Published OnlineFirst June 11, 2019; DOI: 10.1158/1055-9965.EPI-18-1259

Research Article

Cancer Epidemiology, Biomarkers & Prevention

Dietary Acrylamide Intake and Risk of Esophageal, Gastric, and Colorectal Cancer: The Japan Public Health Center–Based Prospective Study

Rong Liu[1], Tomotaka Sobue[1], Tetsuhisa Kitamura[1], Yuri Kitamura[1], Junko Ishihara[2], Ayaka Kotemori[3], Ling Zha[1], Sayaka Ikeda[1], Norie Sawada[3], Motoki Iwasaki[3], and Shoichiro Tsugane[3] of the JPHC Study Group

Abstract

Background: Acrylamide has been classified as a probable human carcinogen based chiefly on laboratory evidence. However, the influence of dietary acrylamide intake on risk of esophageal, gastric, and colorectal cancer has not been extensively studied. We aimed to evaluate the association between dietary acrylamide intake and esophageal, gastric, and colorectal cancer using data from the Japan Public Health Center–based Prospective Study.

Methods: Our study included 87,628 participants who completed a food-frequency questionnaire at enrollment in 1990 and 1993. We used Cox proportional hazards regression models to estimate hazards ratios and 95% confidence intervals (CI) after adjusting for confounding factors.

Results: After 15.5, 15.3, and 15.3 mean years of follow-up for esophageal, gastric, and colorectal cancer, we identified and analyzed 391 esophageal, 2,218 gastric, and 2,470 colorectal cancer cases, respectively. Compared with the lowest quintile of acrylamide intake, the multivariate HR for the highest quintile was 0.86 (95% CI, 0.53–1.39; P_{trend} = 0.814), 0.84 (95% CI, 0.69–1.01; P_{trend} = 0.301), and 0.93 (95% CI, 0.79–1.08; P_{trend} = 0.165) for esophageal, gastric, and colorectal cancer, respectively, in the multivariable-adjusted model. Furthermore, no significant associations were observed when the participants were stratified by cancer subsites.

Conclusions: In conclusion, this study demonstrated that dietary acrylamide intake was not associated with increased risk of esophageal, gastric, or colorectal cancer among the Japanese population.

Impact: It is the first time to assess the effect of dietary acrylamide intake on risk of digestive system cancer in Asian populations.

Introduction

Acrylamide, an important industrial monomer, is widely used in the manufacture of water-soluble polymers used for water treating, paper, mining, and sugar processing (1–5). In 1994, acrylamide was classified as a probable human carcinogen (Group 2A) by the International Agency for Research on Cancer (IARC) based on laboratory studies (6). For a long time, specific occupations and smoking were thought to be the main sources of acrylamide exposure (Food Safety Commission of Japan. Evaluation document of dietary acrylamide produced by heating. Tokyo: Food Safety Commission of Japan **2016**; https://www.fsc.go.jp/osirase/acrylamide1.data/acrylamide_hyokasyo1.pdf). In 2002, Swedish investigators reported that acrylamide is formed in commonly consumed starchy foods cooked at high temperature (>120°C), suggesting that the meals are another main source of acrylamide (7). The carcinogenic effect of dietary acrylamide is considered to occur through a genotoxic pathway (8). Acrylamide has a small hydrophilic molecule and can reach every organ and tissue in the body. Therefore, theoretically, all tissues can be targets for carcinogenesis due to acrylamide. There are two metabolic pathways for acrylamide, a direct pathway of glutathione conjugation of acrylamide by GST, and a secondary pathway of glycidamide by cytochrome P450 and conjugation by GST. Both acrylamide and glycidamide are capable of combining with DNA and lead to genotoxicity (9).

The association between acrylamide exposure in occupational settings and risk of cancers has been extensively studied (1–5); however, the results do not support the conclusion that acrylamide is an occupational carcinogen. Meanwhile, epidemiologic studies conducted in Western countries have reported that dietary acrylamide is not associated with increased risk of most cancers. However, borderline associations with dietary acrylamide were observed for kidney cancer, and for endometrial and ovarian cancers in never smokers only (10).

Thus far, there are four (11–14), two (12, 15), and six studies (11, 12, 15–18) examining the relationship between

[1]Division of Environmental Medicine and Population Sciences, Department of Social and Environmental Medicine, Graduate School of Medicine, Osaka University, Suita, Osaka, Japan. [2]Department of Food and Life Science, Azabu University, Sagamihara, Kanagawa, Japan. [3]Epidemiology and Prevention Group, Center for Public Health Sciences, National Cancer Center, Tokyo, Japan.

Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

Corresponding Author: Tomotaka Sobue, Division of Environmental Medicine and Population Sciences, Department of Social and Environmental Medicine, Graduate School of Medicine, Osaka University, 2-2 Yamada-Oka, Suita, Osaka 565-0871, Japan. Phone: 816-6879-3920; Fax: 816-6879-3929; E-mail: tsobue@envi.med.osaka-u.ac.jp

Cancer Epidemiol Biomarkers Prev 2019;28:1461–8

doi: 10.1158/1055-9965.EPI-18-1259

Published OnlineFirst June 11, 2019; DOI: 10.1158/1055-9965.EPI-18-1259

dietary acrylamide exposure and esophageal, gastric, and colorectal cancer, respectively. However, these epidemiologic studies were all conducted in Western countries. To our knowledge, no study has assessed the effect of dietary acrylamide intake on the risk of esophageal, gastric, or colorectal cancer in Asian populations. In addition, the main sources of dietary acrylamide are coffee and green tea, followed by confectioneries, vegetables, and potatoes in Japan, whereas in Western countries, they are potato-based foods, wheat-based products, and coffee (19). Therefore, it is necessary to examine the influence of acrylamide intake on cancers in various countries with different dietary sources of the chemical. This study aimed to investigate the association between dietary acrylamide intake and risk of esophageal, gastric, and colorectal cancer among the Japanese population.

Materials and Methods

Study cohorts and participants

This study was based on the Japan Public Health Center-based Prospective Study (JPHC Study), whose design was previously reported in detail (20). The JPHC Study began in 1990 (Cohort I) and 1993 (Cohort II), covering 11 public health center areas throughout Japan and including 140,420 residents (68,722 men and 71,698 women) aged 40 to 69 years. The JPHC Study aimed to investigate the association between lifestyle and lifestyle diseases, providing evidence for prevention and control of cancer and cardiovascular disease. A self-administered lifestyle questionnaire was delivered to all participants. Vital status, mortality, migration, and incidence of cancer and cardiovascular disease were recorded for every participant. A follow-up survey that included the lifestyle questionnaire was conducted 5 years after the baseline survey and 5 years after each succeeding survey. Particularly, a dietary survey using a self-administered food frequency questionnaire (FFQ) was conducted at baseline and at 5- and 10-year follow-ups. The FFQ of the 5-year follow-up survey obtained more-detailed dietary information than that of the baseline survey since it included more food items and portion size options. Therefore, we used the 5-year follow-up survey as the starting point of our study.

