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Original Contribution

Dietary Acrylamide Intake and Risk of Premenopausal Breast Cancer

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Acrylamide, a probable human carcinogen, is formed during high-temperature cooking of many commonly consumed foods. It is widespread; approximately 30% of calories consumed in the United States are from foods containing acrylamide. In animal studies, acrylamide causes mammary tumors, but it is unknown whether the level of acrylamide in foods affects human breast cancer risk. The authors studied the association between acrylamide intake and breast cancer risk among 90,628 premenopausal women in the Nurses' Health Study II. They calculated acrylamide intake from food frequency questionnaires in 1991, 1995, 1999, and 2003. From 1991 through 2005, they documented 1,179 cases of invasive breast cancer. They used Cox proportional hazards models to assess the association between acrylamide and breast cancer risk. The multivariable-adjusted relative risk of premenopausal breast cancer was 0.92 (95% confidence interval: 0.76, 1.11) for the highest versus the lowest quintile of acrylamide intake ($P_{trend} = 0.61$). Results were similar regardless of smoking status or estrogen and progesterone receptor status of the tumors. The authors found no associations between intakes of foods high in acrylamide, including French fries, coffee, cereal, potato chips, potatoes, and baked goods, and breast cancer risk. They found no evidence that acrylamide intake, within the range of US diets, is associated with increased risk of premenopausal breast cancer.

acrylamide; breast neoplasms; diet

Abbreviations: CI, confidence interval; ER, estrogen receptor; FFQ, food frequency questionnaire; PR, progesterone receptor; RR, relative risk.

Acrylamide is classified as a probable human carcinogen (1), and it is formed during high-temperature processing of many commonly consumed foods (2). The discovery of acrylamide in foods in 2002 caused considerable concern worldwide. Acrylamide is widespread in the food supply, with approximately 38% of calories consumed in the United States coming from foods that contain acrylamide (3). Potatoes, cold breakfast cereal, coffee, and baked goods are major sources of acrylamide intake in the United States (4). Prior to the discovery of acrylamide in foods, industrial use and tobacco use were thought to be the major sources of acrylamide exposure in humans (1).

In animal tests, acrylamide administered in high levels in drinking water causes several types of hormone-sensitive cancers, including mammary tumors in female rats (5, 6). Given the burden of breast cancer, it is of interest to study the association between acrylamide intake in humans and the risk of breast cancer. Epidemiologic studies have had mixed results. Two prospective studies of dietary acrylamide exposure in humans found no association with pre- or postmenopausal breast cancer risk (7, 8). Both of these reports used food frequency questionnaires (FFQs) to assess acrylamide intake. A prospective study in the Danish Diet, Cancer, and Health Cohort used a biomarker of acrylamide exposure, acrylamide adducts to hemoglobin, and found an increased risk of breast cancer among postmenopausal women with higher adducts. The increased risk appeared limited to smokers and to estrogen receptor-positive cancers (9).

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We used data from the Nurses' Health Study II to assess the association between acrylamide intake and premenopausal breast cancer risk. This cohort has repeated measures of diet, which allows us to study acrylamide intake over an extended time. We previously reported on the creation of an acrylamide food composition database for this cohort (10); we found a moderate association between calculated acrylamide intake and hemoglobin adducts of acrylamide in a subset of the cohort.

MATERIALS AND METHODS

Study population

The Nurses' Health Study II is a prospective cohort study of 116,671 female registered nurses aged 25–42 years at the start of the study in 1989. Follow-up questionnaires have been sent biennially to update information on lifestyle and health. Beginning in 1991, and every 4 years thereafter, a semiquantitative FFQ was sent to participants to assess their usual dietary intake over the previous year. Women who completed the first FFQ in 1991 ($n = 97{,}807$) form the study population for this analysis.

