食事由来アクリルアミド摂取量の曝露評価方法に関する基礎的検討　および大規模コホートデータを用いたアクリルアミド摂取量とすい臓がんのリスクに関する疫学的解析

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麻布大学大学院　環境保健学研究科
環境保健科学専攻　博士後期課程
栄養疫学
DE1801　鬼頭　久美子

Study on the assessment method of dietary acrylamide exposure and Epidemiologic analyses of the association between dietary acrylamide intake and pancreatic cancer risk using large-scale cohort data

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Laboratory of Nutritional Epidemiology
The Graduate School of Environmental Health Sciences
Azabu University

DE1801 Kumiko Kito

目次

要旨

アクリルアミドは国際がん研究機関の発がん性分類で、「ヒトに対しておそらく発がん性がある物質」とされる。2016 年の食品安全委員会による健康影響評価では、「日本人における発がん性については懸念がないとは言えない」と評価され、アクリルアミド摂取とがん罹患に関する研究が求められている。本研究では、まずアクリルアミド摂取量の曝露評価方法に関する基礎的検討を行い、次に大規模コホートデータを用いたすい臓がんの発がんリスクに関する疫学的解析を行った。

1　食事由来アクリルアミド摂取量の曝露評価方法に関する基礎的検討

【背景】

曝露と疾病リスクとの疫学的検討に先がけ、曝露評価方法の基礎的検討が必要である。アクリルアミド摂取量の曝露評価方法には、食事記録法（dietary record, DR）、食物摂取頻度調査法（food frequency questionnaire, FFQ）などが用いられている。しかしながら、既存調査の多くは短期間の調査で、推定された摂取量が個人の習慣的な摂取量を反映するか不明である。習慣的な摂取量を個人レベルで把握するためには、摂取量の変動要因を理解し、その影響を考慮する必要がある。摂取量の変動要因として個人内変動と個人間変動があるが、アクリルアミド摂取量の個人内・個人間変動を検討した研究はこれまでに行われていない。

また FFQ は、アクリルアミド摂取量と疾病との関連を検討する際に使用されることが多い。これまでに日本人を対象としたコホート研究では、FFQ の妥当性が示唆されるとともに、日本人のアクリルアミド摂取量が欧米の集団と比較して少ないことが報告されている。しかしながら、それらは 1990 年代に実施した調査であり、より近年の研究は少ないのが現状である。

そこで本研究では、DR を用いたアクリルアミド摂取量の個人内・個人間変動の検討およびアクリルアミド摂取量推定における FFQ の妥当性を検討した。

1.1 食事記録法(DR)を用いたアクリルアミド摂取量の個人内・個人間変動の検討

【方法】

全国 5 地域に在住の男女 240 名(40～74 歳)を対象とした。2012～13 年に実施した 12 日間の DR(3 日間×4 季節)をもとにアクリルアミド含有量のデータベースを用いて、個人のアクリルアミド摂取量を推定した。DR から推定されたアクリルアミド摂取量を用い、混合効果モデルによって個人内・個人間変動を算出した。さらに個人内・個人間変動を用いて、個人の習慣的な摂取量の推定および集団における個人の順位付けに必要な食事調査日数を推計した。また、アクリルアミド摂取量の個人間変動を予測する食品については、ステップワイズ法を用いた重回帰分析を実施し、食品グループごとに偏寄与率、累積偏寄与率を算出した。

【結果】

個人間変動に対する個人内変動の分散比は 3.9 であった。個人の習慣的な摂取量を推定するために必要な食事調査日数として、個人の真値の 95%信頼区間の 10%および 20%の誤差範囲に入るためには、255 日および 64 日と推定された。また集団における個人の順位付けに必要な食事調査日数は、観測値と真の値の間の相関係数を 0.8 と想定した場合、7 日必要であると推計された。また、個人間変動を予測する主な食品は、コーヒー、じゃがいも、緑茶類などで、それらを含む上位 7 食品で個人間変動の約 90%以上をカバーした。

【考察】

個人の習慣的なアクリルアミド摂取量を推定するには、エネルギーなどの主要な栄養素と比較して、長期間の日数を要することが明らかになった。また集団内において、ある程度の精度で個人を順位付けするには 1 週間程の調査日数が必要であることが判明した。したがって、食事由来のアクリルアミド推定曝露量は個人内変動が大きいため、曝露評価を行う際に短期間の食事調査方法を用いると、個人内変動に起因する測定誤差が大きくなることが示唆された。個人間変動を予測する食品については、限られた食品数で個人間変動を予測できることが示唆された。

【結論】

DR を用いたアクリルアミド曝露評価において、集団内の順位付けおよび個人の習慣的な摂取量を推定するためには、長期間の食事調査日数を要することが明らかになった。

1.2 食事由来のアクリルアミド摂取量の推定における食物摂取頻度調査票(FFQ)の妥当性の検討

【方法】

2012～13 年に 1 年間隔で実施した 2 回の FFQ を用いて、個人ごとのアクリルアミド摂取量を推定した。DR を比較基準とした Spearman の順位相関係数、DR と FFQ 間の順位付けの一致度を示すκ係数(一致度 100%を1とする)を算出し、FFQ の精度を評価した。

【結果】

体重 kg あたりのアクリルアミドの平均摂取量は、DR で 0.17μg/day、FFQ で 0.16μg/day と推定された。アクリルアミド摂取量に寄与する主な食品(寄与割合%)は、コーヒー・ココア(25%)、緑茶(12%)、じゃがいも(7%)、和干菓子類(6%)、ビスケット(5%)であった。また FFQ の精度は、エネルギーおよび日間変動を調整した相関係数は男性で 0.39、女性で 0.33 であった。κ係数は、男性で 0.83、女性で 0.81 であった。

【考察】

本研究の平均アクリルアミド摂取量は、欧米の報告値の半分以下で、2012 年の食品安全委員会のモンテカルロシミュレーションによる推定値に近似していた。本研究の推定値は、1990 年代の研究と比較してやや多く、コーヒーや菓子類の摂取量が多くなったことに起因していると考えられた。

FFQ の精度は、DR と FFQ 間の相関係数が類似の妥当性研究と近似していることや、DR と FFQ 間で高い一致度が確認されたことから、集団内における個人の順位付けにおいて、ある程度の正確性があると考えられた。

【結論】

DR と FFQ 間の高いκ係数より、疫学研究において、集団内の個人の順位付けに FFQ の使用が可能であると考えられた。

2　大規模コホートデータを用いた食事由来アクリルアミド摂取量とすい臓がんのリスクに関する疫学的解析

【背景】

アクリルアミドの一部は、シトクロム P450（CYP2E1）によってグリシダミドに代謝される。グリシダミドは、ヘモグロビンや DNA と付加体を形成し、遺伝毒性を有すると考えられている。現在、膵臓がんのリスクと食事中のアクリルアミド摂取量との関連について検討が行われている。欧米の 4 報の疫学研究を統合したメタアナリシス（複数の疫学研究を統合し、解析する研究方法）では、膵臓がんの罹患リスクは認められていない。しかしながら、研究数が少なくエビデンスの根拠として乏しい。さらに、既存研究はすべて欧米で実施され、アジアにおいて検討されていない。そこで本研究では、食事に由来するアクリルアミド摂取量とすい臓がん罹患の関連を検討した。

【方法】

1990～1993 年に全国 10 地域に居住していた 40～69 歳の男女約 14 万人のデータを用いた。対象者の選択基準を 5 年後調査時の FFQ に回答した者とし、除外基準を 1)追跡できない者（研究エリア外に在住、研究開始前の転出、外国籍、対象外年齢、重複登録）、2)がんの既往がある者、3)FFQ の推定エネルギー量が極端な者とし、約 8.9 万人を解析対象者とした。研究デザインは、前向きコホート研究（経時的に対象集団を追跡する研究）で、5 年後調査時点（1995 年または 1998 年）を起点とし、すい臓がんの罹患の有無を 2013 年まで追跡した。

FFQ によるアクリルアミド摂取量は、アクリルアミド含有量のデータベースを用いて推定した。Cox 比例ハザード回帰モデルを用いて、アクリルアミド摂取量の最も少ないグループを基準とし、各グループのハザード比と 95%信頼区間を算出した。さらに喫煙状態、体格指数、飲酒量など、アクリルアミドの代謝やすい臓がんの罹患に影響する可能性のある要因について、対象者を層別にして、ハザード比を算出した。

【結果】

15.2 年追跡し、すい臓がん 576 症例が特定された。1日あたりのアクリルアミド摂取量の平均値±標準偏差は、6.92±3.81 μg/d であった。最も摂取量の多いグループは、年齢が若く、喫煙者の割合が多く、コーヒーの摂取量が多い

特徴が確認された。最も摂取量の多いグループの調整後のハザード比は、0.83(95%信頼区間: 0.65-1.05, P for trend = 0.07)であり、すい臓がんの罹患リスクは認められなかった。さらに、性別、喫煙状態、体格指数、飲酒量、コーヒー摂取量、緑茶摂取量による層別解析においても関連は認められなかった。

【考察】

FFQ より推定したアクリルアミド摂取量とすい臓がんの罹患には関連がないことが示唆された。これまでに日本人を対象とし、発がんリスクを検討した研究では、一貫して関連は認められていない。その一因として、欧米と比較して、日本人のアクリルアミド摂取量が少ないことが考えられる。また日本人のアクリルアミドの主な摂取源は欧米と異なるが、本研究の結果は欧米で得られた知見と同様であることから、アクリルアミド摂取に対する感受性に人種間の差がない可能性を示した。さらに、体格指数や飲酒量などによる層別解析でも、すい臓がんの罹患に関連は認められなかったが、これらの要因はアクリルアミド代謝に影響を与えることが報告されているため、今後バイオマーカーを使用し、これらの影響を考慮した発がんリスクの検討が必要である。

【結論】

日本人において、FFQ より推定したアクリルアミド摂取量の多寡によるすい臓がんの罹患には関連がないことが示唆された。

【総括】

アクリルアミドは、人への発がんリスクの可能性から、定量的な曝露評価が期待されているが、本研究より、アクリルアミド摂取の個人内変動が高いため、個人の摂取量（絶対値）の推定には、長期間の食事調査日数が必要であることが明らかになった。本研究結果は、食品安全政策におけるアクリルアミドの健康影響を評価する際の曝露評価方法の基礎資料として貢献し得る。

また、アクリルアミド摂取量とすい臓がんのリスクに関する疫学的解析から、関連がないことが確認されたが、これまで世界的にも検討が少なく、アジアでは初の検討となることから、公衆衛生学上の意義が大きいと考えられる。

Abstract

Acrylamide (AA) was classified as 'probably carcinogenic to humans' by the International Agency for Cancer Research. According to the report of an assessment conducted by the Food Safety Commission of Japan in 2016, the neoplastic risk related to acrylamide intake for Japanese could not be excluded because of the insufficient margin of exposure (MOE). Therefore, more epidemiologic studies on dietary acrylamide intake and cancer risk are warranted. We first conducted this study on the method of assessing acrylamide exposure and then performed epidemiologic analyses of the pancreatic cancer risk using large-scale cohort data. The summary is as follows:

1. Study on the assessment method of dietary acrylamide exposure

【Introduction】

Before the epidemiologic study of exposure and disease risk, studies on dietary acrylamide exposure assessments are needed. Methods such as dietary records (DRs) and food frequency questionnaires (FFQs) are used to assess dietary acrylamide exposure. However, because most of these

surveys are conducted over a short period, it is unknown whether the estimated intake represents the actual long-term acrylamide exposure at the individual level. To grasp the habitual acrylamide intake at the individual level, it is necessary to understand the variation factors of intake and to consider their effects. Within-individual and between-individual variations in dietary intake are known as variation factors. However, no studies have evaluated these variation factors in dietary acrylamide intake.

