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ORIGINAL ARTICLE – CLINICAL ONCOLOGY

Dietary acrylamide exposure was associated with increased cancer mortality in Chinese elderly men and women: a 11-year prospective study of Mr. and Ms. OS Hong Kong

Zhao-min Liu[1] · Lap Ah Tse[2] · Suzanne C. Ho[2] · Suyang Wu[2] · Bailing Chen[3] · Dicken Chan[2] · Samuel Yeung-shan Wong[2]

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Abstract

Aim Our study aims to investigate the association between dietary acrylamide exposure and cancer mortality among Chinese elderly.

Methods A prospective cohort of 4000 elderly men and women aged 65 years and above (Mr. and Ms. OS Hong Kong study) was recruited from local communities from 2001 to 2003. Dietary exposure to acrylamide was evaluated at baseline based on a validated food frequency questionnaire and an acrylamide database from the 1st Hong Kong Total Diet Study. Data on mortality statistics through March 2014 were obtained from the Death Registry of the Department of Health of Hong Kong with a median follow-up of 11.1 years. Cox proportional hazards models were used to examine the association between the acrylamide exposure and cancer mortality. Sex hormones were assessed in men.

Results During a median follow-up of 11.1 years (39,271 person-years), we ascertained 330 cancer deaths. Vegetables (43.7%) and cereals (28.9%) products were the major contributors to dietary acrylamide. Compared with the lowest quartile of acrylamide intake (<9.9 μg/day), the multivariable hazard ratios for the highest quartile (>17.1 μg/day) were 1.9 (95% CI 1.3–2.8; $P_{trend} < 0.01$), 1.9 (95% CI 1.0–3.6; $P_{trend} = 0.05$), and 2.0 (95% CI 1.0–4.0; $P_{trend} = 0.06$) for the cancer mortality from overall, digestive and respiratory system, respectively. The associations were attenuated to null after further adjustment for circulating free estradiol in men. No statistically significant interactions were observed between acrylamide exposure and sex, obesity and overall lifestyle pattern scores.

Conclusions The longitudinal data provided evidence that dietary acrylamide, in amounts that Chinese elderly are typically exposed to, was associated with increased cancer mortality. Circulating free estradiol may mediate the association in men.

Keywords Dietary exposure · Acrylamide · Cancer mortality · Chinese elderly

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✉ Zhao-min Liu
liuzhm8@mail.sysu.edu.cn

✉ Lap Ah Tse
shelly@cuhk.edu.hk

[1] Department of Nutrition, School of Public Health, Sun Yat-sen University, Guangzhou, People's Republic of China

[2] Division of Occupational and Environmental Health, Jockey Club School of Public Health and Primary Care, The Chinese University of Hong Kong, Hong Kong SAR, People's Republic of China

[3] Department of Spine Surgery, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, People's Republic of China

Introduction

Cancer has become the most important cause of death in China and throughout the world (Stewart 2014). Acrylamide was classified as a probable human carcinogen by the International Agency for Research on Cancer (IARC) on the basis of its carcinogenicity in rodents. Animal studies have shown acrylamide is a multisite carcinogen in rodents and causes tumors in skin,mesothelioma, lung, mammary gland, uterus, ovary, testis, thyroid, Harderian gland oral cavity and central nervous system (Bull et al. 1984; Johnson et al.

1986; Friedman 2003). A recent meta-analysis (Pelucchi et al. 2015) indicates that dietary acrylamide has a modest association with kidney cancer and with endometrial and ovarian cancer in never smokers.

Acrylamide is commonly present in carbohydrate-rich foods processed at high temperatures (>120 °C) and formed by Maillard browning reactions, in which amino acids, particularly asparagine, react with reducing sugars (Mottram et al. 2002). High levels of acrylamide have been found in fried and baked potato products and in cereal products such as crisp bread, breakfast cereals and cookies (Mottram et al. 2002). Due to its ubiquitous presence in foods with concentrations at considerably higher levels than other well-known food carcinogens (i.e., polycyclic aromatic hydrocarbons and ethyl carbamate); acrylamide might be responsible for a considerable part of the diet-related cancer incidences and mortality (JECFA 2005). Some studies suggest that acrylamide may affect the cancer risk through hormonal pathways (Hogervorst et al. 2013; Nagata et al. 2015).

Dietary acrylamide can be rapidly and extensively absorbed from the gastrointestinal tract, then metabolized and excreted in urine, mainly as mercapturic acid derivatives of acrylamide and glycidamide (GA). Many observational studies have focused on dietary acrylamide exposure and the incidences of individual cancers (Pelucchi et al. 2011). Few cohort studies have examined the association of acrylamide exposure and cancer mortality, especially among elderly populations. This study aimed to investigate the relationship of dietary acrylamide and cancer mortality, and explore whether endogenous sex hormones may mediate the association based on an 11-year follow-up of an elderly population in Hong Kong.