Residents who were aged 40 and 50 years were asked to enroll Medical Examination conducted by the local health center of age-biased areas in 1990 and 1993. Then, the residents who took part in Medical Examination were included in JPHC study. Therefore, we excluded participants in age-biased cohort areas where the participants were aged 40 and 50 years when they received the baseline questionnaire. We also excluded participants who did not meet the follow-up criteria and did not respond to the 5-year follow-up survey (Fig. 1). A total of 94,816 participants completed the questionnaire.

Participants were also excluded from analysis if they had a history of esophageal, gastric, and colorectal cancer before the baseline survey ($n = 907$) or during the time from the baseline survey to the 5-year follow-up survey ($n = 579$), if they were lost to follow-up ($n = 37$), and if they did not provide complete dietary data (those whose total energy intake could not be calculated or who reported extremely low or high energy values; $n = 5{,}665$). Finally, a total of 87,628 subjects (40,732 men and 46,896 women) were eligible for analysis (Fig. 1).

This study was approved by the Institutional Review Boards of the National Cancer Center Japan, Osaka University, and Azabu University.

Assessment of acrylamide intake

The FFQ was used to estimate nutrient and food intake among the subjects of the JPHC Study. Information regarding the usual consumption of 147 food items during the previous year was collected (21). Food intake was categorized into nine frequencies (never, 1–3 times/month, 1–2 times/week, 3–4 times/week, 5–6 times/week, once/day, 2–3 times/day, 4–6 times/day, and $\geq$7 times/day). Portion sizes were specified in three categories (less than half the standard portion size, standard portion size, and >1.5 times the standard portion size). The FFQ was previously validated by comparing intake with 28-day weighted dietary records (DRs) as reference in a subcohort of the JPHC Study (21–23). Daily nutrient intake was calculated based on the Fifth Revised and Enlarged Edition of the Standard Tables of Food Composition in Japan (5th FCT; ref. 24).

Acrylamide intake was estimated using an acrylamide database (25) developed from measured values of acrylamide content in common Japanese foods reported elsewhere (26–30; Ministry of Agriculture, Forestry and Fisheries. Risk profile sheet relating to the food safety; for acrylamide. Ministry of Agriculture, Forestry and Fisheries 2015; http://www.maff.go.jp/j/syouan/seisaku/risk_analysis/priority/pdf/150807_rp_aa.pdf; National Institute for Environmental Studies, Japan. Study on statistical estimate of acrylamide intake from foods. National Institute for Environmental Studies, Japan 2015; http://www.fsc.go.jp/fsciis/technicalResearch/show/cho99920141408; National Institute of Health Sciences. Acrylamide analysis in food. 2016; http://www.mhlw.go.jp/topics/2002/11/tp1101-1a.html; Food Safety Commission of Japan. Study on estimate of acrylamide intake from food; interim report. Food Safety Commission of Japan 2016; https://www.fsc.go.jp/fsciis/technicalResearch/show/cho99920151507; Food Safety Commission of Japan. Information clearing sheet for acrylamide. Food Safety Commission of Japan 2016; https://www.fsc.go.jp/fsciis/attachedFile/download?retrievalId=kai20111222sfc&fileId=520). Briefly, first, acrylamide-containing foods were identified from the foods listed in the 5th FCT. Out of 1,878 food items in the 5th FCT, 282 food items were designated as acrylamide-containing foods, 1,276 were non-acrylamide–containing foods, and 320 were not classifiable. Furthermore, because the acrylamide concentration of the same food differed depending on the cooking method, 39 heated food items were added to the items. Therefore, there were 321 food items (17% of total food items) considered as acrylamide-containing foods for estimating DR-derived acrylamide intake (25). The development of the acrylamide database was finished by linking the food list and measured values of acrylamide content reported previously (26–30; Ministry of Agriculture, Forestry and Fisheries. Risk profile sheet relating to the food safety; for acrylamide. Ministry of Agriculture, Forestry and Fisheries 2015; http://www.maff.go.jp/j/syouan/seisaku/risk_analysis/priority/pdf/150807_rp_aa.pdf; National Institute for Environmental Studies, Japan. Study on statistical estimate of acrylamide intake from foods. National Institute for Environmental Studies, Japan 2015; http://www.fsc.go.jp/fsciis/technicalResearch/show/cho99920141408; National Institute of Health Sciences. Acrylamide analysis in food. 2016; http://www.mhlw.go.jp/topics/2002/11/tp1101-1a.html; Food Safety Commission of Japan. Study on estimate of acrylamide intake from food; interim report. Food Safety Commission of Japan 2016; https://www.fsc.go.jp/fsciis/technicalResearch/show/cho99920151507; Food Safety Commission of Japan. Information clearing sheet for

