Dietary acrylamide intake and risk of breast cancer: The Japan Public Health Center-based Prospective Study

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Acrylamide forms during cooking and is classified as a probable carcinogen in humans, mandating the need for epidemiological studies of dietary acrylamide and cancers. However, the risk of dietary acrylamide exposure to breast cancer in Japanese women has not been assessed. We investigated the association between dietary acrylamide intake and risk of breast cancer in the Japan Public Health Center-based Prospective Study. The present study included 48,910 women aged 45-74 years who responded to a 5-year follow-up survey questionnaire. Dietary acrylamide intake was assessed using a validated food frequency questionnaire. Cox proportional hazards regression models were used to estimate hazard ratios and 95% confidence intervals. During an average of 15.4 years of follow up, 792 breast cancers were diagnosed. Energy-adjusted dietary acrylamide intake was not associated with the risk of breast cancer (adjusted hazard ratio for highest versus lowest tertile = 0.95, 95% confidence intervals: 0.79-1.14, P-trend = .58). Further, no significant associations were observed when stratified analyses were conducted by smoking status, coffee consumption, alcohol consumption, body mass index, menopausal status, estrogen receptor status, and progesterone receptor status. In conclusion, dietary acrylamide intake was not associated with the risk of breast cancer in this population-based prospective cohort study of Japanese women.

KEYWORDS
acrylamide, Asia, breast cancer, diet, epidemiology

1 | INTRODUCTION

Acrylamide was classified as a probable human carcinogen (group 2A) by The International Agency for Research on Cancer in 1994. Until 2002, the main sources of acrylamide exposure were thought to be through specific occupations or smoking. However, Swedish researchers found that acrylamide occurs in carbohydrate-rich foods cooked at over 120°C, showing that one of the most common forms of acrylamide exposure in the population was from meals.

The carcinogenicity of dietary acrylamide is considered to occur through a genotoxic pathway. Acrylamide is soluble in water, absorbed from the gastrointestinal tract, and transported to several organs. Acrylamide is metabolized by 2 pathways, a direct pathway by glutathione conjugation of acrylamide by GST, and a second by...
glycidamide by cytochrome P450 and conjugation by GST. Both acrylamide and glycidamide can combine with DNA and cause genotoxicity.5

From the national dietary survey in Japan in 2012, acrylamide intake was estimated by Monte Carlo simulation to be 0.166 μg/kg bodyweight per day.6 This level is less than half of that reported in Western populations, namely 0.45 μg/kg bodyweight per day in the Dutch7 and 0.41 μg/kg bodyweight per day in Norwegians.8 These levels are lower than in animal studies;9,10 however, when the benchmark dose lower confidence limit (BMDL10) is 0.31 mg/kg bodyweight per day for mammary tumors in rats, the MOE is <10 000.2 Therefore, the Food Safety Commission of Japan is vigilant about the possibility of a carcinogenic effect of dietary acrylamide.2

Currently, 8 studies have examined the relationship between dietary acrylamide exposure and breast cancer.11-18 A recent meta-analysis of these studies observed that dietary acrylamide intake was not associated with the risk of breast cancer.19 However, these studies were all conducted in Western countries and no study has assessed the risk of acrylamide intake on breast cancer in Asians. Moreover, the meta-analysis included 7 studies, and some estimates were from stratified analyses, such as in premenopausal women16 or by hormone receptor status of breast cancer.17 The results might therefore not be robust, and further investigation among a variety of populations with various levels of acrylamide intake may be necessary.

The aim of the present study was to investigate the association between dietary acrylamide intake and the risk of breast cancer in the JPHC Study.

2 | MATERIALS AND METHODS

2.1 | Study participants

The JPHC Study is a population-based prospective study which aims to investigate the associations between lifestyle and lifestyle diseases in 2 cohorts. Cohort I was launched in 1990 in Iwate, Akita, Nagano, Okinawa-Chubu, and Tokyo, whereas Cohort II was started in 1993 in Ibaraki, Niigata, Kochi, Nagasaki, Okinawa-Miyako, and Osaka. The study protocol has been described previously.20,21 Participants were 140 420 inhabitants (68 722 men and 71 698 women) aged 40-69 years in the jurisdictional area of these 11 public health centers. Inhabitants in the Tokyo area were not included as participants in this study because their incidence data were not available. The study protocol was approved by the institutional review boards of the National Cancer Center, Tokyo, Japan, Osaka University and Azabu University. The authors confirm that some access restrictions apply to the data underlying the findings.

