (5)
Post-menopausal, current estrogen	4545 (15)	2365 (13)	2636 (11)	2315 (10)
Post-menopausal, current estrogen & progestin	4975 (16)	2822 (15)	3360 (14)	2898 (12)
Other	3976 (13)	2483 (13)	2957 (13)	2847 (12)
Incident cancer				
Bladder	135 (0.44)	59 (0.31)	73 (0.31)	77 (0.33)
Breast	2,404 (7.90)	1,475 (7.91)	1,733 (7.45)	1,739 (7.45)
Kidney	80 (0.26)	54 (0.29)	54 (0.23)	50 (0.21)
Lung	441 (1.45)	226 (1.21)	237 (1.02)	196 (0.84)
Pancreatic	166 (0.55)	82 (0.44)	91 (0.39)	72 (0.31)
Pancreatic (adenocarcinoma only)	104 (0.34)	45 (0.24)	64 (0.28)	51 (0.22)
Physical Activity (hr/wk)	3 (1, 6)	3 (2, 6)	4 (2, 6)	4 (2, 7)

[a] among ever smokers only;

[b] 938 participants missing ever pregnancy data

Standard serving size for rice (1/2 cup or 79 g (cooked) (USDA, 2012)

Table 2.

Hazard Ratios (95% CI) for risk of incident bladder, breast, kidney, lung, and pancreatic cancers by rice consumption quartiles

	Incident Cancer, HR (95% CI)				
	Overall adjustments			Cancer-specific adjustments	
	N cases/controls	Model 1	Model 2	N cases/controls	Model 3
Bladder					
Q1: <9.6 g/d	135/30,315	1.00 (ref)	1.00 (ref)	129/28,896	1.00 (ref)
Q2: 9.7-15.6 g/d	59/18,598	0.82 (0.60, 1.11)	0.82 (0.60, 1.12)	59/17,789	0.88 (0.65, 1.20)
Q3: 15.7-42.7 g/d	73/23,200	0.89 (0.67, 1.20)	0.90 (0.67, 1.21)	68/22,207	0.90 (0.66, 1.21)
Q4: ≥42.8 g/d	77/23,287	1.04 (0.77, 1.41)	1.11 (0.82, 1.51)	72/22,322	1.11 (0.81, 1.52)
p-trend		*0.5*	*0.3*		*0.5*
Continuous (10g/d)	344/95,400	0.98 (0.94, 1.02)	0.98 (0.94, 1.03)	328/91,214	0.98 (0.94, 1.02)
Breast					
Q1: <9.6 g/d	2,404/28,048	1.00 (ref)	1.00 (ref)	2,255/26,499	1.00 (ref)
Q2: 9.7-15.6 g/d	1,475/17,182	1.04 (0.97, 1.11)	1.04 (0.97, 1.11)	1,402/16,319	1.04 (0.98, 1.12)
Q3: 15.7-42.7 g/d	1,733/21,539	1.01 (0.94, 1.07)	1.01 (0.95, 1.08)	1,659/20,455	1.02 (0.96, 1.09)
Q4: ≥42.8 g/d	1,741/21,622	1.04 (0.98, 1.11)	1.06 (0.99, 1.13)	1,646/20,485	1.07 (1.00, 1.15)
p-trend		0.5	0.4		0.3
Continuous (10g/d)	7,353/88,391	1.01 (1.00, 1.02)	1.01 (1.00, 1.02)	6,962/83,758	1.01 (1.00, 1.02)
Kidney					
Q1: <9.6 g/d	80/30,370	1.00 (ref)	1.00 (ref)	80/29,484	1.00 (ref)
Q2: 9.7-15.6 g/d	54/18,603	1.20 (0.84, 1.69)	1.21 (0.86, 1.72)	50/18,087	1.16 (0.81, 1.66)
Q3: 15.7-42.7 g/d	54/23,219	1.02 (0.72, 1.46)	1.02 (0.72, 1.16)	53/22,593	1.05 (0.73, 1.51)
Q4: ≥42.8 g/d	50/23,314	1.01 (0.94, 1.47)	1.01 (0.69, 1.48)	49/22,736	1.07 (0.72, 1.59)
p-trend		0.9	0.9		0.7
Continuous (10g/d)	238/95,506	1.00 (0.94, 1.07)	1.00 (0.94, 1.07)	*232/92,900*	1.01 (0.95, 1.09)
Lung					
Q1: <9.6 g/d	441/30,009	1.00 (ref)	1.00 (ref)	427/29,137	1.00 (ref)
Q2: 9.7-15.6 g/d	226/18,430	0.97 (0.82, 1.14)	0.96 (0.82, 1.13)	218/17,918	1.06 (0.90, 1.25)
Q3: 15.7-42.7 g/d	237/23,036	0.90 (0.77, 1.06)	0.89 (0.76, 1.05)	227/22,419	0.96 (0.81, 1.13)
Q4: ≥42.8 g/d	196/23,168	0.83 (0.69, 0.99)	0.82 (0.68, 0.99)	188/22,597	0.87 (0.72, 1.04)
p-trend		*0.2*	*0.2*		*0.3*
Continuous (10g/d)	1,100/94,643	0.98 (0.95, 1.00)	0.98 (0.96, 1.00)	1,060/92,071	1.00 (0.98, 1.02)
Pancreatic					
Q1: <9.6 g/d	166/30,284	1.00 (ref)	1.00 (ref)	161/29,403	1.00 (ref)
Q2: 9.7-15.6 g/d	82/18,575	0.933 (0.71, 1.22)	0.94 (0.72, 1.22)	81/18,056	0.98 (0.75, 1.28)
Q3: 15.7-42.7 g/d	91/23,182	0.92 (0.71, 1.20)	0.91 (0.70, 1.19)	88/22,558	0.85 (0.72, 1.18)
Q4: ≥42.8 g/d	72/23,292	0.81 (0.60, 1.09)	0.78 (0.70, 1.06)	71/22,714	0.88 (0.65, 1.18)
p-trend		0.3	0.3		0.5
Continuous (10g/d)	411/95,333	0.98 (0.95, 1.02)	0.98 (0.94, 1.02)	401/92,731	0.99 (0.95, 1.03)
Pancreatic (adenocarcinoma)					