Methods

The study of Mr. and Ms. OS Hong Kong was originally designed to investigate the risk factors of osteoporosis. Elderly men and women aged 65 years and above were recruited from 2001 to 2003 through advertisements placed in community centers and housing estates. Those who were unable to walk without assistance of another person, had bilateral hip replacement or were not competent to give informed consent were excluded. The participants were stratified so that approximately 33% were in each of the age groups: 65–69, 70–74, and 75 and above. The study enrolled 4000 participants. Details of the study design have previously been published (Lau et al. 2006). The study was approved by the Clinical Research Ethics Committee of the Chinese University of Hong Kong and complied with the Declaration of Helsinki. The informed consent for this study was obtained before study enrolment and during the data collection.

Eligible participants were invited to the Research Center for baseline clinical assessment, and face-to-face interviews based on structured and standardized questionnaires. Information collected included social demographic data, family and medical history, current use of medications, smoking and drinking of alcohol, tea and coffee. Dietary intakes were assessed by a validated food frequency questionnaire (FFQ) based on the data from the Hong Kong Adult Dietary Survey (Woo et al. 1997). Physical activity was measured by the Physical Activity Scale for the Elderly Questionnaire (PASE) (Washburn et al. 1993). Height was measured by the Holtain Harpenden stadiometer (Holtain Ltd., Crosswell, UK). Body weight was measured by the Physician Beam Balance Scale (Healthometer, IL, USA).

A total of 1489 male subjects were randomly selected to have stored serum analyzed for sex hormones and their precursors (sex hormone-binding globulin (SHBG), estradiol, androstenedione, dehydroepiandrosterone, 5-androstene-3b,17b-diol and dehydroepiandrosterone sulfate). Free fractions of estradiol were calculated as described by Sodergard et al. (1982). All hormone assays were performed by Gas chromatography–mass spectrometry (GC/MS) (Labrie et al. 2009).

Acrylamide intake assessment and the 1st total diet study in Hong Kong

The validated FFQ containing 329 food items was used to estimate dietary nutrients and acrylamide intakes at baseline (Woo et al. 1997). Acrylamide level in individual food items was based on the acrylamide database of the 1st Hong Kong Total Diet Study (HKTDS) (Centre for Food Safety and Department 2011). The food items in FFQ that were used in the acrylamide intake assessment were assigned the mean value of the acrylamide detected in the TDS food items or a value of one half the quantitation limit when concentrations were lower than the quantitation limit (Centre for Food Safety and Department 2011). Dietary acrylamide intake was estimated from the mean acrylamide level (Centre for Food Safety and Department 2011), the frequency of consumption and the portion size of the intake of food items. TDS has been recognized internationally as one of the most cost effective way to estimate dietary exposures to food chemicals for various population groups and to assess their associated health risks. Due to its nature of covering total diet, TDS can identify potentially contaminated foods or food groups that may be present at very low levels. In the 1st HKTDS, a total of 1800 samples for the 150 TDS food items were collected and prepared into table-ready forms on four occasions. On each occasion, three samples of each TDS food item were purchased from various retail outlets in different regions of the territory. The three samples of the same food item were then prepared as for normal consumption, i.e., table-ready, in a manner most representative of and consistent with cultural habits in Hong Kong as far as

practicable. They were then homogenized individually and combined into 600 composite samples for the laboratory analysis on food chemicals.

Case ascertainment and follow-up

Data on mortality statistics were obtained from the Death Registry of the Department of Health of Hong Kong till March 2014 with a median follow-up of 11.1 years. Cancer deaths were identified by the cause of death reported on the death certificate, and classified according to the International Classification of Disease (ICD) version 10 codes as those ranging from C00 to D48 for neoplasms. Follow-up of participants continued until death attributable to cancers, with censoring at the time of death for those who died from causes other than cancers.

Statistical analysis

Statistical analysis was conducted using SPSS version 21.0. All *P* values were two sided with significance level at 0.05. The contributions of 15 TDS food groups to overall dietary acrylamide exposure were calculated as percentages. We categorized participants into quartiles of dietary exposure of acrylamide based on its distribution in the entire cohort. Differences in the participants' characteristics by quartiles of dietary acrylamide exposure were compared using Chi-square test for categorical variables or analysis of variance (ANOVA) for continuous variables. Participants contributed person-time from baseline until the date of death, death from any cancers, or 31st March 2014, whichever occurred first. Participants with medical history of any cancers at baseline were excluded and 3823 remained for analysis. Cox proportional hazards models were used to estimate hazard risks (HR) with their 95% confidence intervals (CIs) for the association between acrylamide intake and overall cancer mortality, and cancer mortality from digestive tract and respiratory system, respectively. In multivariable analysis, we controlled for age, sex, education, body mass index (BMI) at baseline, physical activities, history of diabetes, cigarette smoking, total energy intake, alcohol, coffee and tea drinking, dietary carbohydrate and fibers. We tested the proportional hazard assumption using the likelihood ratio test and found no departure from the assumption. Tests for trend were conducted by assigning the median value of acrylamide exposure to each quartile and modeling this variable as a continuous variable. Because cigarette smoking is an important source of acrylamide exposure, we conducted a sensitivity analysis excluding the current smokers. To check for the influence of protopathic bias, the analyses were also done with exclusion of cancer deaths occurring in the first 2 years of follow-up.