We excluded women who had an implausible energy intake (<800 or >4,200 kcal/day) or who left more than 70 food items blank ($n = 2{,}361$). We also excluded women who reported a diagnosis of cancer (excluding nonmelanoma skin cancer) before baseline in 1991 ($n = 1{,}308$).

The analysis was limited to premenopausal women, so women who were postmenopausal at baseline were excluded ($n = 3{,}462$), and women were censored after they reached natural or surgical menopause. Women who had a hysterectomy without a bilateral oophorectomy were excluded ($n = 48$) or censored at the time of surgery because their menopausal status was unknown. This left a total of 90,628 premenopausal women with baseline diet information for the analysis. The response rate was approximately 90% among these women through the end of follow-up on June 1, 2005. This study was approved by the human research committees at the Harvard School of Public Health and Brigham and Women's Hospital.

Assessment of acrylamide intake

FFQs with over 130 food items were completed in 1991, 1995, 1999, and 2003. Participants were asked how frequently they had consumed a specified portion size of each item over the previous year with 9 possible responses, ranging from never or less than once a month to 6 or more times per day. The FFQ includes the major acrylamide-contributing foods according to US Food and Drug Administration surveys: French fries, cold breakfast cereal, potato chips, cookies, coffee, breads, baked goods, and snack foods (4).

We previously reported on the creation and validation of an acrylamide food composition database for the FFQ (10). Briefly, 42 food items on the FFQ were assigned acrylamide contents based on published data from the US Food and Drug Administration and additional analyses of US foods by the Swedish National Food Administration. We calculated daily acrylamide intake for each participant by multiplying the acrylamide content of 1 serving of food by the frequency of consumption of that food and summing across all food items on the questionnaire. Acrylamide intake from cold breakfast cereal was based on participants' reporting of which brand they use most often. The correlation between 1999 acrylamide intake and a biomarker of acrylamide exposure, the sum of hemoglobin adducts of acrylamide and its metabolite glycidamide, was 0.34 ($P < 0.0001$) among 296 nonsmoking women from the Nurses' Health Study II cohort. The accuracy of reporting for individual food items on a similar FFQ was measured by comparing FFQ responses and 28 days of diet records in a subset of women in the Nurses' Health Study (11). The correlation between FFQ and diet records for the top acrylamide-contributing foods was 0.73 for French fries, 0.78 for coffee, 0.60 for potato chips, and 0.79 for cold breakfast cereal.

Because acrylamide may have an effect on carcinogenesis over an extended period of time, we used the cumulative average intake of acrylamide to represent long-term dietary intake. That is, 1991 intake was used for the 1991–1995 follow-up period, the average of 1991 and 1995 intakes was used for the 1995–1999 follow-up period, the average of 1991, 1995, and 1999 intakes was used for the 1999–2003 follow-up period, and the average of all 4 questionnaires was used for the 2003–2005 follow-up period. Data from the previous FFQ were carried forward to the next time period for participants with incomplete FFQ information after baseline. In secondary analyses, we examined the association between baseline acrylamide intake and breast cancer risk.

Ascertainment of breast cancer cases

Biennial follow-up questionnaires were used to identify newly diagnosed cases of breast cancer. Deaths were documented by responses to questionnaires by family members, by the postal service, or through the National Death Index. Cause of death was confirmed by medical record review, information from relatives, or review of death certificates.

When participants reported breast cancer, we asked the participant for confirmation of the diagnosis and permission to obtain relevant medical records. Pathology reports confirmed 98% of the self-reported breast cancers. Information on estrogen and progesterone receptor status was obtained from pathology reports and was available for 78% of cases. A recent validation study in the Nurses' Health Study I cohort demonstrated that pathology reports provide accurate information on estrogen receptor status (12). Cases of carcinoma-in-situ were not included in the analysis.