FFQs are often widely used to study the association between acrylamide intake and disease. A previous Japanese cohort study suggested the validity of the FFQ; it has been reported that dietary acrylamide intake in the Japanese population is lower than that in the Western population. However, these surveys were conducted in 1995 and 1998, and almost no studies have been conducted recently.

This study aimed to identify variations in the estimated dietary acrylamide intake of the Japanese population and to validate the FFQs for the estimation of acrylamide intake.

1.1 Study on within-individual and between-individual variations in acrylamide intake using dietary records

【Methods】

The study included 240 participants aged 40–74 years living in five areas in Japan. Twelve-day DRs were collected between 2012 and 2013. Dietary acrylamide intake was estimated from an acrylamide content database. Within-individual and between-individual variations were calculated using the random-effects model.

Furthermore, using the calculated within-individual and between-individual variations, we estimated the number of days for a dietary survey required to evaluate individuals' usual intake and rank individuals in a group. For foods that predict between-individual variations in acrylamide intake, multiple regression analysis using the stepwise method was performed, and the partial contribution rate and cumulative partial contribution rate were calculated for each food group.

【Results】

The ratio of within-individual variation to between-individual variation was 3.9, and within-individual variation was larger than between-individual

variation. Days of DRs necessary for estimating the true intake within 10% and 20% were 255 days and 64 days, respectively. The number of days required to ensure an R-value of 0.8 for ranking individuals was seven days. Foods that contributed to the between-individual variations were in the following order: coffee/cocoa, potatoes, green tea, sweet potatoes, and biscuits/cookies. These top seven foods accounted for approximately 93% of the total variation.

【Discussion】

We demonstrated that estimating the habitual dietary acrylamide intake from DRs requires an extended data collection period due to the large within-individual variation in dietary acrylamide intake. We indicated that the number of days of dietary recording required to estimate individuals' intragroup ranking with a certain degree of accuracy is approximately seven days. Therefore, when the variation ratio and/or within-individual variation is large, the estimation of acrylamide intake using short-term dietary surveys may lead to a misclassification of rankings and may not represent an individual's habitual intake. For foods predicting between-individual variation, our results suggest that it is possible to rank the acrylamide intake according to several kinds of foods.

【Conclusion】

Estimating acrylamide intake using DRs requires an extended data collection period to evaluate individuals' intragroup ranking and habitual intake.

1.2 Study on the validity of the Food Frequency Questionnaire (FFQ) in estimating dietary acrylamide intake

【Methods】

FFQs were administered twice between 2012 and 2013 at an interval of 1 year. Dietary acrylamide intake was estimated from an acrylamide content database. FFQ validity was assessed by Spearman's correlation coefficients between the FFQ and DR estimations and by weighted kappa coefficients, which indicate the degree of agreement of the ranking between the DRs and FFQs.

【Results】

The mean ± standard deviation (SD) dietary acrylamide intake values were 0.17 μg/day in DRs and 0.16 μg/day in FFQs. The main food groups from the DRs that contributed to the acrylamide intake were coffee/cocoas

(25%), green tea (12%), potatoes (7%), traditional dry confections (6%), and biscuits/cookies (5%). The value of the estimated acrylamide intake determined using the FFQ indicated that the energy-adjusted and deattenuated correlation coefficients were 0.39 for men and 0.33 for women. The weighted kappa coefficients were 0.83 for men and 0.81 for women.

【Discussion】

The mean intake in our study was half of that in Western populations and was similar to that of the previous Monte Carlo simulation studies of Japanese populations. Therefore, compared to the surveys in the 1990s, our results suggested that the acrylamide intake increased slightly, and the foods that contributed to the intake were almost the same, but the contribution proportion was different in some foods.

In this study, the validity of estimating acrylamide intake using the FFQ was similar to that in the previous study, and high kappa values were found. Therefore, the FFQ is suitable for ranking individual intragroup.

【Conclusion】

The high kappa-values between DR and FFQ suggest that FFQ is appropriate for individuals' rank within a population in epidemiological

studies.

2. Epidemiologic analyses of the association between dietary acrylamide intake and pancreatic cancer risk using large-scale cohort data

【Introduction】

Some acrylamide is metabolized to glycidamide by cytochrome P450 (CYP2E1). Glycidamide is known to cause genotoxicity by forming an adduct that binds to hemoglobin and DNA. Epidemiological studies have investigated the association between pancreatic cancer risk and dietary acrylamide intake.

A recent meta-analysis, including four studies conducted in Western countries, showed that dietary acrylamide intake was not associated with the risk of pancreatic cancer. However, the evidence for the risk of pancreatic cancer may be insufficient owing to the very small number of studies. Moreover, all previous studies were conducted in Western countries and did not examine the relationship between dietary acrylamide intake and the risk of pancreatic cancer among Asians. This study aimed to identify the association between dietary acrylamide intake and pancreatic cancer

risk in the Japanese population.

【Methods】

The study included approximately 140,000 participants aged 40–69 years who lived in 10 public center areas between 1990 and 1993. The inclusion criterion for participants was respondents to the 5-year follow-up survey. The exclusion criteria were as follows: 1) ineligible participants (living in different targeting areas, late report of migration occurring before the starting point, non-Japanese nationality, incorrect birth date, duplicate registration, participants who had died, moved out of the study area, or were lost to follow-up before the starting point); 2) participants with a history of cancer identified using the questionnaire; and 3) participants with missing or extreme energy intake dates. The final analysis included approximately 90,000 participants.

The study design was prospective cohort study, and the participants were followed up from the starting point of the 5-year follow-up survey (1995 or 1998) until 2013 for pancreatic cancer incidence.

Acrylamide intake for each participant was estimated using the database. The Cox proportional hazards model was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for energy-adjusted acrylamide

intake and pancreatic cancer risk by percentile. The lowest acrylamide intake group was used as a reference. Furthermore, we stratified the analyses based on variables that were pancreatic cancer risk factors, such as smoking status, coffee intake, green tea intake, alcohol consumption, and body mass index (BMI).

【Results】

After a mean follow-up of 15.2 years, a total of 576 pancreatic cancer cases were identified. The mean acrylamide intake (SD) was 6.92 ± 3.81 μg/d, corresponding to 0.13 ± 0.16 μg/kg body weight/day. The group with the highest acrylamide intake (Q4) was younger, had a higher proportion of current smokers, and a higher intake of coffee.

We found no association between dietary acrylamide intake and pancreatic cancer. In the multivariate-adjusted model, the HR of the highest quartile vs. the lowest was 0.83 (95% CI: 0.65–1.05) (P for trend = 0.07). There were also no significant associations on the stratified analyses by sex, smoking status, coffee intake, green tea intake, alcohol consumption, and BMI.

【Discussion】

In a large prospective cohort of Japanese patients, no association was

found between pancreatic cancer risk and dietary acrylamide intake. Previous studies that assessed dietary acrylamide intake and cancer risk (such as breast cancer and digestive system cancer) in the Japanese population have consistently indicated a null association. A lower dietary acrylamide intake in the Japanese population compared to that in the Western population is considered a reason for the lack of association. In addition, our findings were consistent with those of previous studies. Therefore, there might not be a substantial difference in susceptibility to acrylamide intake between Asian and Western populations.

In stratified analyses by sex, smoking status, coffee consumption, green tea consumption, alcohol consumption, and BMI, no association was found between pancreatic cancer risk and dietary acrylamide intake. However, multiple factors related to diet and lifestyle may affect acrylamide metabolism. Therefore, further studies are warranted to explore the factors that affect acrylamide metabolism using biomarkers.

【Conclusion】

Dietary acrylamide intake was not associated with the pancreatic cancer risk in Japanese individuals.

【Summary】

Acrylamide is expected to be quantitatively evaluated in terms of its potential carcinogenic risk to humans. However, this study identified that the individual intake (absolute value) estimation requires long-term dietary survey records owing to large within-individual variations. These results may serve as primary data for exposure assessment methods in the health impact assessment of acrylamide in food safety policies.

In addition, epidemiological analysis of acrylamide intake and risk of pancreatic cancer showed no association, but there have been few studies worldwide so far, and since this is the first study in Asia, it has great significance from the viewpoint of public health.

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Variations in the estimated intake of acrylamide from food in the Japanese population

Kumiko Kito[1], Junko Ishihara[2*], Junpei Yamamoto[2], Takayuki Hosoda[2], Ayaka Kotemori[2], Ribeka Takachi[3], Kazutoshi Nakamura[4], Junta Tanaka[5], Taiki Yamaji[6], Taichi Shimazu[6], Yuri Ishii[6], Norie Sawada[6], Motoki Iwasaki[6], Hiroyasu Iso[7], Tomotaka Sobue[8] and Shoichiro Tsugane[6]

Abstract

Background: Due to concerns of carcinogenicity, it is necessary to assess long-term acrylamide exposure in individuals. Whether the available methods of estimating acrylamide intake can indicate long-term exposure remains unknown. We examined variations in the estimated dietary acrylamide intake of the Japanese population.

Methods: The study included 240 participants aged 40–74 years who were a part of the Japan Public Health Center-based Prospective Study for the Next Generation (JPHC-NEXT). Twelve-day dietary records (DRs) were collected over a one-year period, and food frequency questionnaires (FFQs) were collected twice during the year. Dietary acrylamide intake was estimated from an acrylamide content database. Within-individual variations and between-individual variations were calculated using the random effects model. A linear regression analysis was performed to identify foods with large between-individual variations.

Results: The ratios of within-individual variance to between-individual variation were 3.2 for men and 4.3 for women. Days of DRs required to estimate the usual individual intake within 20% of the true mean intake with 95% confidence were 60 days for men and 66 days for women. Coffee/cocoa, potato, and green tea contributed to between-individual variations, in that order, and seven foods contributed to 93% of the between-individual variation.

Conclusions: Estimating the acrylamide intake using DRs requires an extended data collection period to estimate the intragroup ranking and habitual intake of individuals. Long-term exposure assessments should be based on methods with less potential for measurement errors, such as the use of biomarkers.

Keywords: Acrylamide, Variation, Validity, Food frequency questionnaire, Dietary record

Introduction

Acrylamide is a Group 2A probable human carcinogen [1] that is widely used in industrial applications [2] and is detected in tobacco smoke [3] and food [4]. Acrylamide in food was first discovered in 2002 as a by-product in carbohydrate-rich, heat-processed foods, such as snacks, potato crisps, and bread [4]. The main dietary sources of acrylamide include coffee, bread, and potato chips [5–7]. Considering its potential carcinogenicity, it is critical to assess the effects of long-term exposure to acrylamide.