Effect modification by other variables on the association between acrylamide intake and cancer mortality was tested. These variables in our analysis were sex, BMI, and score of AHA-DLR (the score of compliance of the guideline of American Heart Association Dietary and lifestyle Recommendation). To evaluate whether sex hormones mediated the association of acrylamide exposure with cancer mortality in men, we added sex hormones individually in the regression model. We tested for potential effect modification by including an interaction term of these variables with the quartiles of acrylamide exposure in the regression models. Subgroup analyses were further conducted.

Results

We observed a mean (±SD) daily intake of acrylamide of 14.6 ± 8.2 μg/day in the study population. The main dietary sources of acrylamide (Table 1) were vegetables and their products (43.7%), followed by cereals and their products (28.9%), then fish, seafood and their products (8.93%), legumes, nuts and seeds and their products (6.75%) and mixed dishes (4.64%).

The participants' characteristics in quartiles of overall acrylamide intake were indicated in Table 2. Compared with the lowest acrylamide group, those in the highest quartile were younger, had higher education, body weight and smoking dosage; more likely to be married and physically active; higher AHA-DLR scores and higher intake of total energy, carbohydrate, protein and dietary fibers; had higher coffee, tea and alcohol intake; higher intake of French fries, fast foods and red/processed meat.

The crude and multivariable-adjusted associations (HR and 95% CI) between acrylamide exposure and cancer mortality are shown in Table 3. We ascertained 330 cancer deaths during total 39,271 person-years of follow-up (mean, 11.1 years). After adjustment for potential covariables, a significant association was observed between acrylamide intake and an overall increased cancer mortality with a HR of 1.9 (95% CI 1.3–2.8; $P_{trend} < 0.01$). Sensitivity analysis excluding current smokers ($n = 274$), or cases that died from cancer during the first 2 years of follow-up ($n = 61$) did not change the results materially. In the current non-smokers, the multivariable-adjusted HR in the highest quartile was 2.0 (95% CI 1.3–3.1; $P_{trend} < 0.01$) compared with the lowest quartile of acrylamide intake. Subgroup analyses for cancer mortality from digestive tract (HR 1.9; 95% CI 1.0–3.6; $P_{trend} = 0.05$) and respiratory system (HR 2.0; 95% CI 1.0–4.0; $P_{trend} = 0.06$) demonstrated similar HRs to those of overall mortality.

Table 4 indicated the results of subgroup analyses between acrylamide intake and potential variables of effect modification. There were no significant interactions between

Table 1 Dietary exposure (μg/day) to acrylamide and its contributions by food groups of total diet study (TDS)

TDS food groups	Dietary exposure (μg/day) Mean ± standard deviation	% Contribution of total exposure
Cereals and their products	3.82 ± 1.68	28.90
Baked cereals and their products	2.67 ± 2.47	20.84
Vegetables and their products	6.52 ± 4.78	43.70
Stir-fried vegetables and their products	4.45 ± 5.16	29.65
Potatoes	0.19 ± 0.289	1.30
Legumes, nuts and seeds and their products	1.02 ± 1.40	6.75
Fruits	0.36 ± 0.29	2.65
Meat, poultry and game and their products	0.15 ± 0.20	1.07
Eggs and their products	0.01 ± 0.02	0.07
Fish, seafood and their products	1.58 ± 4.58	8.93
Dairy products	0.04 ± 0.08	0.27
Fats and oils	0.01 ± 0.08	0.19
Beverages, alcoholic	0.02 ± 0.01	0.07
Beverages, non-alcoholic	0.25 ± 0.32	1.86
Coffee	0.13 ± 0.38	0.94
Mixed dishes	0.63 ± 0.51	4.64
Snack foods	0.13 ± 0.59	0.74
Potato crisps	0.044 ± 0.079	0.30
Sugars and confectionery	0.02 ± 0.12	0.12
Condiments, sauces and herbs	0.00 ± 0.01	0.01
Total	14.57 ± 8.15	100