Statistical analysis

Each participant contributed person-time from the date of return of the 1991 questionnaire until the time of breast cancer diagnosis, menopause, death, or June 1, 2005, whichever

Table 1. Age-standardized Characteristics of the Nurses' Health Study II Cohort in 1991[a]

	Calorie-adjusted Acrylamide Intake				
	Quintile 1, Low (n = 20,934)	Quintile 2 (n = 17,416)	Quintile 3 (n = 16,768)	Quintile 4 (n = 16,331)	Quintile 5, High (n = 19,179)
Acrylamide intake, μg/day	10.8	16.6	20.2	24.6	37.8
Acrylamide by body weight, μg/kg/day	0.17	0.26	0.32	0.38	0.58
Age, years	36	36	36	36	36
Body mass index, kg/m^2	25	25	24	24	25
Current smokers, %	9	10	11	13	17
Physical activity, METs/week	24	22	20	20	17
Age at menarche <12 years, %	25	24	24	24	25
Nulliparous, %	32	28	26	26	27
Current oral contraceptive users, %	11	10	11	11	11
Family history of breast cancer, %	6	6	6	6	6
History of benign breast disease, %	33	32	33	34	33
Nutrient intakes					
Energy intake, kcal/day	1,796	1,854	1,805	1,724	1,772
Alcohol, g/day	3.0	3.1	3.3	3.3	2.9
Animal fat, g/day[b]	35	35	35	35	35
Glycemic load[b,c]	123	122	121	120	120
Intakes of high acrylamide foods, servings/day					
French fries	0.03	0.1	0.1	0.1	0.2
Coffee	0.7	1.2	1.6	2.1	2.3
Breakfast cereal	0.3	0.4	0.4	0.4	0.4
Potato chips	0.1	0.1	0.2	0.2	0.3
Potatoes (baked, roasted, mashed)	0.3	0.3	0.3	0.3	0.3

Abbreviation: MET, metabolic equivalent.

[a] All data (except for mean age) are standardized to the age distribution of the cohort in 1991. Means or percentages are shown.

[b] Animal fat and glycemic load are adjusted for total energy intake.

[c] Each unit of dietary glycemic load represents the glycemic equivalent of 1 g of carbohydrate from white bread. Intakes shown are per day.

came first. Participants were divided into quintiles based on their acrylamide intake and their consumption of acrylamide-rich foods. Acrylamide intake was adjusted for total energy intake by using the residual method. Relative risks of breast cancer were calculated as the incidence rate for a given quintile of consumption divided by the rate in the lowest quintile.

We used Cox proportional hazards regression to adjust for potential confounding by other breast cancer risk factors. To control as finely as possible for confounding by age, calendar time, and any possible 2-way interactions between these 2 time scales, we stratified the analysis jointly by age in months at the start of each follow-up period and calendar year of the current questionnaire cycle. We used multivariable models to adjust for the following factors: body mass index (<18.5, 18.5–19.9, 20.0–22.4, 22.5–24.9, 25.0–29.9, and ≥30 kg/m^2), height (<62, 62–<65, 65–<68, and ≥68 inches; 1 inch = 2.54 cm), oral contraceptive use (never, former use <4 years, former use ≥4 years, current use <8 years, and current use ≥8 years), parity and age at first birth (nulliparous, 1–2 children and age at first birth <25 years, 1–2 children and age at first birth 25–<30 years, 1–2 children and age at first birth ≥30 years, 3 or more children and age at first birth <25 years, 3 or more children and age at first birth ≥25 years), age at menarche (<12, 12, 13, or ≥14 years), family history of breast cancer (yes/no), history of benign breast disease (yes/no), smoking (never, former smoker of <25 cigarettes/day, former smoker of ≥25 cigarettes/day, current smoker of <25 cigarettes/day, and current smoker of ≥25 cigarettes/day), physical activity (≤18 and >18 metabolic equivalent (MET)-hours/week), animal fat (quintiles), glycemic load (quintiles), alcohol intake (continuous g/day), and total energy intake (continuous kcal/day). We adjusted for animal fat and glycemic load as they have previously been associated with breast cancer risk in this cohort (13, 14). We also considered adjustment for quintile of vegetable fat intake, *trans* fat intake, and glycemic index, as these dietary factors were most correlated with acrylamide intake, but they were not included in final models because