Methods such as dietary records (DRs), 24-h dietary recalls (24 h-Rs), duplicate methods (DMs), and total diet studies are used to assess dietary acrylamide exposure [5, 8–11]. DRs and 24 h-Rs are commonly used to assess the validity of food frequency questionnaires (FFQs) used to estimate the dietary acrylamide intake [5, 8]. Furthermore, total diet studies have been conducted to assess the risk associated with acrylamide intake [10, 11]. However, because most of these surveys are conducted over a brief period, it is difficult to assess the long-term acrylamide exposure from dietary intake at

* Correspondence: j-ishihara@azabu-u.ac.jp
[2]Department of Food and Life Science, Azabu University, 1-17-71 Fuchinobe, Chuo-ku, Sagamihara-city, Kanagawa 252-5201, Japan
Full list of author information is available at the end of the article

the individual level. Particularly for nutrients and ingredients that have large within-individual variations, it is necessary to consider whether the estimated intake is representative of the individual's true intake.

Estimating the true mean intake of acrylamide is important for determining the accurate risk of acrylamide exposure from food. FFQs are well-suited for ranking individuals, but it is difficult to set a threshold because FFQs cannot sufficiently estimate the absolute intake of individuals. However, we can determine the number of days of DRs required to estimate the usual individual intake because long-term DRs allow for the estimation of the individual's absolute value and variations. An estimation of the true mean intake can be a useful resource for risk assessment and assessing the association with diseases. The estimated value may lead to reference values that can be used for guidelines, as evidence of public health comments, and for individual dietary counseling. To the best of our knowledge, no reported studies have evaluated variations in the estimated within-individual and between-individual dietary acrylamide intakes or investigated the number of days of DRs needed to estimate the individual habitual intake and individual ranking in groups.

FFQs are widely used in large-scale epidemiological studies to determine the effects of long-term dietary acrylamide intake [12, 13]. As with most epidemiologic applications of FFQs, ranking is the primary objective. To rank individuals, FFQs must include foods that have between-individual differences in intake within the group. Although population studies have been performed and reported foods that contribute to the absolute intake of dietary acrylamide [5–7], studies predicting between-individual variations for foods are limited. This study aimed to identify variations in the estimated dietary acrylamide intake of the Japanese population.

Methods

Data collection and study participants

Details of the study design and participant characteristics have been described previously [14]. Validation studies of the FFQ were conducted in five areas (Yokote, Saku, Chikusei, Murakami, and Uonuma) according to the protocol of the Japan Public Health Center-based Prospective Study for the Next Generation (JPHC-NEXT) between November 2012 and December 2013 [14]. FFQs were administered twice, with an interval of 1 year. DR reference intake data were obtained from all participants using a consecutive 3-day weighed food record (which included a weekend) at 3-month intervals across all seasons (winter, spring, summer, autumn) [14]. A group of 253 participants completed the 12-day DRs and FFQs. Of the participant group of 253 individuals, this study included 240 participants (98 men and 142 women) 40–74 years of age.

Database of acrylamide-containing foods

We used an established database of foods that contain acrylamide to estimate the acrylamide intake from the DRs and FFQs [5]. The database was developed using 10 published reports of acrylamide measurements in common Japanese foods [15–24]. The database consists of foods listed in the Standard Tables of Food Composition in Japan, Fifth Revised and Enlarged Edition (5th FCT). Of the 1878 foods listed in 5th FCT, 282 foods contain acrylamide and 1276 foods do not contain acrylamide. The remaining 320 foods do not have appropriate measurements; therefore, they were treated as missing values. Details of the development of the database have been described previously [5]. The database includes heat-processed foods such as bread, biscuits, cookies, and coffee, and home-cooked foods such as stir-fried vegetables, toast, and fried batter [5]. Cooking methods such as deep-frying and baking are considered for the following foods in this database: potatoes, onions, bean sprouts, asparagus, sweet peppers, squash, cabbage, string beans, eggplant, broccoli, podded peas, sweet potatoes, toasted bread, deep-fried batter, and stir-fried rice [5].

Calculation of dietary acrylamide intake from the dietary records

The study participants recorded menus, food and beverage names, and the amounts consumed (according to weight) in a food diary. Dieticians checked the DRs and coded each food using item numbers from the Standard Tables of Food Composition in Japan - 2010 (FCT 2010) [14]. Acrylamide intake from specific cooked foods not listed in the FCT 2010, such as toasted bread, was calculated by dieticians using the menu to determine how the foods were cooked. The nine cooking methods employed were coded as follows: raw, boiled, deep-fried, deep-fried with batter, baked, stir-fried, steamed, lightly stir-fried, and unclear. The dietary acrylamide intake was calculated by multiplying the amount of each food and its acrylamide-intake value from the database of acrylamide-containing foods. Energy intake was also calculated using the FCT 2010.

Calculation of dietary acrylamide intake from the food frequency questionnaire

An FFQ was designed to estimate the habitual dietary intake for the previous 1 year [14]. Of the 172 food items considered, the following 36 (21%) were designated as acrylamide-containing foods: rice, miso, beer, baked eel, baked fish paste, fried fish paste, bread, rice cake, Japanese-style confectionary, rice crackers, cakes,

biscuits and cookies, chocolates, potato chips, peanuts, fried tofu, roasted and ground beans, sesame, sencha (a type of green tea), bancha (a type of green tea), oolong tea, black tea, coffee, instant coffee, soup, potatoes, sweet potatoes, onions, bean sprouts, asparagus, sweet peppers, squash, cabbage, eggplant, snap beans, and broccoli. For rice, bread, potato, sweet potato, and vegetables (onions, bean sprouts, asparagus, sweet peppers, squash, cabbage, eggplant, snap beans, and broccoli), the acrylamide intake was calculated by considering the cooking methods, because our original FFQ estimated the amount of acrylamide from raw food intake only. Weighted averages were used to estimate the acrylamide intake values of these foods after considering the proportion of acrylamide for each cooking method, which was obtained from DRs of the Japan Public Health Center-based Prospective Study (JPHC Study) [5]. The cooking proportions from the JPHC study were used to limit potential overestimation of validity that could occur by using the cooking proportion calculated from DRs for comparison purposes when examining the validity of the FFQ. The dietary acrylamide intake was estimated by multiplying the acrylamide concentration, consumption frequency, and portion size of each food.

The estimated acrylamide intake value for fried batter was calculated using the participants' responses to the following question in the original FFQ: "How often do you consume deep-fried foods with batter?" Respondents chose their response from the following six frequency categories: almost never, 1–3 times/month, 1–2 times/week, 3–4 times/week, 5–6 times/week, and daily. Acrylamide intake from these foods was estimated by multiplying the frequency of fried-food consumption with batter by the value of daily acrylamide intake from fried batter calculated from the DRs of the JPHC study [5]. The total acrylamide intake calculated from the FFQ was the sum of the acrylamide intake for each food item and the fried batter.

Statistical analysis

Mean (with standard deviations [SDs]) and median with 5th and 95th percentile values of dietary acrylamide intake were calculated according to sex. Percentage differences in acrylamide intake according to the DR and FFQ methods were computed using the following formula:

$$((\text{acrylamide intake from FFQ} - \text{acrylamide intake from DR})/\text{acrylamide intake from DR}) \times 100$$

Data were analyzed using the random effects model:

$$\text{Nutrient } Y_{ijk} = \mu + \text{participant}_i + \text{Season } X_{ij} + \text{day } X_{ijk} + \varepsilon_{ijk}$$

where μ is the mean of acrylamide intake; participant_i is the random variable for variation among subjects; Season $X_{ij,}$ day X_{ijk} represents the random effects of the season and day; and the error term (ε_{ijk}) represents the random within-person variance. Using this calculation, acrylamide intake data (level 1) were nested for seasons (level 2), which were nested within participants (level 3). Estimates of within-individual variance ($\hat{\sigma}_w^2$) and between-individual variance ($\hat{\sigma}_b^2$) were calculated by setting mean squares (MSs) equal to their expected values. Variances were estimated using the Mixed procedure in SAS (version 9.4; SAS Institute Inc., Cary, NC, USA). We used untransformed data to analyze within-individual and between-individual variations because a previous study suggested that transformed data are likely to underestimate the number of days required for ranking individuals in a group [25].

We also calculated the number of days of DRs needed to estimate an individual's habitual intake with 95% confidence within a specified percentage deviation using the following formula [26, 27]:

$$D = (Z_\alpha CV_w/E)^2$$

where D is the number of days needed per person; Z_α is 1.96; CV_w is the within-individual coefficient of variation; $\frac{\sqrt{\hat{\sigma}_w^2}}{\text{mean acrylamide intake}} \times 100$; and E is the specific degree of error as a percentage of long-term habitual intake (10% or 20%).

The number of days (D) needed to obtain a given unobservable correlation between the observed and true mean intake was calculated using the following formula [26]:

$$D = \frac{r^2}{1-r^2} \times \frac{\hat{\sigma}_w^2}{\hat{\sigma}_b^2}$$

where r is the unobservable correlation between the observed and true mean nutrient intakes of an individual during the period of observation and D indicates days. The chosen value of r is dependent on the degree of acceptable misclassification [26]. We set the r values to 0.9, 0.8, and 0.5 to estimate the number of days required to rank individuals.

A linear regression analysis with stepwise selection was used to identify foods that contributed to between-individual variations, with acrylamide intake from each food item as the explanatory variable and the total acrylamide intake according to the DRs as the response variables. A partial R-squared model value was developed for the selected food items.

The following analysis was conducted to determine the validity and reproducibility of the FFQ and the contribution

of each food to the total acrylamide intake. The results are summarized in Additional file 1: Table S1 and Additional file 2: Table S2. We used log-transformed data for energy and acrylamide intake for this analysis. Spearman's rank correlation coefficients for DR and FFQ estimations were computed for crude and energy-adjusted values, and the energy was adjusted using the residual method. Additionally, deattenuated correlation coefficients were calculated as the correlation coefficients for DR and the FFQ estimations that were attenuated by individual variations in daily intake. Deattenuation was calculated using the following formula:

$$\text{Deattenuated correlation coefficient} = \text{energy–adjusted correlation coefficient} \times \sqrt{1+\frac{\lambda}{n}}$$

where λ is the ratio of within-individual variations and between-individual variations of DRs, and n is the number of DRs for each participant (12 days). For the cross-classification analysis, energy-adjusted acrylamide intake from DRs and the FFQ were categorized into quintiles, and the proportion of participants among the same, adjacent, and opposite categories were calculated using both quintile numbers. In addition, weighted kappa coefficients were computed. The contribution of each food to the total acrylamide intake was computed as the percentage of acrylamide intake from each food for the total amount of acrylamide intake from DR data. In addition, Spearman's correlation coefficients for the FFQ and DR estimations were calculated as FFQ validity. All analyses were performed using SAS (version 9.4).