Half of limit of detection (LOD) is used for all results less than LOD in calculating the exposure estimates. Baked cereals included: pasta, instant noodles, bread, bun, biscuit, cakes, pastries, breakfast cereals and deep-fried dough. Fried vegetables and their products included 22 kinds of vegetables such as zucchini, eggplant, sweet pepper, tomato, garlic, onion, spring onion, mung bean sprout, spinach, and water spinach

TDS total diet study

quartiles of acrylamide intake and any of the variables on overall cancer mortality. The associations were largely consistent across sex, BMI (<24 and ≥24 kg/m^2) and AHA-DRL scores (above and below median). In men, after adjustment for circulating estradiol but not other sex hormones, the HRs were reduced to around 1, suggesting that the effect of acrylamide exposure on cancer mortality may be mediated through circulating free estradiol. When the analyses were further restricted to the subgroup of elderly who had never smoked, the associations (HRs) were similar but were marginally significant due to reduced power.

Discussion

Summary of current findings

This 11-year Chinese elderly cohort study provides the first epidemiologic evidence that dietary acrylamide exposure could potentially increase overall cancer mortality. The association was also present in current non-smokers. Similar increased risks were observed in cancer mortality from digestive tract and respiratory system.

The average acrylamide intakes were 15.9 ± 8.5 μg/day (0.26 μg/kg bw/day) for men and 13.2 ± 7.6 μg/day (0.24 μg/kg bw/day) for women. The intake levels were similar to those reported in a previous survey in Hong Kong adults (Wong et al. 2014) (0.21 μg/kg bw/day) and in the Chinese general population (0.286 μg/kg bw/day) (Zhou et al. 2013); but were in the lower range of the WHO estimate of 0.3–0.8 μg/kg bw/day for developed countries (Wong et al. 2014). This could be due to the lower intake of fried and baked foods among Chinese elderly compared with that of the Western populations (WHO/FAO 2002). Our results indicated the majority of the participants (82%) never consumed acrylamide-rich snack foods.

The major contributors of dietary acrylamide in our data were fried vegetables, baked cereals and their products. The findings were similar to that reported by the 1st Total Diet Study in Hong Kong adults (Wong et al. 2014). Although fried potato or snack foods such as potato chips and biscuits contain the highest acrylamide level, they had only a minor contribution to the overall exposure due to the low

Table 2 Characteristics of participants across quartiles of daily dietary acrylamide exposure (μg/day)