A dietary survey using a self-administered FFQ was conducted at baseline, and at 5- and 10-year follow up. The FFQ of the 5-year follow-up survey obtained more detailed dietary information than the FFQ of the baseline survey because it included more food items and portion size options than the baseline survey questionnaire. We therefore used the 5-year follow-up survey as the starting point of the present study.

After excluding participants who were disqualified (non-Japanese nationality, incorrect late report of migration occurring before the starting point, or incorrect birth data) or had died, moved out of a study area, or were lost to follow up before the starting point, 62 750 women were eligible for participation. Of these, 52 483 women responded to the 5-year follow-up questionnaire (response rate 83.6%).

Participants with a past history of breast cancer as identified by the questionnaire (N = 478) and those diagnosed with breast cancer from the baseline survey to the time of the 5-year follow-up survey were excluded (N = 27). Participants with missing or extreme (upper and lower 2.5 percentiles) energy intake data were also excluded (N = 3068). Finally, 48 910 participants were included in the study (Figure 1).
2.2  Assessment of energy and acrylamide intake from FFQ

The FFQ is based around a list of 138 food and beverage items, each with 9 categories of eating frequency (never, 1-3 times/mo, 1-2 times/wk, 3-4 times/wk, 5-6 times/wk, 1 time/d, 2-3 times/d, 4-6 times/d, or ≥7 times/d). The food items also have 3 categories of portion size (less than half the standard portion size, standard portion size, or more than 1.5-fold the standard portion size). Intake amount of each food and beverage was estimated by multiplying the eating frequency with the portion size.

Energy intake was estimated using the Fifth Revised and Enlarged Edition of the Standard Tables of Food Composition in Japan. A validation study of the FFQ was previously conducted by comparing intake from a 28-day DR as reference in a subcohort of the JPHC study. Correlation coefficients of energy intake among women were 0.41 and 0.24 in Cohort I and II, respectively. We previously reported the validity of acrylamide in Cohort II, or vice versa. The de-attenuated correlation coefficients of energy-adjusted acrylamide intake calculation of acrylamide in Cohort II, or vice versa. The de-attenuated correlation coefficients of energy-adjusted acrylamide intake from FFQ was previously conducted by comparing intake from a 28-day DR as reference in a subcohort of the JPHC study. Correlation coefficients of energy intake among women were 0.41 and 0.24 in Cohort I and II, respectively. We previously reported the validity of acrylamide intake measurement from the FFQ using this existing data and our database of measured values of acrylamide content in common Japanese foods elsewhere. Briefly, we developed a database of acrylamide-containing foods commonly consumed in Japan using published reports of measurements and selected the values of the following foods and beverages: miso, beer, baked fish paste, bread, rice cake, Japanese-style confectionary, cake, biscuits and cookies, chocolate, peanuts, fried tofu, green tea, oolong tea, black tea, coffee, and soup. Further, we considered the amount of acrylamide consumed from homemade cooking. Acrylamide intake from heated starchy vegetables (potato, sweet potato), vegetables (onion, bean sprouts, sweet pepper, squash, cabbage, snap beans, broccoli), toast, boiled or stir-fried rice, and fried batter was calculated by multiplying the amount of raw food, the proportion of heated food calculated from the DR and the concentration of acrylamide in each heated food. Because Cohort I and Cohort II are independently conducted studies which collected DR among different populations, we used the proportion of cooking methods among Cohort I in the calculation of acrylamide in Cohort II, or vice versa. The de-attenuated correlation coefficients of energy-adjusted acrylamide intake among women were 0.48 and 0.37 in Cohorts I and II, respectively.

2.3  Follow up and identification of breast cancer

All participants were followed from the starting point until December 31, 2013 (until December 31, 2012 in the Osaka area only). Residence status was confirmed annually through the residential registry. During the follow-up period, 6059 (12.4%) participants died, 3330 (6.8%) moved out of the study area, and 33 (0.1%) were lost to follow up.

Incidence of breast cancer was identified through the following data sources: active patient notification from major local hospitals in the study area and data linkage with population-based cancer registries. Death certificates were used as a supplementary information source. Cases were coded using the ICD-O-3; breast cancer is C500-509. The proportion of cases ascertained by DCO was 1.9%. This percentage was considered satisfactory for the present study. With a mean follow-up period of 15.4 years, a total of 792 newly diagnosed breast cancer cases were identified by December 31, 2013.