Results

Participant characteristics

Participants in this study had mean ages of 57.4 years (men) and 57.0 years (women). The mean body mass index (BMI) values were 23.7 kg/m^2 for men and 22.8 kg/m^2 for women. The percentages of current smokers were 26.5% for men and 2.1% for women [14]. Participant characteristics according to acrylamide intake are shown in Table 1. The mean ± SD dietary acrylamide intake values for men were 4.7 ± 1.3, 8.8 ± 1.2, and 15.8 ± 4.3 μg/day for the lowest, middle, and highest tertile of dietary acrylamide intake, respectively. For women, these values were 5.7 ± 1.3, 9.3 ± 1.2, and 15.6 ± 5.2 μg/day for the lowest, middle, and highest tertile of dietary acrylamide intake, respectively. The coffee intake (g/day) increased linearly from the lowest to the highest tertile for both men and women. Table 2 shows the mean, standard deviation, median, and the 5th–95th percentiles of acrylamide intakes estimated from the DRs and FFQs. The mean acrylamide intake values estimated from DRs

Table 1 Characteristics of the participants

	Tertiles of acrylamide intake		
	Lowest	Middle	Highest
	T1 Mean ± SD or %	T2 Mean ± SD or %	T3 Mean ± SD or %
Men No. of participants	32	33	33
Acrylamide intake			
Mean (μg/day)[a]	4.7 ± 1.3	8.8 ± 1.2	15.8 ± 4.3
Median (μg/day) [a]	4.9	8.9	14.6
Age			
Mean (years)	60 ± 8	55 ± 8	57 ± 10
Median (years)	62.0	56.0	57.0
Body mass index			
Mean (kg/m^2)	22.9 ± 2.2	24.0 ± 3.2	24.1 ± 2.9
Median (kg/m^2)	23.2	24.5	24.0
Smoking (n,%)			
Never smoker	7 21.9	10 30.3	6 18.2
Ex-smoker	18 56.3	13 39.4	18 54.5
Current smoker	7 21.9	10 30.3	9 27.3
Education (n,%)			
Junior high school	6 18.8	2 6.1	1 3.0
High school	13 40.6	14 42.4	10 30.3
Some college	7 21.9	10 30.3	8 24.2
College or more	6 18.8	7 21.2	14 42.4
Dietary intake Mean			
Energy intake (kcal) [a]	2082 ± 363	2287 ± 383	2570 ± 456
Coffee (g/day) [a]	32 ± 42	141 ± 109	192 ± 199
Green tea (g/day) [a]	333 ± 312	267 ± 194	437 ± 465
Potato (g/day) [a]	18 ± 12	18 ± 15	33 ± 27
Biscuit and cookies (g/day) [a]	0.5 ± 1	1 ± 2	3 ± 3
Women No. of participants	47	48	47
Acrylamide intake			
Mean (μg/day) [a]	5.7 ± 1.3	9.3 ± 1.2	15.6 ± 5.2
Median (μg/day) [a]	6.1	9.3	13.9
Age			
Mean (years)	58 ± 9	57 ± 8	56 ± 9
Median (years)	57	59	56
Body mass index			
Mean (kg/m^2)	23.5 ± 3.6	22.2 ± 2.5	22.7 ± 3.0
Median (kg/m^2)	23.0	22.3	22.3
Smoking (n,%)			
Never smoker	44 93.6	47 97.9	41 87.2
Ex-smoker	2 4.3	0 0.0	5 10.6

Table 1 Characteristics of the participants *(Continued)*

	Tertiles of acrylamide intake		
	Lowest	Middle	Highest
	T1 Mean ± SD or %	T2 Mean ± SD or %	T3 Mean ± SD or %
Current smoker	1 2.1	1 2.1	1 2.1
Education (n,%)			
Junior high school	6 12.8	3 6.3	4 8.5
High school	20 42.6	17 35.4	14 29.8
Some college	16 34.0	27 56.3	22 46.8
College or more	4 8.5	1 2.1	6 12.8
Other	1 2.1	0 0.0	1 2.1
Dietary intake Mean			
Energy intake (kcal)	1672 ± 216	1775 ± 246	1969 ± 371
Coffee (g/day) [a]	40 ± 41	92 ± 101	224 ± 257
Green tea (g/day) [a]	390 ± 276	382 ± 308	497 ± 397
Potato (g/day) [a]	16 ± 9	18 ± 12	23 ± 21
Biscuit and cookies (g/day) [a]	1 ± 2	3 ± 3	4 ± 5

[a] Crude intake

were 0.15 μg/kg body weight/day for men and 0.19 μg/kg body weight/day for women, and the 95th percentile values were 0.27 μg/kg body weight/day for men and 0.32 μg/kg body weight/day for women. The percentage differences in the means estimated by DR and FFQ were underestimated by 7 and 5% for body weight of men and women, respectively.

Between-individual and within-individual variations

Table 3 shows the relative contributions of between-individual and within-individual variances to the total variance in acrylamide intake and the coefficients of within-individual variance (CV_w) and between-individual variance (CV_b). In addition, Table 3 includes the number of days of DRs required to estimate the individual's habitual intake within 10 and 20% of their true mean intake. The ratios of within-individual variation to between-individual variation were 3.2 for men and 4.3 for women. Days of DRs necessary for estimating the true intake within 20% were 60 days for men and 66 days in women. Days required to ensure an r value of 0.8 for ranking individuals were 6 days for men and 8 days for women. In the sensitivity analysis, ratios of within-individual variance to between-individual variance and the number of days were calculated by the log-transformed data; the ratios of within-individual variation to between-individual variance were 1.9 for men and 2.8 for women. Therefore, the number of days for ranking was underestimated as a previous study suggested [25]. In the additional sensitivity analysis, we calculated the ratios of within-individual variance to between-individual variance using 12-day independent records without considering the data of consecutive 3-day records, and these variance ratios were almost the same.

Table 4 shows the foods that best predicted the between-individual variations in acrylamide intake. Foods that contributed to the between-individual variations were, from highest to lowest contribution, as follows: coffee/cocoa, potatoes, green tea, sweet potatoes, and biscuits/cookies. The top seven foods accounted for approximately 93% of the total variation.

The validity of the estimated acrylamide intake determined by using the FFQ indicated that the energy-adjusted correlation coefficients were 0.34 for men and 0.28 for women, and that the deattenuated correlation coefficients were 0.39 for men and 0.33 for women. The reproducibility of the FFQ indicated that the energy-adjusted correlation coefficients were 0.62 for men and 0.65 for women (Additional file 1: Table S1). In the sensitivity analysis, the acrylamide intake calculated using the cooking proportion from the DRs was compared to the validity of the FFQ, and the Spearman's correlation coefficients for crude and energy-adjusted intake were

Table 2 Comparison of acrylamide intake mean values from dietary records and food frequency questionnaires

	DR					FFQ					%[a]
	Mean	(SD)	Median	(5^{th}percentile, 95^{th}percentile)		Mean	(SD)	Median	(5^{th}percentile, 95^{th}percentile)		
Crude acrylamide intake (μg/day)											
Men ($n = 98$)	9.80	(5.34)	8.87	(3.54,	21.24)	9.27	(5.14)	8.44	(3.20,	22.86)	-5
Women ($n = 142$)	10.21	(5.15)	9.33	(4.14,	17.60)	9.98	(4.88)	9.39	(3.80,	18.97)	-2
All ($n = 240$)	10.04	(5.22)	9.00	(4.00,	19.16)	9.69	(4.99)	8.99	(3.60,	19.50)	−3
Crude acrylamide intake (μg/kg body weight/day)											
Men (n = 98)	0.15	(0.08)	0.13	(0.05,	0.27)	0.14	(0.08)	0.12	(0.05,	0.33)	−7
Women (n = 142)	0.19	(0.10)	0.17	(0.07,	0.32)	0.18	(0.09)	0.17	(0.07,	0.36)	−5
All (n = 240)	0.17	(0.09)	0.15	(0.06,	0.31)	0.16	(0.09)	0.15	(0.06,	0.34)	−6

DR dietary record, *FFQ* food frequency questionnaire for validation analysis, *SD* standard deviation
[a] Percentage differences (%) were calculated from the following formula: ("mean FFQ" – "mean DR")/ "mean DR" × 100

Table 3 Relative contributions of within- and between-individual variance values, coefficients of within-individual variance (CV_w) and between-individual variance (CV_b), the number of days required for collecting food records necessary to estimate the true intake within 10 and 20% of the true mean, and the number of days required to ensure r = 0.9, 0.8 and 0.5 between observed and true mean intake

	Percentage contributions of variance components within-individual	Percentage contributions of variance components between-individual	VR	Mean intake (μg/day)	CV_w[a] (%)	CV_b[b] (%)	D_1 10%(days) [c]	D_2 20%(days) [c]	D_3 r = 0.9 (days)[d]	D_4 r = 0.8 (days)[d]	D_5 r = 0.5 (days)[d]
Men (n = 98)	76.3	23.7	3.2	9.80	79.1	44.0	240	60	14	6	1
Women (n = 142)	81.2	18.8	4.3	10.21	83.0	39.9	265	66	18	8	1
All (n = 240)	79.8	20.2	3.9	10.04	81.5	41.5	255	64	16	7	1

CV_w, coefficient of within-individual variation; CV_b, coefficient of between-individual variation; VR, ratio of within- to between- individual variance $(\frac{\hat{\sigma}_w^2}{\hat{\sigma}_b^2})$

[a] $CVw = \frac{\sqrt{\hat{\sigma}_w^2}}{\text{mean acrylamide intake}} \times 100$

[b] $CVb = \frac{\sqrt{\hat{\sigma}_b^2}}{\text{mean acrylamide intake}} \times 100$

[c]Number of days needed to lie within specified % of the true means: $D_{1,2} = (Z_\alpha CV_w/E)^2$, where D = number of days needed per person, Z_α = normal deviate (1.96), E = specific error admitted as a percentage of the true usual intake; 10% or 20%

[d]Number of days required to ensure r = 0.9 or 0.8 or 0.5 between observed and true mean intake: $D_{3,4,5} = [\frac{r^2}{(1-r^2)}] \times VR$, where r = the unobservable correlation coefficient between the observed and true mean nutrient intakes of the individual

unchanged. The food groups from the DRs that contributed most the acrylamide intake were beverages, confections, vegetables, potatoes and other starches, and cereals (Additional file 2: Table S2).

Discussion

We demonstrated that estimating the habitual dietary acrylamide intake from DRs requires an extended data collection period because of the large within-individual variation in dietary acrylamide intake. Furthermore, the between-individual variation was largely accounted for by seven foods.

Although there have been no reports of the within-individual and between-individual variations of acrylamide intake according to DRs, many other nutrients tend to have larger within-individual variations than between-individual variations; for example, the variance ratios are 1.0–2.2 for energy, 1.6–3.1 for protein, and 3.2–5.4 for fat [25, 28–31]. For reference, the variance ratios determined by this study were approximately 1 for energy, 1.3 for protein, and 1.8 for fat. It was also revealed that confections and potatoes greatly contributed to the absolute intake of acrylamide. As a Japanese study previously reported, there is large within-individual variation in the consumption of these foods [28]. Therefore, we think that these foods are likely to be consumed sporadically, which explains their large within-individual variations. The within-individual variation of non-smokers was also reported to be high in a previous study that examined within-individual variation using hemoglobin adducts, which are biomarkers of acrylamide consumption [32], and our results are consistent with those. As such, it is necessary to choose a precise method of exposure assessment based on the large within-individual variation.