Published OnlineFirst June 11, 2019; DOI: 10.1158/1055-9965.EPI-18-1259

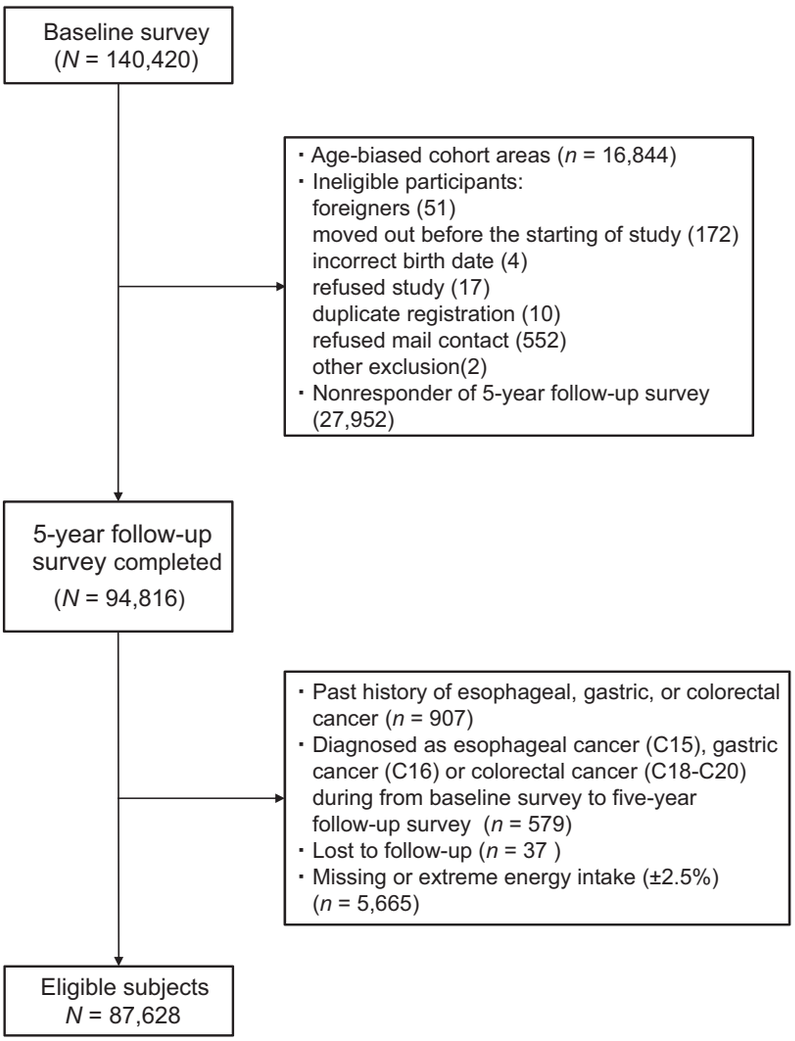

Figure 1.
Flow chart of study participants: JPHC Study. Figure 1 is a flow-chart describing the analysis sample of the JPHC Study ($N = 140,420$), exclusion criteria, and eligible analysis subjects ($N = 87,628$).

acrylamide. Food Safety Commission of Japan 2016; https://www.fsc.go.jp/fsciis/attachedFile/download?retrievalId=kai20111222sfc&fileId=520).

In the food list of the FFQ, 28 (19%) of 147 food items were also identified as acrylamide-containing foods. The amount of raw food intake is usually used for calculating most nutrient intakes in the FFQ; however, the amount of acrylamide present differs between cooking methods. Therefore, FFQ-derived acrylamide intake was calculated by considering cooking methods for following food items and using the proportion of these heated food calculated from the DR: starchy vegetables (potato, sweet potato), vegetables (onion, bean sprouts, sweet pepper, squash, cabbage, snap beans, broccoli), rice (toast, boiled, or stir-fried), and fried batter (Food Safety Commission of Japan. Study on estimate of acrylamide intake from food; interim report. Food Safety Commission of Japan 2016; https://www.fsc.go.jp/fsciis/technicalResearch/show/cho99920151507).
The Spearman's correlation coefficients for energy-adjusted dietary acrylamide intake between DRs and FFQ ranged from 0.34 to 0.48 (25).

Follow-up and identification of cancer cases

The subjects were followed from the start of the 5-year follow-up survey until December 31, 2013. Residential status was confirmed annually through the residential registry. During the study period, 4,991 subjects (5.7%) moved out of the study area and 14,714 (16.8%) died.

Cases were identified from major local hospitals through data linkage with population-based cancer registries. Because in some study areas the completion of the cancer registry was low, members of the JPHC research group checked the clinical records of major local hospitals in these areas and compiled active patient identification for cancers, including date of diagnosis, diagnostic method, diagnostic name, International Classification of Disease for Oncology Codes (Third Edition), histologic type, and histologic codes, among other data. Death certificates were used as a supplementary source of information. The endpoints of this analysis were incidences of esophageal, gastric, and colorectal cancer defined as the ICD-O-3 (International Classification of Diseases for Oncology, Third Edition) codes C15, C16, and C18-C20, respectively. Until the end of the follow-up period, 391

Published OnlineFirst June 11, 2019; DOI: 10.1158/1055-9965.EPI-18-1259

esophageal, 2,218 gastric, and 2,470 colorectal cancer cases were newly identified in the study population. Among 391 esophageal cancer cases, there were 20 adenocarcinomas (EAC, M8140, 8211, 8260, 8560), 305 squamous cell carcinomas (ESCC, M8070), and 66 unclassified cases. Among the 2,218 gastric cancer cases, 138 cardia gastric cancer cases (CGC, ICD-O-3 C16) and 2,080 non-cardia gastric cancer cases (NCGC, ICD-O-3 C16.1-C16.9) were identified. Of the 2470 colorectal cancers, there were 1,721 colon cancer cases (ICD-O-3 C18) and 749 rectal cancer cases (ICD-O-3 C19, C20).

Statistical analysis

Person-years of follow-up for each subject were calculated from the start of the 5-year follow-up survey to the date of diagnosis of esophageal or gastric or colorectal cancer, date of death from any cause, date of relocation from the study area, or end of follow-up (December 31, 2013), whichever came first. The mean follow-up period was 15.5 years for esophageal cancer, 15.3 years for gastric cancer, and 15.3 years for colorectal cancer.

Our study used the residual method to adjust acrylamide intake by energy intake. Subjects were divided into quintiles (i.e., Q1, Q2, Q3, Q4, and Q5 groups) according to energy-adjusted intakes of acrylamide. Cox proportional hazards models were used to estimate HRs and 95% confidence intervals (CI) to determine the association between quintiles of energy-adjusted dietary acrylamide intake and incidence of esophageal, gastric, or colorectal cancer, with Q1 as the reference group. Trends were assessed by assigning ordinal values for the quintiles of energy-adjusted acrylamide intake. Based on the 5-year follow-up survey, characteristics of dietary and non-dietary variables were compared between quintiles, Q1, Q2, Q3, Q4, and Q5 using the Kruskal–Wallis test or χ^2 test as appropriate.