	Incident Cancer, HR (95% CI)				
	Overall adjustments			Cancer-specific adjustments	
	N cases/controls	Model 1	Model 2	N cases/controls	Model 3
Q1: <9.6 g/d	104/30,284	1.00 (ref)	1.00 (ref)	101/23,403	1.00 (ref)
Q2: 9.7-15.6 g/d	45/18,575	0.79 (0.56, 1.13)	0.79 (0.56, 1.13)	44/18,056	0.82 (0.56, 1.18)
Q3: 15.7-42.7 g/d	64/23,182	0.99 (0.71, 1.36)	0.96 (0.70, 1.33)	62/22,558	1.02 (0.73, 1.41)
Q4: ≥42.8 g/d	51/23,292	0.85 (0.60, 1.22)	0.79 (0.55, 1.15)	51/22,731	0.95 (0.66, 1.37)
p-trend		0.3	0.2		0.4
Continuous (10g/d)	264/95,333	0.98 (0.93, 1.02)	0.97 (0.93, 1.02)	258/92,731	0.98 (0.94, 1.03)

Model 1: Adjusted for age and total caloric intake

Model 2: Adjusted for age, total caloric intake, BMI, race, and physical activity

Model 3: Cancer-Specific Adjustment: **Bladder**: Model 2 further adjusted for pack-years and NSAIDS use ; **Breast**: Model 2 further adjusted for height, alcohol use, ever pregnant, years oral contraceptive use, combination menopause and hormone replacement therapy **Kidney**: Model 2 further adjusted for pack-years, % calories from fat, and height; **Lung**: Model 2 further adjusted for pack-years and alcohol use; **Pancreatic**: Model 2 further adjusted for pack-years, % calories from fat, height, and alcohol use

Table 3.

Hazard Ratios (95% CI) for risk of incident bladder, breast, kidney, lung, and pancreatic cancers by quartiles of rice intake stratified by smoking status