2.4  Statistical analysis

Person-years of follow up were determined from the starting point until the date of diagnosis of breast cancer, date of death, date of relocation from the study area, or end of the study period (December 31, 2012 for the Osaka area and December 31, 2013 for other areas), whichever occurred first. For participants lost to follow up, data were censored on the last confirmed date of presence in the study area.

A Cox proportional hazards model was used to estimate HR and 95% CI of breast cancer by tertile of dietary acrylamide intake, using the lowest (T1) versus the middle (T2) or highest (T3) group. Trends were assessed by assignment of ordinal values for tertile of dietary acrylamide intake. For further analysis, 9 quantiles were also used in the Cox proportional hazards model. Acrylamide intake was adjusted for energy intake using the residual method. HR were adjusted for the following potential confounding factors: age, PHC area, smoking status (current, past, never, or missing), alcohol intake (≥150 g/wk or ≥150 g/wk), BMI (<25, ≥25, or missing), family history of breast cancer (yes or no), age at menarche (≤13, 14, 15, ≥16, or missing), age at first delivery (<26, ≥26, or missing), number of deliveries (0, 1-2, 3, ≥4, or missing), menopausal status and age at menopause (pre or postmenopause, postmenopause from age <49, post-menopause from age 50 to 54, postmenopause from >55, or missing) and exogenous hormone use (yes, no, or missing). These variables were obtained from the questionnaire, and are known or suspected risk factors for breast cancer in the JPHC study. Further, we also adjusted for physical activity (metabolic equivalents) and isoflavone intake; as the results did not substantially change, however, we did not use these variables for adjustment in the final model. In a sensitivity analysis, we repeated the same analysis after excluding 120 breast cancer cases diagnosed in the first 3 years of follow up.

To elucidate the interaction effect, we conducted stratified analysis by smoking status (current smoker, past smoker, or never smoker), coffee consumption (<1 cup/wk, 1 cup or more/wk), alcohol consumption (<150 g/wk or ≥150 g/wk), BMI (<25 or ≥25), and menopausal status at starting point (pre or post-menopause). Further stratified analysis was conducted for tumor subtype defined by ER/PR status, namely ER+, ER−, PR+, PR−, ER+/PR+, and ER−/PR−. All P-values were 2-sided and statistical significance level was set at P < .05 using SAS 9.3 (SAS Institute Inc., Cary, NC, USA).
3 | RESULTS

3.1 | Characteristics of participants

Table 1 shows participant characteristics according to acrylamide intake. Mean (SD) dietary acrylamide intake overall was 7.0 (3.7) µg/d, corresponding to 0.14 (0.13) µg/kg bodyweight/day. There were significant differences in the following characteristics between tertiles. The highest acrylamide intake group tended to be younger and have a lower BMI; have a higher proportion of current smoking, younger menarche, premenopausal status, and exogenous female hormone non-use; have a lower proportion of older first delivery, and non- or few deliveries; and to consume less alcohol, and more coffee, green tea, biscuits and cookies, potatoes, and vegetables. There was no significant difference between tertiles in the proportion of a family history of breast cancer.

Figure 2 shows the contribution of acrylamide-containing foods among the total study population. The food group with the greatest contribution was beverages (total 49%; 24% for coffee, 23% for green tea, and 2% for others), followed by confectioneries (total 19%; 13% for biscuits and cookies, 3% for chocolate, and 3% for others), potatoes and starches (total 13%; 12% for potatoes and 1% for others), vegetables (total 11%; 4% for sweet pepper, 3% for onion, 3% for bean sprouts, and 1% for others), and cereals (total 6%; 3% for rice and 3% for others). The main contributing foods were common in each acrylamide intake group, but the trend slightly differed (Figure 3). As acrylamide intake increased, the contribution from coffee, green tea, and biscuits and cookies increased, whereas that from potatoes, vegetables and rice decreased.

3.2 | Association between dietary acrylamide intake and breast cancer

Table 2 shows the results of dietary acrylamide intake and risk of breast cancer. There was no association between dietary acrylamide intake and breast cancer. Compared to the lowest group, HR (95% CI) was 1.00 (0.84-1.18) in the middle group and 0.95 (0.79-1.14) in the highest (P for trend = .58). This result was consistent with the results obtained when cases occurring within 3 years after the start of follow up were excluded.