The common (based on literature) potential confounders in multivariable-adjusted model were age (continuous), sex, area (10 public health center area), body mass index (<23.0, 23.0–24.9, 25.0–26.9, ≥27.0 kg/m^2, or missing), smoking status (never, former, current, or missing), pack years (<10.0, 10.0–19.9, 20.0–29.9, 30.0–39.9, ≥40.0, or missing), physical activity (continuous), alcohol intake (<150 or ≥150 g/week). The confounders that were energy-adjusted consumption of food and beverage (in grams per day, continuous) were different in multivariable-adjusted model according to type of cancer studied. Particularly, vegetables, fruits, and dairy were adjusted for esophageal cancer; vegetables, fruits, and salted fish, for gastric cancer; and vegetables, fruits, meat, and dairy, for colorectal cancer (see footnotes of Tables 2–4). In a sensitivity analysis, we excluded 53 esophageal, 332 gastric, and 292 colorectal cancer cases that were diagnosed in the first 3 years of follow-up. We also conducted an analysis that did not include esophageal, gastric, or colorectal carcinoma in situ. In addition, considering differences in risk factors between the subsites of cancers studied, we further performed stratified analyses for ESCC and EAC, CGC and NCGC, and colon and rectal cancer. Concerning esophageal cancer, obesity is a risk factor for EAC but not ESCC, while alcohol use is a risk factor for ESCC but not EAC (31). On the other hand, obesity is also a risk factor for CGC (32). Regarding colorectal cancer, physical activity is more strongly associated with colon cancer rather than rectal cancer (33). Therefore, risk factors in the

Table 1. Characteristics of participants (n = 87,628) for esophageal, gastric, and colorectal cancer analysis

	Quintiles of energy-adjusted acrylamide intake					
Characteristics	**Quintile 1**	**Quintile 2**	**Quintile 3**	**Quintile 4**	**Quintile 5**	***P*-value[a]**
Number of participants	17,526	17,526	17,525	17,526	17,525	
Number of men (%)	23.1	20.3	19.0	18.5	19.1	
Number of women (%)	17.3	19.8	20.9	21.3	20.8	
Dietary variables						
Acrylamide intake						
Range, μg/d	0.0–3.8	3.8–5.3	5.3–6.9	6.9–9.4	9.4–63.5	
Mean and SD, μg/d	2.8 ± 0.8	4.6 ± 0.4	6.0 ± 0.5	8.0 ± 0.7	12.7 ± 3.6	
Mean and SD, μg • kg body weight^{-1} • d^{-1}	0.05 ± 0.04	0.08 ± 0.06	0.11 ± 0.10	0.15 ± 0.12	0.24 ± 0.28	
Coffee, g/d	27.6 ± 43.3	65.0 ± 69.6	103.0 ± 96.1	169.8 ± 147.2	337.6 ± 317.7	*<0.001*
Green tea, g/d	255.3 ± 290.5	422.8 ± 383.9	517.5 ± 420.9	596.4 ± 470.1	859.5 ± 761.1	*<0.001*
Alcohol intake, g/d	161.1 ± 256.5	116.5 ± 202.5	93.4 ± 180.4	81.8 ± 164.8	61.1 ± 133.5	*<0.001*
Vegetables, g/d	173.2 ± 119.7	211.2 ± 126.0	226.3 ± 131.7	231.6 ± 135.5	229.5 ± 146.8	*<0.001*
Potato, g/d	8.5 ± 8.1	14.5 ± 12.1	18.2 ± 15.0	20.1 ± 18.2	21.8 ± 26.8	*<0.001*
Fruit, g/d	169.2 ± 165.8	206.6 ± 161.4	221.1 ± 167.3	221.5 ± 166.0	208.1 ± 166.9	*<0.001*
Meat, g/d	58.5 ± 46.0	58.0 ± 38.4	56.9 ± 36.4	56.8 ± 35.3	55.5 ± 35.4	*<0.001*
Fish, g/d	85.3 ± 59.5	89.5 ± 51.3	88.7 ± 48.2	86.6 ± 48.2	81.1 ± 47.5	*<0.001*
Dairy food, g/d	198.0 ± 229.0	183.6 ± 186.2	178.5 ± 169.9	171.1 ± 163.6	152.2 ± 156.3	*<0.001*
Soy food, g/d	92.5 ± 100.8	90.7 ± 77.8	87.6 ± 69.6	84.4 ± 67.1	79.3 ± 62.4	*<0.001*
Biscuits, g/d	0.6 ± 1.0	1.3 ± 1.6	2.0 ± 2.5	3.2 ± 4.1	5.9 ± 9.5	*<0.001*
Total energy intake, kcal/d	1984.5 ± 653.7	2025.6 ± 616.9	2017.0 ± 610.4	2021.4 ± 608.5	1920.3 ± 606.9	*<0.001*
Nondietary variables						
Age at 5-year follow-up study, y	58.1 ± 7.5	57.6 ± 7.8	57.3 ± 7.9	56.7 ± 8.1	55.8 ± 8.0	*<0.001*
Body mass index, kg/m^2	23.7 ± 3.1	23.6 ± 3.0	23.6 ± 3.0	23.5 ± 3.0	23.4 ± 3.0	*<0.001*
Smoking status, %						
Never	59.5	64.4	65.1	64.2	59.3	
Former	10.4	9.4	9.2	8.2	8.0	*<0.001*
Current	25.0	21.9	21.0	23.2	28.4	
Missing	5.0	4.4	4.7	4.5	4.3	
Pack years, for former and current smokers	34.7 ± 25.8	34.4 ± 19.6	34.5 ± 19.8	35.8 ± 24.8	37.8 ± 21.5	*<0.001*
Physical activity (METs)	36.0 ± 10.1	37.4 ± 9.6	37.5 ± 9.5	37.6 ± 9.4	37.5 ± 9.5	*<0.001*

NOTE: Values are mean ± SD, or percentages.

[a]Kruskal–Wallis test for continuous variables and χ^2 test for categorical variables.

Published OnlineFirst June 11, 2019; DOI: 10.1158/1055-9965.EPI-18-1259

stratified analysis of subsites were also adjusted accordingly (see footnotes of Tables 2–4).

Cigarette smoke is a major source of acrylamide, and smokers have on average 4 times higher levels of acrylamide-hemoglobin adducts (which mark internal acrylamide dose) than nonsmokers (34). To elucidate the interaction effect, subgroup analyses were conducted for never smoker, and former and current smokers. We also performed stratified analysis for alcohol consumption (<150 or ≥150 g/week), coffee consumption (never drinker or drinker), and green tea consumption (never drinker or drinker). All *P* values were two-sided, with significance set at <0.05. All statistical analyses were performed with Stata version 13.1 (Stata Corp.).

Results

Characteristics of the study population according to acrylamide intake are shown in Table 1. The mean (±SD) daily intake of acrylamide was 6.8 ± 3.8 μg/day overall, corresponding to 0.13 ± 0.16 μg/kg body weight/day. Foods that mainly contributed to total acrylamide intake were coffee (28%), green tea (22%), biscuits (11%), potatoes (11%), and vegetables (11%). Compared with the lowest acrylamide consumption group (Q1), the highest consumption group (Q5) comprised younger subjects, a larger proportion of current smokers, and a higher number of pack years. Moreover, the food and beverage consumption of the Q5 group consisted of more coffee, green tea, vegetables, potatoes, fruits, and biscuits but less alcohol, meat, fish, dairy, soy food, and energy diet.