Variables	Q1	Q2	Q3	Q4	*P*
No.	1000	1000	1000	1000	
Acrylamide exposure range (μg/day)	0	9.94	12.94	17.09	
Average acrylamide intake (μg/day)	7.89 ± 1.61	11.47 ± 0.86	14.81 ± 1.18	24.20 ± 10.89	<0.001
Average acrylamide intake (μg/kg/day)	0.143 ± 0.037	0.202 ± 0.037	0.259 ± 0.049	0.410 ± 0.208	<0.001
Male/female (no.)	364/636	438/562	537/463	661/339	
Age (years)	73.3 ± 5.5	72.5 ± 5.2	72.3 ± 5.2	71.8 ± 4.8	<0.001
Education above university, *n* (%)	56 (5.6)	90 (9.0)	109 (10.9)	135 (13.5)	<0.001
Married or cohabitation, *n* (%)	605 (60.5)	673 (67.3)	739 (73.9)	812 (81.2)	<0.001
Body weight (kg)	56.4 ± 9.5	58.3 ± 9.4	58.7 ± 9.6	60.8 ± 10.2	<0.001
BMI (kg/m^2)	23.6 ± 3.4	23.8 ± 3.29	23.6 ± 3.2	23.9 ± 3.2	0.113
Smoking status, *n* (%)					<0.001
Current smoking	65 (6.5)	60 (6.0)	65 (6.5)	85 (8.5)	
Ever smoking	254 (25.4)	269 (26.9)	320 (32.0)	348 (34.8)	
No smoking	681 (68.1)	671 (67.1)	615 (61.5)	567 (56.7)	
Smoking dosage (packs/year)	9.4 ± 21.3	8.9 ± 20.0	11.4 ± 22.29	14.2 ± 27.1	<0.001
Physical activity (total PASE scores)	80.9 ± 36.3	90.1 ± 41.6	93.7 ± 45.2	101.2 ± 46.5	<0.001
Medical history at baseline, *n* (%)					
Any cancer	42 (4.2)	50 (5.0)	41 (4.1)	44 (4.4)	0.764
Bladder cancer	2 (0.2)	5 (0.5)	5 (0.5)	4 (0.4)	0.680
Diabetes	161 (16.1)	171 (17.1)	121 (12.1)	126 (12.6)	0.002
Stoke	53 (5.3)	35 (3.5)	44 (4.4)	43 (4.3)	0.274
CVDs	103 (10.3)	97 (9.7)	97 (9.7)	96 (9.6)	0.951
AHA-DLR score	42.1 ± 9.7	44.4 ± 10.0	44.8 ± 10.4	45.7 ± 9.7	<0.001
Dietary variables					
Total energy (kcal/day)	1395.9 ± 399.4	1677.1 ± 419.9	1945.3 ± 449.6	2349.1 ± 597.4	<0.001
Carbohydrate (g/day)	198.1 ± 60.1	237.6 ± 64.9	271.2 ± 73.8	320.3 ± 87.3	<0.001
Protein (g/1000 kcal)	37.4 ± 10.1	40.2 ± 8.9	41.8 ± 8.6	44.6 ± 8.7	<0.001
Fat (g/1000 kcal)	31.7 ± 8.1	31.1 ± 7.0	31.6 ± 6.9	31.5 ± 6.4	0.374
Fiber (g/day)	6.0 ± 3.4	8.0 ± 3.4	9.8 ± 4.3	13.1 ± 5.3	<0.001
Fruits (g/1000 kcal)	136.5 ± 95.2	144.7 ± 94.3	143.6 ± 91.3	149.1 ± 89.7	0.028
Vegetables (g/1000 kcal)	112.0 ± 55.1	144.4 ± 62.2	163.9 ± 73.6	211.3 ± 129.4	<0.001
Coffee (ml/day)	16.4 ± 58.0	20.0 ± 65.1	24.2 ± 66.7	34.7 ± 84.6	<0.001
Alcohol drinking (g/day)	7.1 ± 42. 9	8.0 ± 44.1	12.3 ± 47.9	29.0 ± 146.7	<0.001
Tea (ml/week)	2986 ± 3267	3346 ± 3264	3801 ± 3928	4254 ± 4032	<0.001
French fries/chips (% Kcal)	0.07 ± 0.30	0.13 ± 0.95	0.23 ± 0.97	0.38 ± 1.21	<0.001
Fast food (% Kcal)	0.47 ± 1.30	0.54 ± 1.18	0.82 ± 2.51	0.80 ± 1.57	<0.001
Red/processed meat (% Kcal)	6.32 ± 5.13	6.94 ± 5.38	7.18 ± 4.77	7.52 ± 4.97	<0.001
SBP (mmHg)	144.1 ± 19.4	142.8 ± 18.2	142.1 ± 19.2	142.1 ± 19.7	0.076
DBP (mmHg)	77.9 ± 9.4	77.0 ± 9.2	78.3 ± 8.8	78.3 ± 9.3	0.007
Serum sex hormones among men (n = 1488)					
n	274	322	395	497	
SHBG (nmol/L)	43.5 ± 14.8	42.9 ± 17. 8	42.0 ± 16.2	44.1 ± 17.5	0.822
Estradiol (pg/ml)	24.0 ± 8.4	24.5 ± 10.0	24.3 ± 10.2	26.1 ± 21.2	0.201
Bioavailable Estradiol (pmol/L)	77.4 ± 18.8	78.0 ± 21. 9	77.0 ± 21.9	78.0 ± 22.0	0.981
Androstenedione (ng/ml)	0.73 ± 0.26	0.75 ± 0.22	0.73 ± 0.24	0.73 ± 0.22	0.482
Free androgen index	38.1 ± 12.0	39.4 ± 12.3	39.6 ± 11.2	40.3 ± 11.5	0.121
Dehydroepiandrosterone (ng/ml)	1.78 ± 1.05	1.95 ± 0.92	1.84 ± 0.99	1.97 ± 1.03	0.057

Table 2 (continued)

Variables	Q1	Q2	Q3	Q4	*P*
5-Androstene-3b,17b-diol (ng/ml)	0.67 ± 0.37	0.67 ± 0.35	0.68 ± 0.36	0.69 ± 0.34	0.826
Dehydroepiandrosterone sulfate (mg/ml)	0.85 ± 0.53	1.02 ± 0.59	0.92 ± 0.54	1.00 ± 0.53	<0.001

Data were presented as mean ± standard deviation for continuous variables or number (%) for categorical variables

ANOVA was used for continuous variables and Chi-square test was used for categorical variables

All hormone assays were performed by gas chromatography–mass spectrometry (GC/MS)

BMI body mass index, *SHBG* sex hormone-binding globulin, Free androgen index: calculated using (TT/SHBG × 100), *PASE* physical activity scale for the elderly, *AHA-DLR scores* adherence index of AHA diet and lifestyle recommendations, *SBP* systolic blood pressure, *DBP* diastolic blood pressure

Table 3 Hazard ratios (HRs and 95% CIs) of the association between dietary acrylamide exposure and cancer mortality from overall, digestive system and respiratory system and sensitivity analysis among current non-smokers by Cox regression model among Hong Kong elderly men and women