	Never Smokers		Ever Smokers		
	N cases/controls	*HR (95% CI)*	*N cases/controls*	*HR (95% CI)*	*p-interaction*
Bladder Cancer					
Q1: <9.6 g/d	65/19,487	1.00 (ref)	64/9,409	1.00 (ref)	*0.9*
Q2: 9.7-15.6 g/d	29/12,211	0.83 (0.54, 1.29)	30/5,578	0.93 (0.60, 1.44)	
Q3: 15.7-42.7 g/d	31/15,402	0.79 (0.51, 1.22)	37/6,805	1.01 (0.67, 1.53)	
Q4: ≥42.8 g/d	38/15,815	1.09 (0.71, 1.66)	34/6,507	1.12 (0.73, 1.73)	
Continuous (10g/d)	163/62,915	0.95 (0.90, 1.00)	165/28,299	1.02 (0.96, 1.08)	*0.1*
Breast Cancer					
Q1: <9.6 g/d	1,353/17,504	1.00 (ref)	902/8,995	1.00 (ref)	*0.3*
Q2: 9.7-15.6 g/d	876/10,958	1.07 (0.99, 1.17)	526/5,361	1.00 (0.90, 1.11)	
Q3: 15.7-42.7 g/d	1,031/13,879	1.04 (0.96, 1.13)	628/6,576	1.00 (0.90, 1.11)	
Q4: ≥42.8 g/d	1,015/14,259	1.04 (0.96, 1.14)	631/6,226	1.11 (1.00, 1.24)	
Continuous (10g/d)	4,275/56,600	1.01 (0.99, 1.02)	2,687/27,158	1.01 (1.00, 1.03)	*0.6*
Kidney Cancer					
Q1: <9.6 g/d	38/19,883	1.00 (ref)	42/10,487	1.00 (ref)	*0.04*
Q2: 9.7-15.6 g/d	29/12,411	1.41 (0.86, 2.29)	25/6,192	0.94 (0.56, 1.59)	
Q3: 15.7-42.7 g/d	39/15,640	1.61 (1.02, 2.55)	15/7,579	0.56 (0.29, 0.99)	
Q4: ≥42.8 g/d	31/16,092	1.37 (0.83, 2.28)	19/7,222	0.80 (0.45, 1.43)	
Continuous (10g/d)	137/64,026	1.06 (0.96, 1.17)	101/31,480	0.97 (0.88, 1.06)	*0.2*
Lung Cancer					
Q1: <9.6 g/d	127/19,794	1.00 (ref)	300/9,343	1.00 (ref)	*0.1*
Q2: 9.7-15.6 g/d	55/12,385	0.79 (0.57, 1.08)	163/5,533	1.20 (0.99, 1.45)	
Q3: 15.7-42.7 g/d	77/15,602	0.95 (0.71, 1.27)	150/6,817	0.96 (0.78, 1.17)	
Q4: ≥42.8 g/d	65/16,058	0.80 (0.58, 1.09)	123/6,539	0.90 (0.72, 1.12)	
Continuous (10g/d)	324/63,839	0.98 (0.94, 1.02)	736/28,232	1.01 (0.98, 1.03)	*0.3*
Pancreatic Cancer					
Q1: <9.6 g/d	99/19,822	1.00 (ref)	62/9,581	1.00 (ref)	*0.4*
Q2: 9.7-15.6 g/d	51/12,389	1.00 (0.71, 1.40)	30/5,667	0.94 (0.61, 1.46)	
Q3: 15.7-42.7 g/d	46/15,633	0.79 (0.55, 1.13)	42/6,925	1.16 (0.77, 1.72)	
Q4: ≥42.8 g/d	45/16,078	0.81 (0.55, 1.13)	26/6,636	0.84 (0.52, 1.34)	
Continuous (10g/d)	241/63,922	1.00 (0.95, 1.06)	160/2,8809	0.97 (0.92, 1.02)	*0.4*
Pancreatic Cancer (adenocarcinomas only)					
Q1: <9.6 g/d	59/19,822	1.00 (ref)	42/9,581	1.00 (ref)	*0.8*
Q2: 9.7-15.6 g/d	26/12,389	0.82 (0.52, 1.31)	18/5,667	0.81 (0.47, 1.41)	
Q3: 15.7-42.7 g/d	32/15,633	0.86 (0.56, 1.34)	30/6,925	1.16 (0.72, 1.87)	
Q4: ≥42.8 g/d	32/16,078	0.87 (0.54, 1.39)	19/6,636	0.83 (0.47, 1.46)	
Continuous (10g/d)	149/63,922	0.99 (0.93, 1.06)	109/28,809	0.97 (0.91, 1.04)	*0.7*

All models adjusted for age (yrs), total caloric intake (kcal), BMI (kg/m^2), race (White, Hispanic, Black, Native American, Others/Mixed Race, Asian/Pacific Islander), physical activity (hr/wk); **Bladder** cancer model further adjusted for pack-years and NSAIDS use; **Breast** cancer model further adjusted for height (in), alcohol use (never, <20g/day, ≥20 g/day), ever pregnant (yes, no), years oral contraceptive use (no use, <1, 1-2, 2-4, 5-9, 10-14, 15-19, 20-24, 25+), combination menopause and menopausal hormone therapy (MHT) (Pre-menopausal; Post-menopausal, no MHT; Post-menopausal, past MHT; Post-menopausal, current estrogen; Post-menopausal, current estrogen & progestin; other); **Kidney** cancer model further adjusted for pack-years, % calories from fat, and height (in); **Lung** cancer model further adjusted for pack-years and alcohol use (never, <20g/day, ≥20 g/day); **Pancreatic** cancer model further adjusted for pack-years, % calories from fat, height (in), and alcohol use (never, <20g/day, ≥20 g/day)

Table 4.