Table 2 shows the results of daily acrylamide intake and risk of esophageal cancer. No association between daily acrylamide intake and esophageal cancer was observed in the overall analysis ($P = 0.814$). There were also no significant associations observed in the sensitivity analysis and the analysis excluding carcinoma in situ as well as in the stratified analysis.

Table 3 shows the associations between daily acrylamide intake and gastric cancer. Overall, acrylamide intake was not associated with total gastric cancer, cardia gastric cancer, or non-cardia gastric cancer. The sensitivity analysis and the analysis excluding carcinoma in situ also showed no significant associations.

Finally, Table 4 shows the comparison between daily acrylamide intake and colorectal cancer. Daily acrylamide intake was significantly associated with decreased risk of colorectal cancer in the age- and area-adjusted model. Subjects in the highest acrylamide intake group (Q5) had approximately 11% lower risk of colorectal cancer than those in the lowest acrylamide intake group (Q1; HR = 0.89; 95% CI, 0.78–1.01). However, after additionally adjusting for factors in the multivariable-adjusted model, the significance of the decreased association was attenuated and no significant association was observed. The results did not change in the sensitivity analysis and when cases of colorectal carcinoma in situ were excluded. Furthermore, colon or rectal cancer was also not associated with acrylamide intake.

Supplementary Tables S1–S3 displayed the associations between daily dietary acrylamide intake and esophageal, gastric and colorectal cancer with stratification analyses by smoking status, alcohol consumption, coffee consumption, green tea consumption, respectively (Supplementary Tables S1–S3). In general, there were also no significant associations observed in these analyses.

Discussion

On the basis of the large-scale prospective cohort of the JPHC Study, we found no association between dietary acrylamide intake and overall risk of esophageal, gastric, or colorectal cancer among the Japanese population.

Table 2. HRs (95% confidence intervals) for esophageal cancer according to quintiles of acrylamide intake

		Quintiles of energy-adjusted acrylamide intake					
	Total	Quintile 1 HR (95% CI)	Quintile 2 HR (95% CI)	Quintile 3 HR (95% CI)	Quintile 4 HR (95% CI)	Quintile 5 HR (95% CI)	*P* for trend
Esophageal cancer							
Number of subjects	87,628	17,526	17,526	17,525	17,526	17,525	
Person-years	1,354,648	268,731	271,612	272,196	271,736	270,372	
Number of cases	391	97	82	80	79	53	
Age- and area-adjusted model[a]		1.00 (Reference)	0.90 (0.67–1.21)	0.93 (0.69–1.25)	0.97 (0.72–1.31)	0.67 (0.48–0.94)	0.078
Multivariable model[b]		1.00 (Reference)	1.03 (0.76–1.38)	1.14 (0.84–1.54)	1.19 (0.87–1.62)	0.84 (0.59–1.19)	0.813
Multivariable model (excluding cases <3 y)[b]		1.00 (Reference)	0.98 (0.71–1.36)	1.17 (0.84–1.62)	1.21 (0.87–1.68)	0.87 (0.60–1.26)	0.960
Esophageal squamous cell carcinoma							
Number of cases	305	73	67	65	58	42	
Age- and area-adjusted model[a]		1.00 (Reference)	0.98 (0.70–1.37)	1.01 (0.72–1.41)	0.95 (0.67–1.35)	0.71 (0.48–1.04)	0.126
Multivariable model[c]		1.00 (Reference)	1.11 (0.79–1.55)	1.24 (0.88–1.74)	1.18 (0.83–1.69)	0.93 (0.62–1.38)	0.963
Esophageal adenocarcinoma							
Number of cases	20	5	4	3	3	5	
Age- and area-adjusted model[a]		1.00 (Reference)	0.90 (0.24–3.38)	0.68 (0.16–2.89)	0.70 (0.17–2.99)	1.15 (0.32–4.11)	0.959
Multivariable model[d]		1.00 (Reference)	1.03 (0.27–3.90)	0.79 (0.18–3.42)	0.79 (0.18–3.45)	1.25 (0.34–4.59)	0.873

Abbreviation: 95% CI, 95% confidence intervals.

[a]Age- and area-adjusted model adjusted for age (continuous), sex, and area (10 public health center areas).

[b]Multivariable model additionally adjusted for: smoking status (never, former, current, missing), body mass index (<23.0, 23.0–24.9, 25.0–26.9, ≥27.0 kg/m^2, missing), physical activity (continuous), intakes of alcohol (<150, ≥150 g/week), and energy-adjusted consumption of vegetables, fruits, and dairy (continuous).

[c]Multivariable model additionally adjusted for: smoking status (never, former, current, missing), physical activity (continuous), intakes of alcohol (<150, ≥150 g/week), and energy-adjusted consumption of vegetables, fruits, and dairy (continuous). BMI was not included since it is not a risk factor for ESCC.

[d]Multivariable model additionally adjusted for: smoking status (never, former, current, missing), body mass index (<23.0, 23.0–24.9, 25.0–26.9, >=27.0 kg/m^2, missing), physical activity (continuous), and energy-adjusted consumption of vegetables, fruits, and dairy (continuous). Alcohol was not included since it is not a risk factor for EAC.

Published OnlineFirst June 11, 2019; DOI: 10.1158/1055-9965.EPI-18-1259

Table 3. HRs (95% confidence intervals) for gastric cancer according to quintiles of acrylamide intake

		Quintiles of energy-adjusted acrylamide intake					
	Total	Quintile 1 HR (95% CI)	Quintile 2 HR (95% CI)	Quintile 3 HR (95% CI)	Quintile 4 HR (95% CI)	Quintile 5 HR (95% CI)	*P* for trend
Gastric cancer							
Number of subjects	87,628	17,526	17,526	17,525	17,526	17,525	
Person-years	1,344,756	266,546	269,623	270,157	269,846	268,585	
Number of cases	2,218	505	442	470	434	367	
Age- and area-adjusted model[a]		1.00 (Reference)	0.92 (0.81–1.05)	1.04 (0.91–1.18)	1.02 (0.90–1.17)	0.92 (0.80–1.06)	0.756
Multivariable model[b]		1.00 (Reference)	0.92 (0.81–1.05)	1.03 (0.91–1.17)	1.01 (0.88–1.15)	0.90 (0.79–1.04)	0.551
Multivariable model (excluding cases <3 y)[b]		1.00 (Reference)	0.90 (0.79–1.04)	1.02 (0.88–1.17)	1.04 (0.90–1.20)	0.92 (0.79–1.07)	0.956
Cardia gastric cancer							
Number of cases	138	28	20	35	29	26	
Age- and area-adjusted model[a]		1.00 (Reference)	0.79 (0.44–1.40)	1.49 (0.90–2.45)	1.33 (0.78–2.24)	1.28 (0.74–2.21)	0.114
Multivariable model[b]		1.00 (Reference)	0.81 (0.46–1.45)	1.57 (0.95–2.62)	1.40 (0.82–2.39)	1.35 (0.77–2.37)	0.082
Non-cardia gastric cancer							
Number of cases	2080	477	422	435	405	341	
Age- and area-adjusted model[a]		1.00 (Reference)	0.93 (0.82–1.06)	1.01 (0.88–1.15)	1.01 (0.88–1.15)	0.90 (0.78–1.04)	0.466
Multivariable model[c]		1.00 (Reference)	0.93 (0.81–1.06)	1.00 (0.88–1.15)	0.99 (0.86–1.13)	0.88 (0.76–1.02)	0.293

Abbreviation: 95% CI, 95% confidence intervals.