Acrylamide exposure	Q1	Q2	Q3	Q4	*P* for trend
Median (min–max) (μg/day)	8.16 (0–9.94)	11.48(9.94–12.94)	14.64 (12.94–17.09)	21.36 (17.09)	
Number	958	950	959	956	
Overall cancer mortality					
Cases/person-years	71/9488	73/9688	86/9969	100/10,116	
Crude HR (95% CI)	1.0 (reference)	0.9 (0.7–1.4)	1.1 (0.8–1.5)	1.3 (0.9–1.7)	0.077
Full adjusted HR (95% CI)	1.0 (reference)	1.2 (0.8–1.6)	1.4 (1.0–2.0)	1.9 (1.3–2.8)	0.001
Cancer mortality from digestive tract					
Cases/person-years	25/9488	31/9698	34/9969	41/10,116	
Crude HR (95% CI)	1.0 (reference)	1.2 (0.7–2.0)	1.3 (0.8–2.1)	1.5 (0.9, 2.4)	0.121
Full adjusted HR (95% CI)	1.0 (reference)	1.3 (0.8–2.2)	1.4 (0.8–2.5)	1.9 (1.0, 3.6)	0.052
Cancer mortality from respiratory system					
Cases/person-years	24/9488	22/9698	26/9969	34/10,116	
Crude HR (95% CI)	1.0 (reference)	0.9 (0.5–1.6)	1.0 (0.6–1.7)	1.3 (0.8–2.2)	0.289
Full adjusted HR (95% CI)	1.0 (reference)	1.2 (0.7–2.2)	1.3 (0.7–2.5)	2.0 (1.0–4.0)	0.056
Overall cancer mortality in non-current smokers					
Number	892	890	893	874	
Cases/person-years	62/8894	65/9173	70/9309	85/9271	
Crude HR (95% CI)	1.0 (reference)	1.0 (0.7–1.4)	1.1 (0.7–1. 5)	1.3 (0.9–1.8)	0.130
Full adjusted HR (95% CI)	1.0 (reference)	1.2 (0.8–1.7)	1.4 (0.9–2.0)	2.0 (1.3–3.1)	0.002

Participants with baseline cancer history were excluded and 3823 were included for the analysis. Cox regression was used for the analysis among overall participants and participants who were non-current smokers. The adjusted variables (by entering method) in Cox regression model included: sex, age, education, total energy (kcal), BMI (kg/m^2), smoking (no, occasional and current), total AHA-DRL score, tea drinking (ml/week), coffee (ml/day), physical activity (PASE total score), medical history of diabetes, dietary carbohydrate (g % kcal), dietary red or processed meats intake (% kcal) and dietary fiber intake (g/day)

consumption in the study participants. Based on our findings, mitigation procedures to minimize the formation of acrylamide in vegetables and cereals by reducing the cooking temperature and time, as well as sugars in foods could probably help to decrease the acrylamide exposure and cancer mortality in the Chinese elderly population.

Studies in rodents have shown positive dose–response relations between acrylamide exposure and cancer in multiple organs (Shipp et al. 2006). However, observational studies on dietary acrylamide intake and its relation with cancer risk have reported inconsistent findings. Some indicated positive association between acrylamide exposure and increased risk of endometrial or ovarian cancer (Hogervorst et al. 2007; Wilson et al. 2010), renal cancer (Hogervorst et al. 2008a, b; Pelucchi et al. 2015), cutaneous malignant melanoma in men (Lipunova 2016), estrogen receptor positive breast cancer (Olesen et al. 2008), lymphatic malignancies (Bongers et al. 2012), colorectal cancer with specific mutations in KRAS and APC (Hogervorst et al. 2014) and lung cancer in smoking men (Hirvonen et al. 2010); but no

Table 4 Hazard ratios (HRs and 95% CIs) of the associations between acrylamide exposure and overall cancer mortality: subgroup analyses by sex (male and female), obesity (BMI< and ≥24) and total AHA-DRL score (< and >median) among Hong Kong elderly men and women