To clarify the risk in extremely high dietary acrylamide consumers among these study participants, we conducted a further analysis between 9 quantiles of acrylamide intake (Figure 4). Mean (SD) dietary acrylamide intake was 2.5 (0.7) µg/d among the lowest 9 quantile consumers and 14.6 (3.6) among the highest 9 quantile consumers. No significant association was observed. Compared to the lowest quantile, HR (95% CI) of the highest quantile was 0.91 (0.66-1.25) and P for trend was .81.

Although we also conducted stratified analyses by major confounding factors, significance associations were not observed among current or past smokers (P for trend = .64), never smokers (P for trend = .43), lower coffee consumers (P for trend = .58), coffee consumers (P for trend = .71), lower alcohol consumers (P for trend = .52), higher alcohol consumers (P for trend = .60), women with a normal BMI (P for trend = .62), obese women (P for trend = .74), premenopausal women (P for trend = .37), or postmenopausal women (P for trend = .97). Further, when stratified by estrogen receptor and progesterone receptor status, there were no significant associations among ER+ (P for trend = .99), ER− (P for trend = .48), PR+ (P for trend = .91), PR− (P for trend = .33), ER+/
PR+ (P for trend = .92), or ER−/PR− (P for trend = .35) (Table 2). Additionally, there were no significant associations when stratified by green tea intake (data not shown).

4 | DISCUSSION

We found that dietary acrylamide intake was not associated with breast cancer risk in a large prospective cohort study among Japanese women. In addition, we also found no associations when stratified analyses were conducted by smoking status, coffee consumption, alcohol consumption, BMI, menopausal status, or the hormone receptor status of breast cancer tumors.

These results showing no association between dietary acrylamide intake and breast cancer are consistent with the results of a meta-analysis by Pelucchi et al of 5 prospective cohort studies, one case-
**TABLE 2**  Acrylamide intake and risk of breast cancer

|                        | Tertile of acrylamide intake |                   |                   |                   | P for trend |
|------------------------|-------------------------------|-------------------|-------------------|-------------------|------------|
|                        | Total                          | Lowest (T1)       | Middle (T2)       | Highest (T3)      |            |
|                        | HR (95% CI)                   | HR (95% CI)       | HR (95% CI)       |                   |            |
| All women              |                               |                   |                   |                   |            |
| No. participants       | 48 910                        | 16 303            | 16 304            | 16 303            |            |
| No. cases              | 792                           | 266               | 268               | 258               |            |
| Person-years           | 754 623                       | 253 736           | 251 712           | 249 176           |            |
| Age- and area-adjusted | 1.00 (Reference)              | 0.95 (0.79-1.13)  | 0.84-1.19         | .55               |            |
| Multivariate-adjusted  | 1.00 (Reference)              | 0.95 (0.79-1.14)  | 0.84-1.18         | .58               |            |
| Multivariate-adjusted (excluding cases <3 y) | 1.00 (Reference) | 0.96 (0.79-1.17) | 0.87-1.26         | .70               |            |
| By smoking status      |                               |                   |                   |                   |            |
| Current or past smoker |                               |                   |                   |                   |            |
| No. participants       | 3014                          | 796               | 871               | 1347              |            |
| No. cases              | 46                            | 15                | 12                | 19                |            |
| Person-years           | 43 381                        | 11 598            | 12 452            | 19 332            |            |
| Multivariate-adjusted  | 1.00 (Reference)              | 0.77 (0.35-1.66)  | 0.83 (0.41-1.70)  | .64               |            |
| Never smoker           |                               |                   |                   |                   |            |
| Number of participants | 42 708                        | 14 359            | 14 388            | 13 961            |            |
| Number of cases        | 701                           | 239               | 238               | 224               |            |
| Person-years           | 666 754                       | 226 260           | 224 636           | 215 859           |            |
| Multivariate-adjusted  | 1.00 (Reference)              | 0.97 (0.81-1.17)  | 0.93 (0.77-1.12)  | .43               |            |
| By coffee consumption  |                               |                   |                   |                   |            |
| <1 cup/wk              |                               |                   |                   |                   |            |
| No. participants       | 13 967                        | 8003              | 3731              | 2233              |            |
| No. cases              | 206                           | 121               | 62                | 23                |            |
| Person-years           | 213 780                       | 123 302           | 56 865            | 33 613            |            |
| Multivariate-adjusted  | 1.00 (Reference)              | 1.19 (0.87-1.62)  | 0.77 (0.49-1.20)  | .58               |            |
| 1 cup or more/wk       |                               |                   |                   |                   |            |
| No. participants       | 34 943                        | 8300              | 12 573            | 14 070            |            |
| No. cases              | 586                           | 145               | 206               | 235               |            |
| Person-years           | 540 843                       | 130 434           | 194 847           | 215 563           |            |
| Multivariate-adjusted  | 1.00 (Reference)              | 0.93 (0.75-1.16)  | 0.95 (0.77-1.18)  | .71               |            |
| By alcohol consumption |                               |                   |                   |                   |            |
| <150 g/wk              |                               |                   |                   |                   |            |
| No. participants       | 47 536                        | 15 800            | 15 887            | 15 849            |            |
| No. cases              | 757                           | 254               | 258               | 245               |            |
| Person-years           | 734 543                       | 246 259           | 245 643           | 242 641           |            |
| Multivariate-adjusted  | 1.00 (Reference)              | 1.00 (0.84-1.19)  | 0.94 (0.78-1.13)  | .52               |            |
| ≥150 g/wk              |                               |                   |                   |                   |            |
| No. participants       | 1374                          | 503               | 417               | 454               |            |
| No. cases              | 35                            | 12                | 10                | 13                |            |
| Person-years           | 20 081                        | 7477              | 6068              | 6535              |            |
| Multivariate-adjusted  | 1.00 (Reference)              | 0.94 (0.38-2.30)  | 1.26 (0.53-3.01)  | .60               |            |
| By BMI                 |                               |                   |                   |                   |            |
| <25 kg/m²              |                               |                   |                   |                   |            |
| No. participants       | 34 090                        | 11 012            | 11 344            | 11 734            |            |
| No. cases              | 506                           | 163               | 173               | 170               |            |