[a]Age- and area-adjusted model adjusted for age (continuous), sex and area (10 public health center areas).

[b]Multivariable model additionally adjusted for: smoking status (never, former, current, missing), body mass index (<23.0, 23.0–24.9, 25.0–26.9, ≥27.0 kg/m^2, missing), physical activity (continuous), intakes of alcohol (<150, ≧150 g/week), and energy-adjusted consumption of vegetables, fruits, and salted fish (continuous).

[c]Multivariable model additionally adjusted for: smoking status (never, former, current, missing), physical activity (continuous), intakes of alcohol (<150, ≧150 g/week), and energy-adjusted consumption of vegetables, fruits, and salted fish (continuous). BMI was not included since it is not considered a risk factor for NCGC.

Importantly, our results were almost consistent with those of previous studies. To date, two case–control studies (11, 13) and two cohort studies (12, 14) have evaluated dietary acrylamide intake and risk of esophageal cancer. In these four studies, there was no overall association between acrylamide intake and risk of esophageal cancer, and the summary risk ratio (RR) for high versus low level of acrylamide intake was 1.14 (95% CI, 0.93–1.38, P_{trend} = 0.41; ref. 10). Two prospective cohort studies (14, 15) also did not support an association between dietary acrylamide intake and risk of gastric cancer, and in these two studies, the summary RR for high versus low level of acrylamide intake was 1.03 (95% CI, 0.94–1.10; P_{trend} = 0.73; ref. 10). In this study, dietary acrylamide intake was also not associated with gastric cancer risk in overall analysis. Meanwhile, six European studies, two case–control studies (11, 16) and four cohort studies (14, 15, 17, 18), were conducted to analyze the association between dietary acrylamide intake and risk of colorectal cancer. In these six studies, the summary RR for high versus low acrylamide intake was 0.94 (95% CI, 0.85–1.04; P_{trend} = 0.65; ref. 10). In our study, the risk estimates have been consistently close to 1.00 for the overall and subgroup analyses.

Although green tea may lower the risks of esophageal, gastric, and colorectal cancer (35), the exposure to acrylamide from green tea is found to contribute substantially to the total dietary

Table 4. HRs (95% confidence intervals) for colorectal cancer according to quintiles of acrylamide intake

		Quintiles of energy-adjusted acrylamide intake					
	Total	Quintile 1 HR (95% CI)	Quintile 2 HR (95% CI)	Quintile 3 HR (95% CI)	Quintile 4 HR (95% CI)	Quintile 5 HR (95% CI)	*P* for trend
Colorectal cancer							
Number of subjects	87,628	17,526	17,526	17,525	17,526	17,525	
Person-years	1,342,251	265,817	268,888	269,901	269,358	268,286	
Number of cases	2,470	569	554	463	458	426	
Age- and area-adjusted model[a]		1.00 (Reference)	1.02 (0.91–1.15)	0.89 (0.78–1.00)	0.92 (0.81–1.04)	0.89 (0.78–1.01)	0.015
Multivariable model[b]		1.00 (Reference)	1.06 (0.94–1.19)	0.93 (0.82–1.05)	0.97 (0.85–1.10)	0.94 (0.83–1.08)	0.172
Multivariable model (excluding cases <3 y)[b]		1.00 (Reference)	1.07 (0.95–1.22)	0.96 (0.84–1.10)	0.95 (0.83–1.09)	0.97 (0.84–1.12)	0.258
Colon cancer							
Number of cases	1,721	410	384	328	314	285	
Age- and area-adjusted model[a]		1.00 (Reference)	0.98 (0.85–1.12)	0.87 (0.75–1.00)	0.87 (0.75–1.01)	0.83 (0.71–0.97)	0.005
Multivariable model[b]		1.00 (Reference)	1.01 (0.88–1.16)	0.91 (0.78–1.06)	0.92 (0.79–1.07)	0.89 (0.76–1.04)	0.068
Rectal cancer							
Number of cases	749	159	170	135	144	141	
Age- and area-adjusted model[a]		1.00 (Reference)	1.14 (0.92–1.42)	0.94 (0.74–1.18)	1.03 (0.82–1.30)	1.02 (0.81–1.30)	0.856
Multivariable model[c]		1.00 (Reference)	1.17 (0.94–1.45)	0.97 (0.76–1.22)	1.07 (0.84–1.35)	1.06 (0.83–1.35)	0.927

Abbreviations: 95% CI = 95% confidence intervals.

[a]Age- and area-adjusted model adjusted for age (continuous), sex and area (10 public health center areas).

[b]Multivariable model additionally adjusted for: smoking status (never, former, current, missing), body mass index (<23.0, 23.0–24.9, 25.0–26.9, >=27.0 kg/m^2, missing), physical activity (continuous), intakes of alcohol (<150, ≧150 g/week), and energy-adjusted consumption of vegetables, fruits, meat, and dairy (continuous).

[c]Multivariable model additionally adjusted for: smoking status (never, former, current, missing), body mass index (<23.0, 23.0–24.9, 25.0–26.9, ≥27.0 kg/m^2, missing), intakes of alcohol (<150, ≧150 g/week), and energy-adjusted consumption of vegetables, fruits, meat, and dairy (continuous). Physical activity was not included since it is not considered a protective factor for rectal cancer.

Published OnlineFirst June 11, 2019; DOI: 10.1158/1055-9965.EPI-18-1259

acrylamide exposure in Japan. Given that green tea is specific to the Japanese population, we conducted a stratified analysis to compare HRs between drinkers and non-drinkers. The results did not alter conclusions regarding the associations between acrylamide intake and the cancers studied. As another common main source of acrylamide both in Japan and Western countries, coffee was associated with decreased risk of colorectal cancer (36). However, no preventive or causative effect was observed in our study between coffee consumption and colorectal cancer (Supplementary Table S3).