Hazard Ratios (95% CI) for risk of incident breast cancers stratified by pregnancy, menopausal status, age and hormone receptor status

	N cases/controls	**HR (95% CI)**	*N cases/controls*	**HR (95% CI)**	*p-interaction*
Pregnancy history	***Never Pregnant***		***Ever Pregnant***		
Q1: <9.6 g/d	514/6,066	1.00 (ref)	1,741/20,433	1.00 (ref)	*0.07*
Q2: 9.7-15.6 g/d	213/3,021	0.87 (0.74, 1.02)	1,189/13,298	1.09 (1.01, 1.17)	
Q3: 15.7-42.6 g/d	286/3,913	0.94 (0.81, 1.08)	1,373/16,542	1.05 (0.97, 1.13)	
Q4: ≥42.7 g/d	303/4,262	0.97 (0.84, 1.13)	1,343/16,223	1.10 (1.02, 1.19)	
Continuous (10g/d)	1,316/17,262	0.99 (0.97, 1.01)	5,646/66,496	1.01 (1.00, 1.03)	*0.1*
Menopausal status	***Pre-menopausal***		***Post-menopausal***		
Q1: <9.6 g/d	559/9,611	1.00 (ref)	1,696/16,888	1.00 (ref)	*0.3*
Q2: 9.7-15.6 g/d	405/7,266	0.96 (0.84, 1.09)	997/9,053	1.08 (1.00, 1.17)	
Q3: 15.7-42.6 g/d	579/9,927	1.01 (0.90, 1.13)	1,080/10,528	1.02 (0.95, 1.11)	
Q4: ≥42.7 g/d	619/10,933	1.00 (0.89, 1.13)	1,027/9,552	1.10 (1.02, 1.20)	
Continuous (10g/d)	2,162/37,737	1.00 (0.98, 1.02)	4,800/46,021	1.01 (1.00, 1.02)	*0.2*
Age	***<50 yrs***		***≥50 yrs***		
Q1: <9.6 g/d	616/10,646	1.00 (ref)	1,639/15,858	1.00 (ref)	*0.05*
Q2: 9.7-15.6 g/d	440/7,946	0.96 (0.85, 1.08)	962/8,373	1.08 (1.00, 1.17)	
Q3: 15.7-42.6 g/d	658/10,845	1.06 (0.94, 1.18)	1,001/9,610	0.99 (0.92, 1.08)	
Q4: ≥42.7 g/d	674/11,989	1.00 (0.90, 1.12)	971/8,496	1.11 (1.02, 1.21)	
Continuous (10g/d)	2,388/41,426	1.00 (0.98, 1.02)	4,574/42,332	1.01 (1.00, 1.02)	*0.2*
ER Status	***ER+ cases vs control***		***ER− cases vs control***		
Q1: <9.6 g/d	1,589/26,352	1.00 (ref)	261/26,352	1.00 (ref)	
Q2: 9.7-15.6 g/d	976/16,202	1.02 (0.95, 1.11)	154/16,202	0.98 (0.81, 1.20)	*0.7*[a]
Q3: 15.7-42.6 g/d	1,150/20,341	0.99 (0.92, 1.07)	221/20,341	1.14 (0.95, 1.37)	*0.1*[a]
Q4: ≥42.7 g/d	1,185/20,361	1.08 (0.99, 1.17)	189/20,361	1.04 (0.85, 1.27)	*0.5*[a]
Continuous (10g/d)	4,900/83,269	1.01 (1.00, 1.02)	825/83,269	1.01 (0.98, 1.04)	*0.9*[a]

Adjusted for age (yrs), total caloric intake (kcal), BMI (kg/m^2), race (White, Hispanic, Black, Native American, Others/Mixed Race, Asian/Pacific Islander), smoking status (never, former, current), physical activity (hr/wk), height (in), alcohol use (never, <20g/day, ≥20 g/day), ever pregnant (yes, no), years oral contraceptive use (no use, <1, 1-2, 2-4, 5-9, 10-14, 15-19, 20-24, 25+), combination menopause and menopausal hormone therapy (MHT) (Pre-menopausal; Post-menopausal, no MHT; Post-menopausal, past MHT; Post-menopausal, current estrogen; Post-menopausal, current estrogen & progestin; other)

[a] p-value from the contrast test