Moreover, the within-individual and between-individual variations of acrylamide intake estimated by DRs showed that estimations of the intragroup ranking and the individual's habitual intake required data collection for an extended period. An analysis using 24 h-Rs with a correlation of 0.8 showed the following relationships between the number of days and variation ratios: approximately 5 days for a variation ratio of 1; 10 days for a variation ratio of 3; and 20 days for a variation ratio of 5; in other words, when the variation ratio is larger, more days of DRs are needed [31]. As shown by our results, when the variation ratio and/or within-individual variation is large, then the estimation of acrylamide intake using short-term dietary surveys may lead to a misclassification of rankings and may not

Table 4 Foods with the highest variations in the estimated between-individual variation in dietary acrylamide from dietary records

	Foods	Partial R-Square [a]	Cumulative R-Square [a]
1	Coffee and Cocoas	0.333	0.333
2	Potatoes	0.212	0.545
3	Green teas	0.156	0.701
4	Sweet potatoes	0.098	0.799
5	Biscuits	0.060	0.859
6	Traditional dry confectionary	0.039	0.898
7	Snacks (Potato chips)	0.035	0.933
8	Beans sprouts	0.017	0.950
9	Chocolates	0.010	0.960
10	Podded pods	0.009	0.969

[a] Foods were selected by stepwise regression analysis using data from DR. Partial and cumulative R-Square values were calculated in the process of performing the regression analysis

represent an individual's habitual intake. This error distorts the correlation coefficient of validation studies and reduces the strength of association with disease in epidemiological studies [27]. In fact, an FFQ validation study using 24 h-Rs suggested that the main reason for the low correlation coefficient was caused by a large within-individual variation in 24 h-Rs [8]. Therefore, methods that estimate acrylamide intake during short periods of time should be cautiously reviewed considering the influence of within-individual variation.

Foods ranked as high for their predicted between-individual variation were also ranked high for their contribution to the absolute intake of acrylamide. This may be because the intake of these foods is highly dependent on individual preference and they contribute significantly to both individual intake and between-individual variation. Although snacks did not contribute significantly to the absolute intake, their ranking among foods contributing to between-individual variation was high. Therefore, it is conceivable that it is essential to analyze snacks to detecting differences in acrylamide intake among individuals. Collectively, our results suggest that it is possible to rank acrylamide intake according to several kinds of foods.

Furthermore, the mean intake in our study was lower than that observed in Western populations, and it was similar to that of the previous Monte Carlo simulation studies of Japanese populations (mean, 0.166 μg/kg body weight/day; 95th percentile, 0.261 μg/kg body weight/day) [33]. In the current study, the mean intake was 0.05 μg/kg body weight/day higher than that of the previous JPHC study [5]. This was primarily due to increases in contribution associated with the intake of coffee/cocoa and confections. The acrylamide intake values of traditional fresh and semi-dry confections in the current study were half that reported by the JPHC study [5], but intake values of chocolate and potato chips were more than 50% higher. Our results indicate the prime importance of evaluating exposure from the viewpoint of risk assessment to mitigate potential health challenges.

To the best of our knowledge, this is the first study to elucidate the within-individual variation and between-individual variation in dietary acrylamide intake. The key contribution of this study was that it assessed the within-individual variation of acrylamide intake, which must be considered as a measurement error that potentially contributes to erroneous findings. These findings highlight the need to use biomarkers to appropriately estimate long-term acrylamide exposure because biomarkers are thought to have fewer measurement errors than other measurement methods. The between-individual variation results of our study also show that it is possible to rank acrylamide intake based on several types of foods, thus implying that a simpler questionnaire could be developed that specifically targets the acrylamide intake of the Japanese population in the future.

There were certain limitations to this study. First, the results of this study depended on the accuracy of acrylamide content database. The database includes approximately 50% of foods that may contain acrylamide. If there are large within-individual variations in foods that are not included in the database, then it may take more days to rank individuals and to estimate habitual intake from DRs. Second, the study did not include individuals 39 years or younger or individuals 75 years or older; therefore, the applicability of the results to all age groups remains uncertain. For other nutrients, within-individual variations tend to be larger in younger people than in older people [30], suggesting that more days may be required to accurately estimate the habitual intake of dietary acrylamide from the DRs of a young population. Finally, a comparison of dietary acrylamide intake and biological markers, such as glycidamide and acrylamide hemoglobin adducts, was not possible. Assessing the within-individual variability and between-individual variability of acrylamide intake from both diet and biomarkers would help to address the current challenges, such as determining the cause of the low correlation between the 24 h-Rs, FFQs, and biomarkers [8]. Importantly, a better estimation of acrylamide exposure would enhance the reliability of evidence in epidemiological studies.

Conclusion

Overall, the study results revealed that the estimation of habitual acrylamide intake and the ranking within the group according to DRs require an extended data collection period because of large within-individual variations. The estimation of acrylamide intake using short-term dietary surveys may lead to the misclassification of rankings and may not represent an individual's habitual intake. Therefore, we conclude that assessing the long-term exposure based on methods that are unaffected by measurement error such as those associated with biomarkers is required, and that a repeated assessment of these biomarkers would be beneficial.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s12937-020-00534-y.

Additional file 1 : **Table S1.** Evaluation of the relationships between dietary records, food frequency questionnaires used for the validation analysis, and food frequency questionnaires.

Additional file 2 : **Table S2.** Contribution of food groups to total acrylamide intake estimated using dietary records.

Abbreviations
24 h-Rs: 24-h dietary recalls; DM: Duplicate method; DR: Dietary record; FCT 2010: The Standard Tables of Food Composition in Japan 2010; FFQ: Food frequency questionnaire; JPHC: The Japan Public Health Center-based Prospective Study; JPHC-NEXT: The Japan Public Health Center-based Prospective Study for the Next Generation

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Authors' contributions
All authors contributed to the study conceptualization and design. Material preparation, data collection, and data analysis were performed by KK, JI, JY, TH, AK, RT, KN, JT, TY, TS, YI, NS, MI, HI, and ST. The first draft of the manuscript was written by KK, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials
We cannot publicly provide individual data due to participant privacy, according to ethical guidelines in Japan. Additionally, the informed consent we obtained does not include a provision for publicly sharing data. The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate
The study was approved by the Institutional Review Board of the National Cancer Center, Tokyo, Japan, and all other collaborating research institutions. The study was also approved by the ethics committee of Azabu University (approval number 2457). This study was conducted in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments. All participants provided informed consent.

Consent for publication
Consent for publication was obtained from all participants.

Competing interests
The authors declare that they have no competing interests.

Author details
[1]Graduate School of Environmental Health, Azabu University, 1-17-71 Fuchinobe, Chuo-ku, Sagamihara-city, Kanagawa 252-5201, Japan. [2]Department of Food and Life Science, Azabu University, 1-17-71 Fuchinobe, Chuo-ku, Sagamihara-city, Kanagawa 252-5201, Japan. [3]Department of Food Science and Nutrition, Nara Women's University Graduate School of Humanities and Sciences, Kitauoyahigashimachi Nara-shi, Nara 630-8506, Japan. [4]Division of Preventive Medicine, Niigata University Graduate School of Medical and Dental Sciences, 1-757 Asahimachidori, Niigata 951-8510, Japan. [5]Department of Health Promotion Medicine, Niigata University Graduate School of Medical and Dental Sciences, 1-757 Asahimachidori, Niigata 951-8510, Japan. [6]Epidemiology and Prevention Group, Center for Public Health Sciences, National Cancer Center, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan. [7]Public Health, Department of Social Medicine, Graduate School of Medicine, Osaka University, 2-2 Yamadaoka, Suita-city, Osaka 565-0871, Japan. [8]Department of Environmental Medicine and Population Sciences, Graduate School of Medicine, Osaka University, 2-2 Yamadaoka, Suita-city, Osaka 565-0871, Japan.

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Publisher's Note

Additional file 1: Table S1.

Evaluation of the relationships between dietary records, food frequency questionnaires used for the validation analysis, and food frequency questionnaires

	Validity[a]			Cross-classification[b]				Reproducibility[c]	
	Crude	Energy-adjusted	Deattenuated[d]	Same category	Same and adjacent category	Extreme category	Weighted κ coefficient	Crude	Energy-adjusted
Men (n=98)	0.39	0.34	0.39	29	63	3	0.83	0.67	0.62
Women (n=142)	0.25	0.28	0.33	20	61	4	0.81	0.74	0.65

DR, dietary record; FFQ_V, food frequency questionnaire for validation analysis.

[a] Spearman's correlation coefficients between DRs and the FFQ_V.

[b] Percentages were presented based on the cross-classification by quintile between DRs and the FFQ_V.

[c] Spearman's correlation coefficients between the two FFQs.

[d]Deattenuated CC = Energy-adjusted CC$\times\sqrt{1+(\lambda/n)}$, where λ is the ratio of within- to between-individual variance and n is the number of DRs.

Additional file 2: Table S2.

Contribution of food groups to total acrylamide intake estimated using dietary records

Food group name	Proportion (%)	Number of assigned foods	Top 5 contributing foods (%)									
			1		2		3		4		5	
Beverages	40.8	22	Coffees and cocoas	(24.8)	Green teas	(11.7)	Fermented alcoholic beverages	(2.4)	Mugi-cha	(1.5)	Fermented teas	(0.5)
Confectionary	19.9	74	Traditional dry confectionary	(5.8)	Biscuits and cookies	(5.0)	Chocolates	(3.7)	Snacks	(2.4)	Cakes, buns and pastries	(1.8)
Vegetables	14.2	33	Bean sprouts	(4.3)	Sweet peppers	(3.2)	Onions	(2.3)	Cabbages	(1.2)	Eggplants	(1.1)
Potatoes and Starches	10.6	7	Potatoes	(6.9)	Sweet potatoes	(3.6)						
Cereals	6.5	46	Rice	(2.7)	Noodles dried by frying	(2.0)	Breads	(1.5)	Bread crumbs	(0.2)	Cornflakes	(0.1)
Seasoning and Spices	2.7	23	Roux	(1.9)	Miso	(0.4)	Soy sauce	(0.3)				
Nuts and Seeds	2.1	13	Sesame seeds	(1.1)	Walnuts	(0.4)	Peanuts	(0.4)	Cashew nuts	(0.1)	Almonds	(0.05)
Fish and Shellfishes	1.1	33	Baked fish	(0.8)	Fish paste products (baked or fried)	(0.3)						
Fruits	0.8	7	Dried fruits	(0.8)								
Pulses	0.7	10	Tofu (baked or fried)	(0.4)	Roasted and ground soybeans	(0.2)	Beans cooked with sugar and salt	(0.04)				
Sugars and Sweeteners	0.4	2	Brown sugar	(0.4)								

nutrients

MDPI

Article

Dietary Acrylamide Intake and the Risk of Pancreatic Cancer: The Japan Public Health Center-Based Prospective Study