We did not observe an overall association between dietary acrylamide intake and risk of digestive organ cancer in this study. A previous study based on the JPHC Study showed that dietary acrylamide intake was also not associated with breast cancer (37). In our study, the average acrylamide intake was 6.8 μg/day, which is lower than 21.7 μg/day of the Netherlands Cohort Study (NLCS) on diet and cancer and 26.2 μg/day of the European Prospective Investigation into Cancer and Nutrition (EPIC; ref. 14). Although there are differences in average acrylamide intake between Japanese and Western populations, results of lack of association between dietary acrylamide intake and risk of esophageal, gastric, or colorectal cancer are common worldwide. This indicates that there might be no substantial difference in sensitivity for acrylamide intake between Asian and Western populations.

This study has several strengths. It has a prospective cohort study design. Recall bias in exposure was avoided since the data were collected before the diagnosis of cancer. Participants were selected from the general population, and the sample size was large. Moreover, the proportion of cases identified by death certificate only (DCO) was 7.1% for esophageal cancer, 4.3% for gastric cancer, and 2.8% for colorectal cancer. Thus, the cancer registries used in this study were of sufficient quality.

There are some limitations in this study. First, the FFQ has its own limitations, as discussed elsewhere (38). However, the FFQ is the only feasible way to assess dietary acrylamide intake over a long period of time in large-scale epidemiologic studies. Acrylamide levels vary greatly among foods, which may lead to misclassification of dietary acrylamide intake. The energy-adjusted correlation coefficients of dietary acrylamide intake from the FFQ and 28-day DRs ranged from 0.34 to 0.48 (25). Furthermore, acrylamide values were estimated based on foods in the 2000s, which may not completely represent foods in the 1990s. Compared with those in the 1990s, the proportion of beverages was lower but the proportion of vegetables was higher in 2012 (Food Safety Commission of Japan. Study on estimate of acrylamide intake from food; interim report. Food Safety Commission of Japan 2016; https://www.fsc.go.jp/fsciis/technicalResearch/show/cho99920151507). Second, esophageal cancer risk factors may differ depending on squamous cell carcinoma or adenocarcinoma. Due to the small number of esophageal cancer cases, it was difficult to discuss what was the frequency of each event, and the statistical power of the stratified analysis might have been affected; hence, the finding should be interpreted with caution. Lastly, although possible confounding factors had been adjusted for in the analysis, other unknown confounding factors may have impacts on the results. In conclusion, this study demonstrated that dietary acrylamide intake was not associated with increased risk of esophageal, gastric, or colorectal cancer among the Japanese population, in both overall and stratified analyses.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: R. Liu, T. Sobue, T. Kitamura, Ishihara, L. Zha, M. Iwasaki, S. Tsugane

Development of methodology: R. Liu, T. Sobue, T. Kitamura, J. Ishihara, A. Kotemori, L. Zha, S. Ikeda

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): T. Sobue, J. Ishihara, N. Sawada, M. Iwasaki, S. Tsugane

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): R. Liu, T. Sobue, T. Kitamura, Y. Kitamura, J. Ishihara, A. Kotemori, L. Zha, S. Ikeda, S. Tsugane

Writing, review, and/or revision of the manuscript: R. Liu, T. Sobue, T. Kitamura, J. Ishihara, A. Kotemori, L. Zha, S. Ikeda, N. Sawada, M. Iwasaki, S. Tsugane

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): R. Liu, T. Kitamura, J. Ishihara, A. Kotemori, L. Zha, S. Ikeda, S. Tsugane

Study supervision: T. Kitamura, L. Zha, S. Tsugane

Acknowledgments

This study was supported by a grant from the Food Safety Commission, Cabinet Office, Government of Japan (Research Program for Risk Assessment Study on Food Safety, No. 1503; principal investigator was T. Sobue); the National Cancer Center Research and Development Fund (since 2011; principal investigator was S. Tsugane); and a Grant-in-Aid for Cancer Research from the Ministry of Health, Labour and Welfare of Japan (1989–2010; principal investigator from 1997 to 2010 was S. Tsugane). Members of the JPHC Study Group are listed at the following site (as of April 2017): http://epi.ncc.go.jp/en/jphc/781/7951.html. We are indebted to the Aomori, Akita, Iwate, Ibaraki, Niigata, Osaka, Kochi, Nagasaki, and Okinawa Cancer Registries for providing incidence data.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received November 28, 2018; revised February 16, 2019; accepted June 5, 2019; published first June 11, 2019.

References

1. Sobel W, Bond GG, Parsons TW, Brenner FE. Acrylamide cohort mortality study. Br J Ind Med 1986;43:785–8.
2. Collins JJ, Swaen GM, Marsh GM, Utidjian HM, Caporossi JC, Lucas LJ. Mortality patterns among workers exposed to acrylamide. J Occup Med 1989;31:614–7.
3. Marsh GM, Lucas LJ, Youk AO, Schall LC. Mortality patterns among workers exposed to acrylamide: 1994 follow up. Occup Environ Med 1999;56:181–90.
4. Marsh GM, Youk AO, Buchanich JM, Kant IJ, Swaen G. Mortality patterns among workers exposed to acrylamide: updated follow up. J Occup Environ Med 2007;49:82–95.
5. Swaen GM, Haidar S, Burns CJ, Bodner K, Parsons T, Collins JJ, et al. Mortality study update of acrylamide workers. Occup Environ Med 2007;64:396–401.
6. International Agency for Research on Cancer. Monographs on the evaluation of carcinogen risk to humans: some industrial chemicals. Lyon, France: International Agency for Research on Cancer; 1994.
7. Tareke E, Rydberg P, Karlsson P, Eriksson S, Törnqvist M. Analysis of acrylamide, a carcinogen formed in heated foodstuffs. J Agric Food Chem 2002;50:4998–5006.
8. Besaratinia A, Pfeifer GP. A review of mechanisms of acrylamide carcinogenicity. Carcinogenesis 2007;28:519–28.