(Continues)
TABLE 2 (Continued)

| Tertile of acrylamide intake | Total | Person-years | No. participants | No. cases | Person-years | No. participants | No. cases | Person-years | Multivariate-adjusted\(^a\) |
|-----------------------------|-------|--------------|-----------------|-----------|--------------|-----------------|-----------|--------------|------------------------|
|                            |       |              |                 |           |              |                 |           |              | HR (95% CI)          |
| Lowest (T1)                 |       |              |                 |           |              |                 |           |              | 1.00 (Reference)      |
| Middle (T2)                 |       |              |                 |           |              |                 |           |              | 1.01 (0.82-1.26)      |
| Highest (T3)                |       |              |                 |           |              |                 |           |              | 0.95 (0.76-1.18)      |
| P for trend                 |       |              |                 |           |              |                 |           |              | .62                   |
| Person-years                | 524 930 | 171 394 | 174 710 | 178 825 | - | - | - | - | - |
| Multivariate-adjusted\(^a\) |       |              |                 |           |              |                 |           |              | .62                   |
| ≥25 kg/m\(^2\)             |       |              |                 |           |              |                 |           |              | -                     |
| No. participants            | 13 495 | 4754 | 4551 | 4190 | - | - | - | - | - |
| No. cases                   | 266 | 97 | 85 | 84 | - | - | - | - | - |
| Person-years                | 211 475 | 75 034 | 71 292 | 65 149 | - | - | - | - | - |
| Multivariate-adjusted\(^a\) |       |              |                 |           |              |                 |           |              | .74                   |
| By menopausal status        |       |              |                 |           |              |                 |           |              | -                     |
| Premenopause                |       |              |                 |           |              |                 |           |              | -                     |
| No. participants            | 10 523 | 2493 | 3422 | 4608 | - | - | - | - | - |
| No. cases                   | 201 | 52 | 72 | 77 | - | - | - | - | - |
| Person-years                | 166 575 | 39 997 | 54 362 | 72 216 | - | - | - | - | - |
| Multivariate-adjusted\(^a\) |       |              |                 |           |              |                 |           |              | .37                   |
| Postmenopause               |       |              |                 |           |              |                 |           |              | -                     |
| No. participants            | 36 803 | 13 000 | 12 450 | 11 353 | - | - | - | - | - |
| No. cases                   | 572 | 203 | 193 | 176 | - | - | - | - | - |
| Person-years                | 564 230 | 201 595 | 190 725 | 171 910 | - | - | - | - | - |
| Multivariate-adjusted\(^a\) |       |              |                 |           |              |                 |           |              | .97                   |
| By hormone receptor status  |       |              |                 |           |              |                 |           |              | -                     |
| ER\(^+\)                    |       |              |                 |           |              |                 |           |              | -                     |
| No. subjects                | 48 344 | 16 113 | 16 117 | 16 114 | - | - | - | - | - |
| No. cases                   | 226 | 76 | 81 | 69 | - | - | - | - | - |
| Person-years                | 749 403 | 252 011 | 249 953 | 247 439 | - | - | - | - | - |
| Multivariate-adjusted\(^a\) |       |              |                 |           |              |                 |           |              | .99                   |