Table 2. Relative Risk (95% Confidence Intervals) of Breast Cancer by Quintile of Calorie-adjusted Acrylamide Intake, Nurses' Health Study II, 1991–2005

	Calorie-adjusted Acrylamide Intake[a]					P_{trend}[b]
	Quintile 1, Low (12 μg/day)	Quintile 2 (17 μg/day)	Quintile 3 (20 μg/day)	Quintile 4 (24 μg/day)	Quintile 5, High (33 μg/day)	
All premenopausal breast cancer						
No. of cases	237	236	232	264	210	
Age-adjusted relative risk	1.00	0.96 (0.80, 1.15)	0.95 (0.79, 1.14)	1.04 (0.87, 1.24)	0.92 (0.76, 1.10)	0.58
Multivariable relative risk[c]	1.00	0.95 (0.79, 1.14)	0.94 (0.78, 1.13)	1.03 (0.87, 1.24)	0.92 (0.76, 1.11)	0.61
By smoking status						
Never smokers						
No. of cases	165	149	148	165	111	
Age-adjusted relative risk	1.00	0.91 (0.72, 1.13)	0.93 (0.75, 1.17)	1.06 (0.85, 1.32)	0.81 (0.64, 1.04)	0.28
Multivariable relative risk[c]	1.00	0.91 (0.73, 1.14)	0.94 (0.75, 1.18)	1.08 (0.86, 1.34)	0.82 (0.64, 1.05)	0.33
Former smokers						
No. of cases	56	64	63	74	68	
Age-adjusted relative risk	1.00	0.98 (0.68, 1.41)	0.91 (0.63, 1.32)	0.99 (0.69, 1.40)	1.05 (0.73, 1.50)	0.70
Multivariable relative risk[c]	1.00	1.00 (0.69, 1.44)	0.92 (0.64, 1.34)	1.01 (0.70, 1.43)	1.09 (0.75, 1.56)	0.57
Current smokers						
No. of cases	16	23	23	25	31	
Age-adjusted relative risk	1.00	1.16 (0.60, 2.25)	1.14 (0.59, 2.21)	0.88 (0.46, 1.69)	0.97 (0.52, 1.81)	0.61
Multivariable relative risk[c]	1.00	1.09 (0.55, 2.17)	1.16 (0.58, 2.30)	0.82 (0.41, 1.62)	1.05 (0.55, 2.02)	0.89
By ER and PR status						
ER+/PR+ breast cancer						
No. of cases	105	129	111	138	114	
Age-adjusted relative risk	1.00	1.16 (0.90, 1.50)	1.00 (0.77, 1.31)	1.19 (0.93, 1.54)	1.13 (0.87, 1.48)	0.38
Multivariable relative risk[c]	1.00	1.14 (0.88, 1.48)	0.98 (0.75, 1.28)	1.16 (0.90, 1.50)	1.11 (0.85, 1.46)	0.45
ER−/PR− breast cancer						
No. of cases	39	45	34	43	35	
Age-adjusted relative risk	1.00	1.10 (0.72, 1.70)	0.86 (0.54, 1.36)	1.06 (0.69, 1.65)	0.93 (0.59, 1.47)	0.73
Multivariable relative risk[c]	1.00	1.09 (0.70, 1.68)	0.85 (0.53, 1.35)	1.04 (0.67, 1.62)	0.90 (0.57, 1.43)	0.62

Abbreviations: ER, estrogen receptor; MET, metabolic equivalent; PR, progesterone receptor; +, positive; −, negative.

[a] Median intake.

[b] Test for trend calculated by using the median intake in each quintile as a continuous variable.