9. Shipp A, Lawrence G, Gentry R, McDonald T, Bartow H, Bounds J, et al. Acrylamide: review of toxicity data and dose-response analyses for cancer and noncancer effects. Crit Rev Toxicol 2006;36:481–608.
10. Pelucchi C, Bosetti C, Galeone C, La Vecchia C. Dietary acrylamide and cancer risk: An updated metaanalysis. Int J Cancer 2015;136:2912–22.
11. Pelucchi C, Galeone C, Levi F, Negri E, Franceschi S, Talamini R, et al. Dietary acrylamide and human cancer. Int J Cancer 2006;118:467–71.
12. Hogervorst JG, Schouten LJ, Konings EJ, Goldbohm RA, van den Brandt PA. Dietary acrylamide intake is not associated with gastrointestinal cancer risk. J Nutr 2008;138:2229–36.
13. Lin Y, Lagergren J, Lu Y. Dietary acrylamide intake and risk of esophageal cancer in a populationbased casecontrol study in Sweden. Int J Cancer 2011;128:676–81.
14. Lujan-Barroso L, González CA, Slimani N, Obón-Santacana M, Ferrari P, Freisling H, et al. Dietary intake of acrylamide and esophageal cancer risk in the European Prospective Investigation into Cancer and Nutrition cohort. Cancer Causes Control 2014;25:639–46.
15. Hirvonen T, Kontto J, Jestoi M, Valsta L, Peltonen K, Pietinen P, et al. Dietary acrylamide intake and the risk of cancer among Finnish male smokers. Cancer Causes Control 2010;21:2223–9.
16. Mucci LA, Dickman PW, Steineck G, Adami HO, Augustsson K. Dietary acrylamide and cancer of the large bowel, kidney, and bladder: absence of an association in a population-based study in Sweden. Br J Cancer 2003;88:84–9.
17. Mucci LA, Adami HO, Wolk A. Prospective study of dietary acrylamide and risk of colorectal cancer among women. Int J Cancer 2006;118:169–73.
18. Larsson SC, kesson A, Bergkvist L, Wolk A. Dietary acrylamide intake and risk of colorectal cancer in a prospective cohort of men. Eur J Cancer 2009;45:513–6.
19. Kotemori A, Ishihara J, Zha L, Liu R, Sawada N, Iwasaki M, et al. Dietary acrylamide intake and the risk of endometrial or ovarian cancers in Japanese women. Cancer Sci 2018;109:3316.
20. Tsugane S, Sobue T. Baseline survey of JPHC study design and participation rate. J Epidemiol 2001;11(Suppl 6):S24–9.
21. Tsugane S, Sasaki S, Kobayashi M, Tsubono Y, Akabane M. Validity and reproducibility of the self-administered food frequency questionnaire in the JPHC Study Cohort I: study design, conduct and participant profiles. J Epidemiol 2003;13(Suppl 1):S2–12.
22. Ishihara J, Sobue T, Yamamoto S, Yoshimi I, Sasaki S, Kobayashi M, et al. Validity and reproducibility of a self-administered food frequency questionnaire in the JPHC Study Cohort II: study design, participant profile and results in comparison with Cohort I. J Epidemiol 2003;13(Suppl 1):S134–47.
23. Ishihara J, Inoue M, Kobayashi M, Tanaka S, Yamamoto S, Iso H, et al. Impact of the revision of a nutrient database on the validity of a self-administered food frequency questionnaire (FFQ). J Epidemiol 2006;16:107–16.
24. Resource Council, Science and Technology Agency, the Government of Japan. Standard tables of food composition in Japan, the fifth revised edition. Tokyo, Japan: Printing Bureau, Ministry of Finance; 2002.
25. Kotemori A, Ishihara J, Nakadate M, Sawada N, Iwasaki M, Sobue T, et al. Validity of a self-administered food frequency questionnaire for the estimation of acrylamide intake in the Japanese population: the JPHC FFQ Validation Study. J Epidemiol 2017;28:482–7.
26. FAO/WHO. Health implications of acrylamide in food. Report of a Joint FAO/WHO Consultation. Geneva: FAO/WHO2002.
27. Yoshida M, Ono H, Ohnishi Kameyama M, Chuda Y, Yada H, Kobayashi H, et al. Determination of acrylamide in processed foodstuffs in Japan. Nippon Shokuhin Kagaku Kogaku Kaishi 2002;49:822–5.
28. Takatsuki S, Nemoto S, Sasaki K, Maitani T. Production of acrylamide in agricultural products by cooking. J Food Hyg Soc Japan 2004;45:44–8.
29. Mizukami Y, Kohata K, Yamaguchi Y, Hayashi N, Sawai Y, Chuda Y, et al. Analysis of acrylamide in green tea by gas chromatography– mass spectrometry. J Agric Food Chem 2006;54:7370–7.
30. Yoshida M, Miyoshi K, Horibata K, Mizukami Y, Takenaka M, Yasui A. Estimation of acrylamide intake from cooked rice in Japan. Nippon Shokuhin Kagaku Kogaku Kaishi 2011;58:525–30.
31. Enzinger PC, Mayer RJ. Esophageal cancer. N Engl J Med 2003;349:2241–52.
32. Colquhoun A, Arnold M, Ferlay J, Goodman K, Forman D, Soerjomataram I. Global patterns of cardia and non-cardia gastric cancer incidence in 2012. Gut 2015;64:1881–8.
33. Wei EK, Giovannucci E, Wu K, Rosner B, Fuchs CS, Willett WC, et al. Comparison of risk factors for colon and rectal cancer. Int J Cancer 2004;108:433–42.
34. Schettgen T, Rossbach B, Kütting B, Letzel S, Drexler H, Angerer J. Determination of haemoglobin adducts of acrylamide and glycidamide in smoking and non-smoking persons of the general population. Int J Hyg Environ Health 2004;207:531–9.
35. Jankun J, Selman SH, Swiercz R, Skrzypczak-Jankun E. Why drinking green tea could prevent cancer. Nature 1997;387:561.
36. Nkondjock A. Coffee consumption and the risk of cancer: an overview. Cancer Lett 2009;277:121–5.
37. Kotemori A, Ishihara J, Zha L, Liu R, Sawada N, Iwasaki M, et al. Dietary acrylamide intake and risk of breast cancer: The Japan Public Health Centerbased Prospective Study. Cancer Sci 2018;109:843–53.
38. Riboldi BP, Vinhas ÁM, Moreira JD. Risks of dietary acrylamide exposure: a systematic review. Food Chem 2014;157:310–22.

Cancer Epidemiology, Biomarkers & Prevention

AACR American Association for Cancer Research

Dietary Acrylamide Intake and Risk of Esophageal, Gastric, and Colorectal Cancer: The Japan Public Health Center–Based Prospective Study

Rong Liu, Tomotaka Sobue, Tetsuhisa Kitamura, et al.

Cancer Epidemiol Biomarkers Prev 2019;28:1461-1468. Published OnlineFirst June 11, 2019.