Kumiko Kito [1], Junko Ishihara [2,*], Ayaka Kotemori [2], Ling Zha [3], Rong Liu [3], Norie Sawada [4], Motoki Iwasaki [4], Tomotaka Sobue [3] and Shoichiro Tsugane [4]

1 Graduate School of Environmental Health, Azabu University, 1-17-71 Fuchinobe, Chuo-ku, Sagamihara, Kanagawa 252-5201, Japan; de1801@azabu-u.ac.jp
2 Department of Food and Life Science, Azabu University, 1-17-71 Fuchinobe, Chuo-ku, Sagamihara, Kanagawa 252-5201, Japan; kotemori@azabu-u.ac.jp
3 Department of Environmental Medicine and Population Sciences, Graduate School of Medicine, Osaka University, 2-2 Yamadaoka, Suita, Osaka 565-0871, Japan; sarin@envi.med.osaka-u.ac.jp (L.Z.); liur8939@163.com (R.L.); tsobue@envi.med.osaka-u.ac.jp (T.S.)
4 Epidemiology and Prevention Group, Center for Public Health Sciences, National Cancer Center, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan; nsawada@ncc.go.jp (N.S.); moiwasak@ncc.go.jp (M.I.); stsugane@ncc.go.jp (S.T.)
* Correspondence: j-ishihara@azabu-u.ac.jp; Tel.: +81-42-769-2669

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Abstract: Acrylamide is a probable carcinogen in humans. Few studies have assessed dietary acrylamide intake and the risk of pancreatic cancer; however, these studies are based on Western populations. Our purpose was to investigate the association of dietary acrylamide intake with the risk of pancreatic cancer utilizing data from the Japan Public Health Center-based Prospective Study. We evaluated the data of 89,729 participants aged 45–74 years, who replied to a questionnaire on past medical history and lifestyle habits from 1995–1998. Dietary acrylamide intake was estimated utilizing a validated food frequency questionnaire. We calculated the hazard ratios and 95% confidence intervals by using Cox proportional-hazards regression models. The average follow-up was 15.2 years, and 576 cases of pancreatic cancer were diagnosed. In the multivariate-adjusted model, an association between dietary acrylamide intake and pancreatic cancer risk was not demonstrated (hazard ratio for the highest vs. lowest quartile = 0.83, 95% confidence interval: 0.65–1.05, p for trend = 0.07). Furthermore, in the analyses stratified by sex, smoking status, coffee consumption, green tea consumption, alcohol consumption, and body mass index, no significant association was detected. Dietary acrylamide intake was not associated with the pancreatic cancer risk in Japanese individuals.

Keywords: acrylamide; Asia; pancreatic cancer; diet; epidemiologic study

1. Introduction

In 1994, acrylamide was classified by the International Agency for Research on Cancer Group as a 2A agent, which means that it is probably carcinogenic in humans [1]. The leading causes of acrylamide exposure are regarded to be tobacco smoking and acrylamide-containing foods [2,3]. Acrylamide in foods is mainly formed during the Maillard reaction, in which asparagine (an amino acid) reacts with reducing sugars such as glucose in the presence of heat (120 °C or more) [2]. Acrylamide is partly metabolized to glycidamide by cytochrome P450 (CYP2E1). Glycidamide is known to cause genotoxicity by forming an adduct that binds to hemoglobin and DNA [4,5].

Currently, there are a few studies that have investigated the association between pancreatic cancer risk and dietary acrylamide intake. Five studies (two prospective cohort studies, one case-cohort study, one case-control study, and one pooled analysis of six case-control studies) have assessed the association of acrylamide intake with pancreatic cancer [6–10]; however, no such association has been established. This finding is supported by a recent meta-analysis, which showed that dietary acrylamide intake was not associated with pancreatic cancer risk [11]. However, in each of these studies, stratification by obesity status yielded inconsistent results. For an increment of 10 μg/d of acrylamide, one study reported a negative association with the pancreatic cancer risk [7], another reported a raised risk [8], and two studies observed no association [9,10]. Studies on the association of pancreatic cancer risk with dietary acrylamide, including the stratified analyses, are limited; therefore, more studies are needed to support these results.

All the prior studies were performed in Western countries and the association between dietary acrylamide and the risk of pancreatic cancer among Asians, has not been examined. Acrylamide intake and the food groups that contribute to acrylamide intake are different in the Japanese population compared with the Western population [12]. Japanese people have an acrylamide intake of 7–10 μg/d [12], which is less than half of that of westerners [6–8,10]. In Japan, food groups that mainly contribute to acrylamide intake are green tea, coffee, confectionery, vegetables, and potatoes [12], whereas in Western countries they are potatoes, bread, cakes, and coffee [13,14]. Considering its potential carcinogenicity, there is a need to evaluate the association of dietary acrylamide intake with pancreatic cancer by targeting populations with different dietary sources and acrylamide intakes.

The present study aimed to identify the association between dietary acrylamide intake and pancreatic cancer in Japanese individuals.

2. Materials and Methods

2.1. Study Participants

The Japan Public Health Center-based Prospective Study (JPHC study) was initiated in the 1990s. It was a large population-based cohort study that aimed to explore the association between lifestyle habits and lifestyle-related diseases. The JPHC study had two cohorts covering 11 public center areas. Cohort I covered areas including Iwate, Akita, Nagano, Okinawa-Chubu, and Tokyo. Cohort II covered areas including Ibaraki, Niigata, Kochi, Nagasaki, Okinawa-Miyako, and Osaka. At baseline, the participants were 140,420 residents (68,722 men and 71,698 women) aged 40–69 years. A self-administered food frequency questionnaire (FFQ) was conducted at the dietary survey at the baseline and at 5 and 10 years of the follow-up. We used the FFQ of the 5-year follow-up survey as the starting point because it provided information about more food items and portion size options than the FFQ of the baseline. The study protocol has been documented in detail elsewhere [15,16]. The protocol of the present study was approved by the institutional review boards of the National Cancer Center, Japan (ethical approval number: 2001-021), Osaka University (approval number: 14020-9), and Azabu University (approval number: 2527). All study participants provided informed consent before participating in the study.

In this study, we excluded inhabitants from the Tokyo area because cancer incidence data were unavailable. We also excluded participants who were of non-Japanese nationality, had a late report of migration before the starting point, an incorrect birth date, died, moved out of the study area, or were lost to follow-up before the starting point. In the present study, 121,181 participants were eligible for inclusion in the analysis. Of those, 98,512 responded to the 5-year follow-up survey (response rate, 81.3%). Furthermore, we excluded the following participants; those with a history of cancer (n = 3001), with pancreatic cancer (n = 7) before the 5-year follow-up survey, and with missing or extreme energy intake data (n = 5775). The final analysis included 89,729 (men: 42,071, women: 47,658) participants (Figure 1).

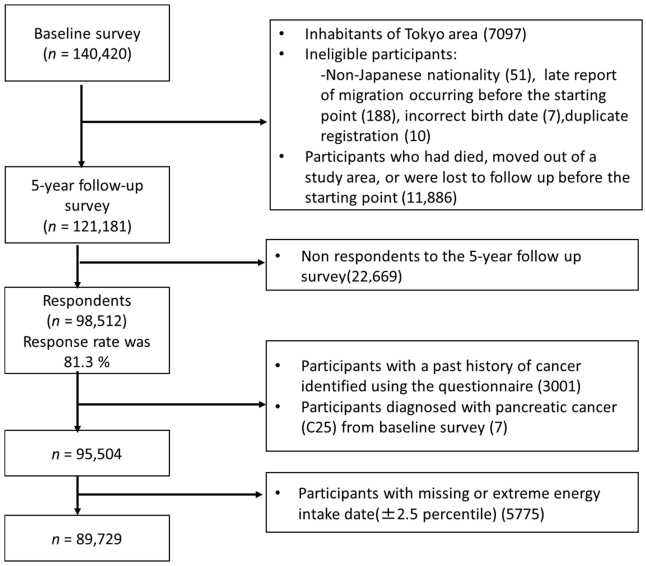

Figure 1. Flow diagram of the study participant selection.

2.2. Food Frequency Questionnaire

We used the FFQ consisting of 138 food and beverage items to calculate the energy and dietary acrylamide intake. The participants were asked about their frequencies of eating and portion sizes during the previous year. The frequencies of eating were categorized into nine categories (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, or ≥7 times/day), and the portion sizes were categorized into three categories (less than half the standard portion size, standard portion size, or >1.5 times the standard portion size). Each beverage was categorized into nine categories of frequency (<1 cup/week, 1–2 cups/week, 3–4 cups/week, 5–6 cups/week, 1 cup/day, 1–3 cups/day, 4–6 cups/day, 7–9 cups/day, or ≥10 cups/day).

The intake for each food and beverage was calculated by the multiplication of the eating frequency and portion size.

2.3. Assessment of Energy and Acrylamide Intake from the FFQ

The energy content in each food item was based on the Fifth Revised and Enlarged Edition of the Standard Tables of Food Composition in Japan [17]. The validity of the FFQ for energy intake using the 28-day dietary records was as follows: 0.53 for men and 0.41 for women in Cohort I (n = 113), and 0.36 for men and 0.24 for women in Cohort II (n = 176) [18–20].

Acrylamide intake for individuals was estimated utilizing the database derived from the published acrylamide measurements in common Japanese foods [12]. In the FFQ, the following food and beverage items contained dietary acrylamide: miso, beer, baked fish paste, bread, rice cake, Japanese-style confectionery, cake, biscuits/cookies, chocolate, peanuts, fried tofu, green tea, oolong tea, black tea, coffee, and soup [21–29]. To further estimate the accuracy of measurement of the acrylamide intake, we estimated the acrylamide intake of each participant considering the acrylamide intake generated from homemade cooking for the following foods: heated starchy vegetables (potato and sweet potato), vegetables (onion, bean sprouts, sweet pepper, squash, cabbage, snap beans, and broccoli), toast, boiled or stir-fried rice, and fried batter [12]. The Spearman rank correlation coefficients for energy-adjusted acrylamide intake between dietary records and FFQ ranged from 0.34–0.48 for validity and 0.56–0.62 for reproducibility. Details of the database have been previously documented elsewhere [12].

2.4. Follow-Up and Identification of Pancreatic Cancer

The study participants were followed from the starting point of the 5-year follow-up survey (1995 for Cohort I and 1998 for Cohort II) until 31 December 2013 (until 31 December 2012, only in

the Osaka area). Residential status was ascertained annually by the residential registry. During the follow-up period, 16,030 participants (17.9%) died, 5 694 (6.4%) moved from the study area, and 74 (0.1%) were lost to follow-up.

Cases of pancreatic cancer were determined through active patient information from major local hospitals in each study area and data linkage with population-based cancer registries. Death certificates were used as sources of additional information. We defined pancreatic cancer cases based on the International Classification of Diseases for Oncology, Third Edition codes C25.0–C25.9, but excluded those with C25.4 (endocrine tumor) because of its different etiology. The proportion of cases determined using Death Certificate Only was 11.5%. During a mean follow-up of 15.2 years, 576 pancreatic cancer cases were identified.