Acrylamide exposure	Q1	Q2	Q3	Q4	*P* for trend
Median (min–max) (μg/day)	8.16 (0–9.94)	11.48 (9.94–12.94)	14.64 (12.94–17.09)	21.36 (17.09)	
Sex (*P* for interaction = 0.259)					
Men					
N/cases/person-years	347/36/3335	414/43/4104	522/62/5383	630/72/6676	
Full adjusted HR (95% CI)	1.0 (reference)	1.3 (0.8, 2.0)	1.5 (1.0, 2.4)	1.9 (1.1, 3.1)	0.011
Women					
N/cases/person-years	611/35/6153	536/30/5593	437/24/4587	326/28/3440	
Full adjusted HR (95% CI)	1.0 (reference)	1.0 (0.6, 1.7)	1.1 (0.6, 2.0)	2.0 (1.0, 3.9)	0.059
BMI (P for interaction = 0.631)					
BMI < 24					
N/cases/person-years	543/36/5350	510/42/5149	553/49/5712	517/52/5494	
Full adjusted HR (95% CI)	1.0 (reference)	1.5 (1.0, 2.4)	1.6 (1.0, 2.6)	2.1 (1.2, 3.6)	0.011
BMI ≥ 24					
N/cases/person-years	415/35/4138	440/31/4549	406/37/4257	438/48/4612	
Full adjusted HR (95% CI)	1.0 (reference)	0.9 (0.5, 1.5)	1.3 (0.8, 2.1)	1.7 (0.9, 3.1)	0.049
AHA-DLR (*P* for interaction = 0.852)					
AHA < median					
N/cases/person-years	589/51/5750	481/40/4829	468/56/4800	446/61/4664	
Full adjusted HR (95% CI)	1.0 (reference)	1.1 (0.7, 1.6)	1.6 (1.0, 2.4)	2.0 (1.3, 3.3)	0.002
AHA ≥ median					
N/cases/person-years	364/20/3688	465/33/4825	490/30/5158	508/39/5439	
Full adjusted HR (95% CI)	1.0 (reference)	1.3 (0.8, 2.4)	1.2 (0.7, 2.3)	1.8 (0.9, 3.5)	0.107

Participants with baseline cancer history were excluded and 3823 were included for the analysis. The adjusted variables (by entering method) in Cox regression model included: sex, age, education, total energy (kcal), BMI (kg/m^2), smoking (no, occasional and current), total AHA-DRL score, tea drinking (ml/week), coffee (ml/day), physical activity (PASE score), medical history of diabetes, red or processed meats (%kcal) and dietary fiber (g/day). For women, we further adjusted for years since menopause (years), age of first menstruation (years), years of contraceptives injection or drugs (years), years of estrogen use (years)

AHA-DLR scores adherence index of AHA diet and lifestyle recommendations

associations were observed for bladder and prostate cancer (Hogervorst et al. 2008a, b, Larsson et al. 2009), colorectal cancer (Mucci et al. 2006; Hogervorst et al. 2008a, b), lung cancer in men (Hogervorst et al. 2009), gastric, pancreatic and oesophageal cancers (Hogervorst et al. 2008a, b). A recent systematic review and meta-analysis (Pelucchi et al. 2015) of epidemiological studies indicated a borderline association with dietary acrylamide emerged for endometrial (RR = 1.23; 95% CI 1.00–1.51) and ovarian (RR = 1.39; 95% CI 0.97–2.00) cancers in never smokers, and a modest association for kidney cancer.

Studies that examined the relationship between dietary acrylamide and cancer mortality or prognosis were limited. Only one longitudinal study (Olsen et al. 2012) investigated the relationship of dietary acrylamide exposure and breast cancer mortality. The cohort of 420 postmenopausal Danish women of breast cancer indicated that pre-diagnostic acrylamide exposure reduced survival after breast cancer diagnosis (Olsen et al. 2012). Among non-smokers, higher concentrations of GA-Hb were associated with an increased risk of breast cancer specific mortality [HR (95% CI) 1.63 (1.06–2.51)] (Olsen et al. 2012). Our results revealed that dietary acrylamide exposure was associated with increased overall cancer mortality. More research is needed to explore the associations of acrylamide exposure with specific cancer mortality or prognosis.

Mechanisms

The biological mechanism by which acrylamide causes cancer development in humans is yet unclear. Both genotoxic and non-genotoxic pathways have been suggested (Besaratinia and Pfeifer 2007). Acrylamide itself and its epoxide metabolite glycidamide, which is generated by cytochrome P4502E1 (CYP2E1), are clastogenic, and glycidamide forms DNA adducts. Acrylamide may also cause cancer through non-genotoxic mechanisms. Oxidative stress, following depletion of glutathione by acrylamide, is one of the proposed mechanisms. Acrylamide reacts with glutathione and may thus alter the redox status of cells

and gene transcription and expression, facilitating cancer development (Catalgol et al. 2009), or it may interfere with DNA repair or hormonal balances (Besaratinia and Pfeifer 2007). In some test systems, aneuploidy was observed upon acrylamide incubation, which might be caused by binding of acrylamide to proteins involved in cell division, such as mitotic/meiotic spindle kinesins (Sickles et al. 2007).