| ER\(^−\)                    |       |              |                 |           |              |                 |           |              | -                     |
| No. subjects                | 48 218 | 16 074 | 16 069 | 16 075 | - | - | - | - | - |
| No. cases                   | 100 | 37 | 33 | 30 | - | - | - | - | - |
| Person-years                | 748 275 | 251 669 | 249 587 | 247 020 | - | - | - | - | - |
| Multivariate-adjusted\(^a\) |       |              |                 |           |              |                 |           |              | .48                   |
| PR\(^+\)                    |       |              |                 |           |              |                 |           |              | -                     |
| No. subjects                | 48 287 | 16 093 | 16 096 | 16 098 | - | - | - | - | - |
| No. cases                   | 169 | 56 | 60 | 53 | - | - | - | - | - |
| Person-years                | 748 965 | 251 875 | 249 815 | 247 275 | - | - | - | - | - |
| Multivariate-adjusted\(^a\) |       |              |                 |           |              |                 |           |              | .91                   |
| PR\(^−\)                    |       |              |                 |           |              |                 |           |              | -                     |
| No. subjects                | 48 268 | 16 094 | 16 086 | 16 088 | - | - | - | - | - |
| No. cases                   | 150 | 57 | 50 | 43 | - | - | - | - | - |
| Person-years                | 748 702 | 251 820 | 249 715 | 247 167 | - | - | - | - | - |
| Multivariate-adjusted\(^a\) |       |              |                 |           |              |                 |           |              | .33                   |
| ER\(^+\)/PR\(^+\)           |       |              |                 |           |              |                 |           |              | -                     |
| No. subjects                | 48 277 | 16 089 | 16 095 | 16 093 | - | - | - | - | - |
| No. cases                   | 159 | 52 | 59 | 48 | - | - | - | - | - |
| Person-years                | 748 933 | 251 862 | 249 808 | 247 262 | - | - | - | - | - |
| Multivariate-adjusted\(^a\) |       |              |                 |           |              |                 |           |              | .92                   |

(Continues)
Acrylamide intake and breast cancer risk in all women, a positive association was observed in premenopausal women in the UK. The authors suggested that this positive association appears to represent a proxy for an unhealthier diet, because mean dietary acrylamide intake was less than in other countries and the main sources of dietary acrylamide intake were chips and crisps.16

In the present study, daily mean (SD) dietary acrylamide intake was 7.0 (3.7) μg in Japanese women. Western women consume 2-3 times more acrylamide than Japanese women, and mean levels of intake among Japanese women correspond to the lowest or second lowest quintile in Western women.11,16-18 This low and narrow intake pattern in Japanese women may affect the association toward null. Therefore, dietary acrylamide intake does not seem to increase the risk of breast cancer in Japanese women. However, 1 reason that most studies showed no association between dietary acrylamide intake and breast cancer is that country-specific analyses failed to ensure a wide distribution of intake such that the influence of dietary acrylamide could be detected.

The main sources in our Japanese population were coffee and green tea. Although green tea is specific for Japanese participants, coffee is also a common contributing food for acrylamide intake in Western countries.11,14,18 In a meta-analysis, coffee had a weakly preventive effect on breast cancer.36 However, no preventive or causative effect was observed for our cohort between coffee or green tea consumption and breast cancer risk.37 Further, stratified analysis by coffee or green tea consumption indicated there was no interaction effect in our study. Although coffee/green tea is the major source of acrylamide intake in Japan, the intake of coffee/green tea did not have a causative effect on breast cancer in this study.