2.5. Statistical Analyses

We determined the person-years of follow-up for each participant from the date of the starting point to the date of diagnosis of pancreatic cancer, death, relocation from the study area, or the end follow-up (31 December 2012 for the Osaka area and 31 December 2013 for all other areas), whichever came first.

We estimated hazard ratios (HRs) and 95% confidence intervals (CIs) using the Cox proportional hazards model for energy-adjusted acrylamide intake and pancreatic cancer risk by quartile. The lowest group was used as the reference for each group. Trends in the HRs were estimated by allocating ordinal scores to the quartiles of acrylamide intake. Acrylamide intake was adjusted for total energy intake using the residual method [30]. Utilizing the known risk factors or potential confounding factors of pancreatic cancer, the model was adjusted for the following variables: age (continuous), sex, study area (10 public health center areas), smoking status (never, past, current <20, 20–39, and ≥40 cigarettes/day, or missing), alcohol intake (0, <150 g/week or ≥150 g/week, or missing), body mass index (BMI; <25 kg/m^2, ≥25 kg/m^2, or missing), family history of pancreatic cancer (yes or no), and medical history of diabetes mellitus (yes or no). These variables were derived from the FFQ. Red meat consumption, processed meat consumption, and physical activity have also been proposed as potential risk factors for pancreatic cancer [31], although we did not include them in the model because their inclusion did not change the HR by at least 10%. For the sensitivity analysis in the multivariate-adjusted model, we conducted the same analysis by excluding cases diagnosed during the first 3 years of follow-up. We also performed subgroup analyses to confirm the effect of interaction based on sex, smoking status (current or past smokers, never smokers), coffee consumption (<1 cup/week, ≥1 cup/week), green tea consumption (<1 cup/week, ≥1 cup/week), alcohol consumption (<150 g/week, ≥150 g/week), and BMI (<25 kg/m^2, ≥25 kg/m^2). Statistical analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). All *p*-values were two-sided, and the statistical significance level was set at $p < 0.05$.

3. Results

Table 1 shows the participant characteristics by quartile for total acrylamide intake. The overall median acrylamide intake was 6.12 μg/d (IQR, 4.30–8.72), and the mean (SD) was 6.92 ± 3.81 μg/d, corresponding to 0.13 ± 0.16 μg/kg body weight/day. The group with the highest acrylamide intake (Q4) was younger, had a higher proportion of current smokers, and had a lower proportion of individuals with a history of diabetes. Regarding dietary intake, the Q4 group had a lower intake of alcohol and a higher intake of coffee, green tea, biscuits/cookies, and potatoes.

Figures 2 and 3 show the proportion contribution of foods to dietary acrylamide intake in the entire study participant and each quartile. Overall, the food groups that contributed the most to acrylamide intake were beverages (total 53%; 28% for coffee, 21% for green tea, 2% for beer, and 2% for others), followed by confections (total 16%; 11% for biscuits/cookies, 3% for chocolate, and 2% for others), vegetables (total 11%; 3% for sweet pepper, 3% for onion, 3% for bean sprouts, and 2% for others), and potatoes (11%). In each acrylamide intake group, green tea was the main contributing food, although the trends of the other foods differed slightly. The proportion of coffee and biscuits

or/and cookies increased linearly (coffee: Q1: 14%, Q4: 36%; biscuits or/and cookies: Q1: 6%, Q4: 13%), whereas the proportion of vegetables decreased linearly (vegetables: Q1: 17%, Q4: 7%).

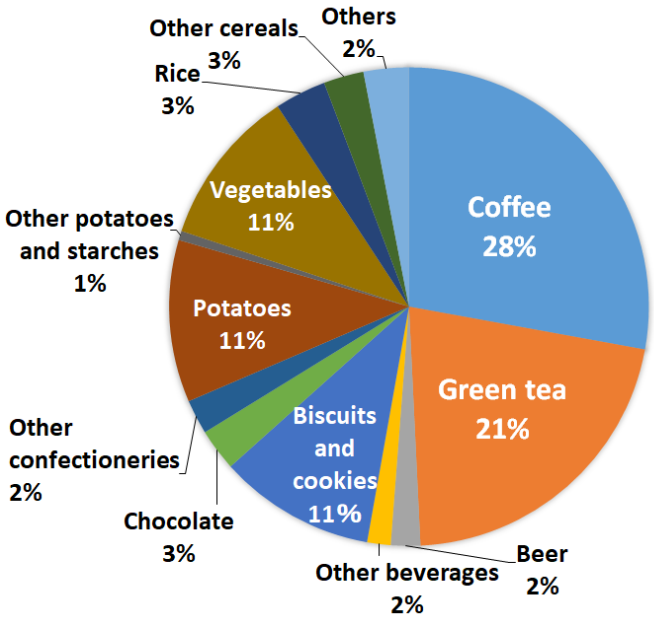

Figure 2. Percentage contribution of acrylamide-containing foods to dietary acrylamide intake.

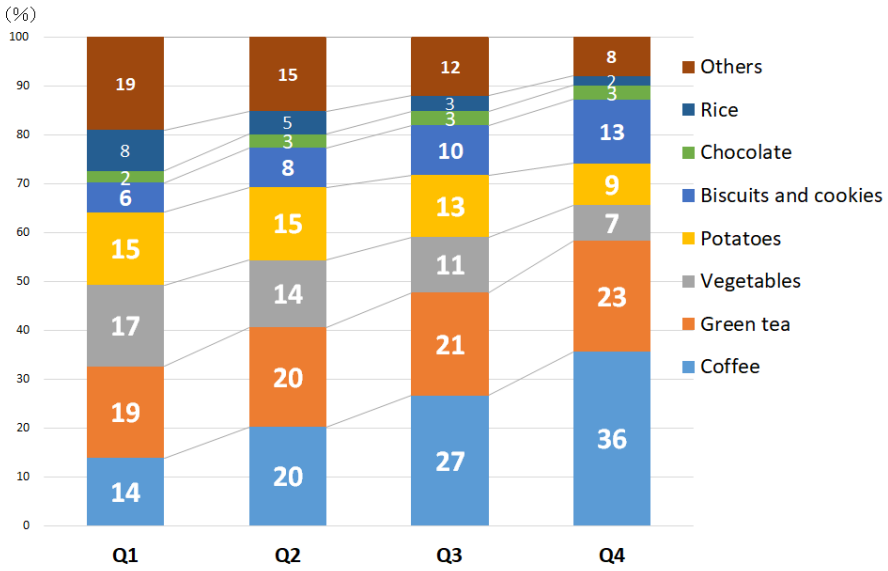

Figure 3. Comparison of the percentage contribution of acrylamide-containing foods to dietary acrylamide intake among quartiles of acrylamide intake.

We observed no association between dietary acrylamide intake and pancreatic cancer (Table 2). In the multivariate-adjusted model, the HR of the highest quartile vs. the lowest was 0.83 (95% CI: 0.65–1.05) (p for trend = 0.07). This risk did not alter even after excluding cancer diagnosed cases within the first 3 years of follow-up. We also conducted stratified analyses using the major confounding factors; however, there were no significant associations in the multivariate-adjusted model: current or past smoking status (p for trend = 0.25), never smoking status (p for trend = 0.23), consumption of <1 cup/week of coffee (p for trend = 0.11), consumption of ≥1 cup/week of coffee (p for trend = 0.15), consumption of <1 cup/week of green tea (p for trend = 0.23), consumption of ≥1 cup/week of green tea (p for trend = 0.18), consumption of <150 g/week of alcohol (p for trend = 0.20), consumption of ≥150 g/week of alcohol (p for trend = 0.19), BMI <25 kg/m^2 (p for trend = 0.11), and BMI ≥25 kg/m^2 (p for trend = 0.71). We performed a sensitivity analysis since the proportion of coffee and biscuits/cookie to dietary acrylamide increased from Q1 to Q4. We added coffee consumption (continuous) and biscuits/cookies intake (continuous) to the multivariate-adjusted model, and in the coffee stratification analysis, we added biscuits/cookies intake (continuous). The results did not change (data not shown).

Table 1. Baseline characteristics of the study participants (n = 89,729) according to quartile of dietary acrylamide intake.

	Quartile of Acrylamide Intake																	
	Quartile 1				Quartile 2				Quartile 3				Quartile 4					
Participants, *n*	22,432				22,432				22,433				22,432					
Male, %	27.8				24.5				23.3				24.3					
Female, %	22.5				25.4				26.5				25.6					
Acrylamide intake																		
Mean, μg/day [a]	3.1	±	0.9		5.2	±	0.5		7.3	±	0.7		12.1	±	3.5			
Median, μg/day [b]	3.3		(2.6	– 3.8)	5.2		(4.7	– 5.6)	7.2		(6.6	– 7.9)	11.0		(9.7	–	13.3)	
Mean, μg/kg body weight/day [a]	0.06	±	0.04		0.10	±	0.09		0.13	±	0.09		0.22	±	0.26			
Age at 5-year follow-up survey, years [b]	58		(52	– 63)	57		(51	– 63)	56		(50	– 62)	55		(48	–	61)	
Body mass index, kg/m^2 [b]	23.4		(21.6	– 25.5)	23.4		(21.5	– 25.4)	23.3		(21.4	– 25.3)	23.1		(21.3	–	25.2)	
Smoking status, %																		
Never smoker	60.6				64.5				64.4				58.9					
Ex-smoker	9.6				9.1				8.0				8.0					
Current smoker	23.2				20.6				21.9				27.7					
Missing	6.6				5.8				5.7				5.5					
History of diabetes mellitus, %	8.2				7.1				6.3				5.6					
Family history of pancreatic cancer, %	0.3				0.4				0.4				0.3					
Dietary intake																		
Energy, kcal/d [a,c]	1999	±	642		1998	±	610		2013	±	612		1977	±	622			
Alcohol intake, g/week [a]	155	±	250		108	±	197		90	±	175		70	±	146			
Coffee, g/d [a,c]	34	±	50		81	±	82		144	±	131		324	±	313			
Green tea, g/d [a,c]	285	±	314		460	±	407		559	±	449		802	±	732			
Potato, g/d [a,c]	9	±	9		16	±	13		19	±	17		21	±	25			
Biscuits and cookies, g/d [a,c]	1	±	1		2	±	2		3	±	3		5	±	8			
Vegetables, g/d [a,c]	178	±	118		208	±	119		221	±	128		221	±	138			

Abbreviation: SD, standard deviation. [a] Data are presented as the mean (standard deviation). [b] Data are presented as the median (interquartile range). [c] Energy adjusted intake by residual method.

Table 2. Hazard ratios and 95% confidence intervals for pancreatic cancer risk according to quartile of acrylamide intake.