Acrylamide may also be carcinogenic through hormonal pathways (Hogervorst et al. 2007). Our results also suggested that additional adjustment of free estradiol level in multivariable regression model reduced the HRs of dietary acrylamide and cancer mortality to around 1. Acrylamide has been shown to alter steroid hormone levels in premenopausal (Nagata et al. 2015) and postmenopausal women (Hogervorst et al. 2013). There could be interactions between acrylamide intake and genes involved in the generation of sex hormones (Hogervorst et al. 2016; Hogervorst et al. 2017). The influence on circulating estrogen levels is the key mechanism behind several of the factors known to be associated with breast cancer incidence and/or prognosis (Kendall et al. 2007; Folkerd and Dowsett 2010).

Strengths

The strengths of this study include the use of a validated FFQ for acrylamide assessment, the prospective nature precluding selection and recall bias, the long duration of follow-up, and the completeness of case ascertainment through linkage to the registries of the Health Authority.

We assessed acrylamide intake based on an analytical acrylamide database with acrylamide values derived from an extensive and elaborate sampling scheme and chemical analysis of all relevant Hong Kong foods. A previous study suggested that using mean acrylamide levels in foods to estimate the total acrylamide intake could be a valid approach (Zhou et al. 2013). For estimating the long-term exposure to the usual acrylamide intake in our study, the mean acrylamide levels for foods are expected to be even more suitable. Finally, protopathic bias was probably not present in our prospective cohort study, as exclusion of death cases in the first 2 years of follow-up did not alter the conclusions.

Limitations

This study has several limitations. First, as in most of epidemiological studies, we used a validated FFQ to estimate dietary acrylamide exposure. Although the use of FFQs has limitations of possible misclassification, they are the only feasible way in large epidemiological studies to assess the intake of the relevant acrylamide-containing foods over a long time period (Wilson et al. 2009). In addition, the non-differential misclassification could only bias the risk estimates toward null. Although acrylamide adducts to hemoglobin are recognized as the internal dose markers of 'exposure' to acrylamide (Dybing et al. 2005), they represent the exposure during the preceding 3–4 months only. The biomarker is not specific with regard to the source of acrylamide. The costs of using biomarkers also limit the size of the population that can be used. In multivariable regression models, we further adjusted for dietary carbohydrate and fibers, the nutrients that are correlated to acrylamide, which suggested that the significant associations of acrylamide and cancer mortality could be due to the acrylamide itself, but not dietary carbohydrate and fiber levels. In addition, dietary intakes by FFQ were only assessed at baseline; we did not conduct the same dietary survey during follow-up. The food intakes that were investigated in 2001–2003 may not be completely representative of the foods that were on the market during follow-up. It has been shown that after 2005, acrylamide levels in some products have decreased (Stadler 2005). However, the reduction of acrylamide mostly occurred in fried potatoes, which had a minor contribution to overall acrylamide exposure in our study population since they had low intake of fried or baked food or snacks.

Second, although both industrial contact and tobacco smoking are important sources of environmental acrylamide exposure (Wirfalt et al. 2008), exposure from diet and drinking water was the major route of acrylamide in our elderly participants since they were non-occupationally exposed and had low prevalence of current smoking (6.8%).

Third, we have not collected the data on new cancer cases during follow-up but only data on cancer mortality. In addition, we did not analyze the association of acrylamide exposure with each kind of cancer mortality due to insufficient individual cancer deaths. However, animal studies have demonstrated that acrylamide-induced cancers affected various tissues. This is because the molecule of acrylamide is small and hydrophilic, it passively diffuses throughout the body and all tissues are theoretical targets for acrylamide carcinogenesis (Friedman 2003). Our subgroup analyses on mortality in either digestive or respiratory system reported similar findings on the associations of acrylamide exposure and cancer deaths. Another limitation is that we did not collect the treatment information after cancer occurrence. However, the treatment is unlikely to be correlated with acrylamide intake, and thus the association would be reduced towards the null. Future studies on acrylamide and cancer mortality should take treatment into account.

Finally, the study was conducted by non-random sampling in a single center in Hong Kong, so the findings may not be generalizable to ethnic Chinese elsewhere. Additionally, potential residual confounders from unmeasured factors such as past occupational exposure to carcinogens and concomitant carcinogens from foods are possible. However, the increased strength of associations after multivariable adjustment indicates that residual confounding by the covariables

is probably not the explanation for the observed acrylamide-associated associations.

Conclusions

Dietary exposure to acrylamide in amounts typically ingested by Chinese elderly was found to be significantly associated with increased overall cancer mortality, and mortality from cancers of the digestive tract and respiratory system. Circulating free estradiol may mediate this association in men. Further prospective studies specifically conducted among new cases of certain cancer are necessary to confirm these findings.

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Author contributions ZML conceptualized the study, analyzed the data, interpreted the results, and drafted the manuscript. Suyang Wu helped in the calculation of dietary acrylamide exposure. All the coauthors critically commented on and revised the manuscript.

Compliance with ethical standards

Conflict of interest None of the authors have competing interests to report.

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