We also found no associations when our study participants were stratified by alcohol consumption and BMI level. When acrylamide was consumed, it is partly metabolized by CYP2E1 to glycidamide, which is a more reactive compound than acrylamide.5 In a cross-sectional study, the ratio of hemoglobin adduct concentrations of acrylamide to glycidamide differed according to alcohol drinking habit and BMI level, because the activity of CYP2E1 is affected by alcohol consumption.
consumption and BMI level. However, we could not detect any associations in a stratified analysis. As acrylamide metabolism is also affected by polymorphisms in CYP2E1, differences in the distribution of these single-nucleotide polymorphisms (SNP) may also have affected the results.

We also conducted stratified analysis by menopausal status and the hormone receptor status of tumors, but observed no associations between dietary acrylamide intake and breast cancer. This result is consistent with previous studies. However, the effect of trace acrylamide intake on hormone concentration in humans is currently under investigation and the results to date are not consistent. Høgervorst et al. reported that the hemoglobin adduct concentration of acrylamide was positively associated with estrogen concentration in premenopausal American women whose BMI was <25. In contrast, Nagata et al. showed that dietary acrylamide intake assessed by FFQ was negatively related to estrogen concentration among premenopausal Japanese women. In a nested case-control study by Olsen et al., the hemoglobin adduct concentration of acrylamide was positively associated with the risk of ER+ breast cancer in smokers. Therefore, further studies are needed before the effect of acrylamide intake on the hormone-related pathway can be conclusively determined.

The major strength of the present study was its prospective cohort study design. Recall bias of exposure and confounding factors was avoided because data collection was conducted before breast cancer was diagnosed. Participants were selected from the general population, the sample size was large, the response rate to the questionnaire was acceptable (83.6%) for study settings such as this, and the loss to follow up (0.1%) was negligible. The proportion of cases ascertained by DCO was 1.9%. Furthermore, the cancer registry in the study population was of sufficient quality to reduce the possibility of misclassification of outcome.

This study has several limitations. First, there is a possibility of misclassification of acrylamide intake groups. The correlation coefficients among dietary acrylamide intake from the DR and FFQ were low to moderate and kappa coefficients in quintiles were over 0.8. High kappa coefficients showed categorical agreement, but the possibility of the attenuation of relative risk by misclassification of exposure assessment still remains. Moreover, the JPHC study and the validation study for the FFQ were conducted in the 1990s, but we calculated acrylamide intake using the measured values of acrylamide in foods in the 2000s because measured values were not available in the 1990s. This time lag may have lead to underestimation and misclassification because of the efforts of food companies in reducing acrylamide content in foods. However, the concentrations of acrylamide in coffee, which was the most important food in total acrylamide intake, did not dramatically differ between the recent decades, and the effect is therefore considered to be relatively small. Second, assessment of dietary acrylamide intake by FFQ may not reflect the true acrylamide and glycidaime exposure because acrylamide metabolism may be affected by individual enzyme activity and lifestyle. Further epidemiological study using biomarkers is needed to clarify acrylamide and glycidaime exposure in terms of internal dose. Third, the occurrence of breast cancer in Japan is less than in Western countries. Despite a reasonably large cohort population (48 910 women) and long follow-up period (average 15 years), the number of cases of breast cancer in this cohort was relatively small (n = 792), reflecting the low incidence rate in Japan (age-standardized rate per 100 000 world population in 2012, 51.5 in Japan and 92.9 in the USA for comparison). The lack of subjects and cases may have rendered some null associations in the stratified analyses less robust, and interpretation may therefore need caution. Fourth, other confounding factors might have affected the results. Although we adjusted for several confounding factors in the statistical model to the maximum degree possible, the effects of unmeasured confounders cannot be totally discarded.

In conclusion, we found that there was no association between dietary acrylamide intake and breast cancer risk regardless of smoking status, coffee consumption, alcohol consumption, BMI, menopausal status, or hormone receptor status of breast cancer tumors in a large prospective cohort study among Japanese women. Our findings suggest that dietary acrylamide intake is unlikely to increase the risk of breast cancer in Japanese women.

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CONFLICTS OF INTEREST
Authors declare no conflicts of interest for this article.

AUTHORS’ CONTRIBUTION
JI and TS designed the research; ST, TS, JI, NS, and MI conducted research; AK contributed to the calculation of dietary acrylamide intake; AK, LZ, and RL carried out statistical analysis; AK interpreted the results and wrote the paper; and JI had primary responsibility for final content. All authors reviewed the manuscript and contributed to the discussion.

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