		Quartile 1		Quartile 2		Quartile 3		Quartile 4		*p* for Trend
	Total	**HR**	**(95% CI)**	**HR**	**(95% CI)**	**HR**	**(95% CI)**	**HR**	**(95% CI)**	
All										
Participants, *n*	89,729	22,432		22,432		22,433		22,432		
Cases, *n*	576	180		143		126		127		
Person-years	1,360,237	340,654		341,672		340,712		337,198		
Age- and area-adjusted [a]		1.00	(Reference)	0.83	(0.66–1.03)	0.77	(0.61–0.97)	0.84	(0.67–1.07)	0.09
Multivariate-adjusted [b]		1.00	(Reference)	0.84	(0.67–1.05)	0.77	(0.61–0.97)	0.83	(0.65–1.05)	0.07
Multivariate-adjusted (excluding cases <3 y)[b]		1.00	(Reference)	0.83	(0.66–1.06)	0.77	(0.60–0.99)	0.82	(0.63–1.05)	0.08
Male										
Cases, *n*	319	108		70		67		74		
Multivariate-adjusted [b]		1.00	(Reference)	0.74	(0.55–1.01)	0.77	(0.56–1.05)	0.85	(0.62–1.17)	0.29
Female										
Cases, *n*	257	72		73		59		53		
Multivariate-adjusted [b]		1.00	(Reference)	0.97	(0.70–1.35)	0.79	(0.56–1.13)	0.83	(0.58–1.20)	0.19
By smoking status										
Current or past smokers										
Cases, *n*	235	73		57		47		58		
Multivariate-adjusted [b]		1.00	(Reference)	0.89	(0.63–1.26)	0.75	(0.52–1.10)	0.84	(0.58–1.21)	0.25
Never smokers										
Cases, *n*	285	89		69		73		54		
Multivariate-adjusted [b]		1.00	(Reference)	0.76	(0.56–1.05)	0.85	(0.62–1.17)	0.78	(0.55–1.11)	0.23
By coffee consumption										
<1 cup/week										
Cases, *n*	173	99		36		21		17		
Multivariate-adjusted [b]		1.00	(Reference)	0.72	(0.49–1.05)	0.66	(0.41–1.07)	0.80	(0.47–1.35)	0.11
≥1 cup/week										
Cases, *n*	403	81		107		105		110		
Multivariate-adjusted [b]		1.00	(Reference)	0.88	(0.66–1.18)	0.78	(0.58–1.05)	0.81	(0.60–1.10)	0.15
By green tea consumption										
<1 cup/week										
Cases, *n*	44	29		9		4		2		
Multivariate-adjusted [b]		1.00	(Reference)	0.98	(0.46–2.10)	0.69	(0.24–2.00)	0.43	(0.10–1.86)	0.23

Table 2. *Cont.*

	Total	Quartile 1		Quartile 2		Quartile 3		Quartile 4		*p* for Trend
		HR	(95% CI)	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)	
≥1 cup/week										
Cases, *n*	532	151		134		122		125		
Multivariate-adjusted [b]		1.00	(Reference)	0.84	(0.67–1.07)	0.79	(0.62–1.01)	0.86	(0.67–1.10)	0.18
By alcohol consumption										
<150 g/wk										
Cases, *n*	416	111		107		95		103		
Multivariate-adjusted [b]		1.00	(Reference)	0.90	(0.69–1.18)	0.79	(0.60–1.04)	0.86	(0.65–1.14)	0.20
≥150 g/wk										
Cases, *n*	160	69		36		31		24		
Multivariate-adjusted [b]		1.00	(Reference)	0.71	(0.47–1.06)	0.75	(0.49–1.15)	0.77	(0.48–1.25)	0.19
By BMI										
<25 kg/m^2										
Cases, *n*	411	122		104		93		92		
Multivariate-adjusted [b]		1.00	(Reference)	0.88	(0.67–1.14)	0.80	(0.61–1.05)	0.81	(0.61–1.08)	0.11
≥25 kg/m^2										
Cases, *n*	141	46		33		31		31		
Multivariate-adjusted [b]		1.00	(Reference)	0.78	(0.50–1.23)	0.80	(0.51–1.28)	0.93	(0.58–1.50)	0.71

Abbreviations: CI, confidence interval; HR, hazard ratio. [a] Age- and area-adjusted model adjusted for age (continuous), sex, and area (10 public health center areas). [b] Multivariable Cox proportional-hazards models were adjusted for area (10 public health centers area), age (years) and sex (men or women), smoking status (nonsmoker, past smoker, current smoker <20, 20–40, ≥40 cigarettes/day, or missing), history of diabetes mellitus (yes or no), family history of pancreatic cancer (yes or no), alcohol consumption (0, <150 g/week, ≥150 g/week, or missing), and body mass index (<25 kg/m^2, ≥25 kg/m^2, or missing).

4. Discussion

We analyzed the association between dietary acrylamide intake and the risk of pancreatic cancer using the FFQ in a large-scale, population-based study of Japanese individuals. The analyses showed that acrylamide intake was not associated with the risk of pancreatic cancer. We also observed no association in the analyses stratified based on the smoking status, coffee intake, green tea intake, alcohol consumption, and BMI.

In the present study, the mean daily intake of acrylamide was 6.92 ± 3.81 μg/d (Q1 = 3.1± 0.9 μg/d, Q2 = 5.2± 0.5 μg/d, Q3 = 7.3 ± 0.7 μg/d, and Q4 = 12.1 ± 3.5 μg/d), which is considerably lower than that reported in studies from Western countries (26.22 ± 14.79 μg/d in the European Prospective Investigation into Cancer and Nutrition [EPIC] cohort study [7] and 22.1 ± 12.7 μg/d in the Netherlands Cohort Study on diet and cancer [NLCS] [8]). However, the mean acrylamide intake in the Q4 (highest) group of this study corresponds to approximately 25% tile of acrylamide intake in the Western population [10]. Previous studies that assessed dietary acrylamide intake and cancer risk (such as breast cancer and digestive system cancer) in the Japanese population have consistently indicated a null association [32–34]. Our results supported the findings of the previous studies on acrylamide intake and cancer risk in the Japanese population.

To date, only five studies on the association of acrylamide intake with pancreatic cancer using an FFQ have been undertaken in Western countries. No association has been observed in all these studies including the recent ones: a large-scale prospective (EPIC) cohort (865 pancreatic cancer cases, HR: 0.77, 95% CI: 0.58–1.04) [7], a recent meta-analysis (1732 pancreatic cancer cases, HR: 0.93, 95% CI: 0.76–1.12) [11], and a pooled analysis of six case-control studies (1975 pancreatic cancer cases, odds ratio: 0.92, 95% CI: 0.66–1.28) [10]. The population of the present study differs from those of the previous studies with respect to the characteristics of acrylamide intake. First, the mean acrylamide intake was lower. Second, the main foods contributing to total acrylamide intake included green tea and vegetables, which differed from the findings of studies conducted in Western countries. Furthermore, in Japan, vegetables are often cooked using methods such as stir-frying, baking, and frying, which can contribute to acrylamide intake [12]. However, as in previous studies, a consistent trend was observed in our study. Therefore, there might not be a substantial difference in susceptibility to acrylamide intake between Asian and Western populations.

In the analyses stratified by BMI (<25 kg/m^2 and ≥25 kg/m^2), we found no association of acrylamide intake with pancreatic cancer. CYP2E1, which is involved in the metabolism of acrylamide to glycidamide, has been reported to be activated at high levels of BMI [35,36]. Previous analyses of acrylamide intake associations with pancreatic cancer risk, stratified by BMI have yielded conflicting results. The EPIC study showed an inverse association between pancreatic cancer risk (lowest vs. highest HR = 0.32, 95% CI: 0.16–0.63) [7], while the PanC4 study (a pooled analysis of six case-control studies conducted in Europe, the United States, and Australia) showed no association (lowest vs. highest HR = 0.90, 95% CI: 0.46–1.78) [10]. Additionally, in the NLCS, an effect modification by obesity was observed (HR for each 10 μg/d increment: 1.59, 95% CI: 0.87–2.89, p for effect modification = 0.04) [8]. This study found no association of dietary acrylamide intake with pancreatic cancer in the analysis stratified by BMI.

In addition, we conducted analyses stratified by alcohol consumption; however, no association was confirmed. Alcohol reportedly inhibits CYP2E1 activity, probably competing with acrylamide as a substrate for acrylamide metabolism [37]. In fact, it has been suggested that people who consume more alcohol tend to have a lower HbGA/HbAA ratio [38–40]. In the analyses stratified by alcohol consumption in previous studies (the Italian case-control study [9] and EPIC study [7]), no association and some interactions with alcohol intake were suggested, respectively. Collectively, although the results of the stratification analyses of BMI and alcohol consumption are not completely consistent, further studies are needed on the possibility of confounding and modification of the effect. This is because these factors are possible risk factors of pancreatic cancer [31] and may also influence acrylamide metabolism [38–40].

Furthermore, as shown in Figures 2 and 3, coffee and green tea ranked first and second, respectively, among the foods that contribute to total acrylamide intake. Particularly, in the Q4 (highest) group, the proportion of total acrylamide intake was 36% for coffee and 23% for green tea. Green tea is a characteristic contributory food in Japan, and coffee is a major contributory food in Western countries. Tea polyphenols have been reported to reduce HbAA concentrations in animals [41], and the EPIC study also indicated an inverse correlation between tea intake and HbAA and HbGA concentrations [38]. We observed no association of dietary acrylamide intake with pancreatic cancer in our analyses stratified by coffee and green tea consumption.

The strengths of this study are attributed to some features of the JPHC Study and are as follows: this was a prospective cohort study; the participants were recruited from a general population; it had a long follow-up period; and the response rate was high (81.3%). In addition, there was no recall bias for exposure because the data were gathered before the diagnosis of cancer.

The present study had several limitations. First, there is a possibility of measurement error resulting from the exposure assessment of acrylamide intake by FFQ. We could not take into account dietary changes of the participants during the follow-up because acrylamide intake was assessed only once. However, we inferred that their dietary habits did not change much because the dietary habits of the study participants (aged 40 years and older) are likely to be well established. In addition, the FFQ was not designed to consider cooking temperature or cooking time, which can affect acrylamide concentration in foods [42]; Cooked vegetables contribute to acrylamide intake in the Japanese population [12]. While we could not include all vegetables in this study, acrylamide intake was estimated for some foods by considering cooking methods such as baking and frying [12]. Moreover, although the present study was conducted in the 1990s, the estimation of dietary acrylamide intake utilizing the FFQ was based on a database of measurements obtained from the 2000s. Second, the number of pancreatic cancer cases may not have been adequate to perform an analysis stratified by subgroups. Accordingly, these results may have been affected by the statistical power, and the results should be interpreted with caution. Finally, the results may have been affected by unmeasured confounders. We examined the analytical model including the major risk factors (such as red meat consumption, saturated fatty acid consumption, and physical activity) so far reported [31], although they were unrelated (data not shown). However, studies using biomarkers have identified factors that influence acrylamide metabolism, such as BMI levels and alcohol intake [38–40,43]. Therefore, multiple factors related to diet and lifestyle may affect acrylamide metabolism, and further studies are required to explore factors that affect acrylamide metabolism using biomarkers.

5. Conclusions

In a large Japanese cohort study, no association was found between pancreatic cancer risk and dietary acrylamide intake, regardless of sex, smoking status, coffee intake, green tea intake, alcohol consumption, and BMI. Our results indicate that dietary acrylamide intake is not likely to increase the risk of pancreatic cancer in the Japanese population, which has a relatively lower dietary acrylamide intake than the Western population.

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出典

本論文は以下に公表した。

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