[c] Multivariable models are stratified by age in months and calendar year and adjusted for the following: body mass index (<18.5, 18.5–19.9, 20.0–22.4, 22.5–24.9, 25.0–29.9, and ≥30 kg/m^2), height (<62, 62–<65, 65–<68, and ≥68 inches; 1 inch = 2.54 cm), oral contraceptive use (never, former use <4 years, former use ≥4 years, current use <8 years, and current use ≥8 years), parity and age at first birth (nulliparous, parity 1–2 and age at first birth <25 years, parity 1–2 and age at first birth 25–<30 years, parity 1–2 and age at first birth ≥30 years, parity ≥3 and age at first birth <25 years, parity ≥3 and age at first birth ≥25 years), age at menarche (<12, 12, 13, or ≥14 years), family history of breast cancer (yes/no), history of benign breast disease (yes/no), smoking (never, former smoker <25 cigarettes/day, former smoker ≥25 cigarettes/day, current smoker <25 cigarettes/day, and current smoker ≥25 cigarettes/day), physical activity (≤18 and >18 MET-hours/week), animal fat (quintiles), glycemic load (quintiles), alcohol intake (continuous), and total energy intake (continuous).

they had no substantial effect on the relative risk or standard error estimates for acrylamide. All covariates except height and age at menarche were updated in each questionnaire cycle. The SAS Proc PHREG procedure (SAS Institute, Inc., Cary, North Carolina) was used for all analyses, and the Anderson-Gill data structure was used to handle time-varying covariates efficiently. To test for a linear trend across quintiles of intake, we modeled acrylamide intake as a continuous variable using the median value for each quintile.

We examined whether the association between acrylamide intake and breast cancer risk was modified by individual characteristics, including age, smoking status, body mass index, alcohol intake, and glycemic load, by modeling the association separately in each group. We tested the significance of interactions by adding cross-product terms between acrylamide intake and the variable of interest to the model and comparing this model to the model without the cross-product term using the likelihood ratio test.

Table 3. Relative Risk (95% Confidence Intervals) of Breast Cancer by Intake of High-Acrylamide Foods, Nurses' Health Study II, 1991–2005

	Intake of High-Acrylamide Foods					P_{trend}[a]
	Quintile 1, Low	Quintile 2	Quintile 3	Quintile 4	Quintile 5, High	
French fries						
Median intake, servings/week	0	0.2	0.5	0.7	1.0	
No. of cases	255	211	255	195	263	
Multivariable relative risk[b]	1.00	1.08 (0.89, 1.31)	0.93 (0.77, 1.11)	0.93 (0.76, 1.13)	0.96 (0.80, 1.16)	0.35
Coffee						
Median intake, servings/day	0	0.2	1	2.5	3.5	
No. of cases	270	155	230	266	258	
Multivariable relative risk[b]	1.00	1.11 (0.91, 1.36)	0.97 (0.81, 1.16)	1.01 (0.85, 1.21)	0.92 (0.77, 1.11)	0.28
Breakfast cereal						
Median intake, servings/week	0	0.7	2.0	3.0	6.0	
No. of cases	207	254	226	272	220	
Multivariable relative risk[b]	1.00	1.11 (0.92, 1.33)	1.07 (0.88, 1.30)	1.13 (0.94, 1.37)	1.10 (0.89, 1.34)	0.55
Potato chips						
Median intake, servings/week	0	0.5	0.6	1.0	3.0	
No. of cases	219	313	204	216	227	
Multivariable relative risk[b]	1.00	1.01 (0.85, 1.20)	1.00 (0.82, 1.22)	1.04 (0.86, 1.26)	0.98 (0.80, 1.19)	0.76
Potatoes (baked, roasted, mashed)						
Median intake, servings/week	0.5	1.0	1.5	2.0	3.0	
No. of cases	221	302	173	174	309	
Multivariable relative risk[b]	1.00	1.04 (0.87, 1.24)	1.01 (0.82, 1.24)	0.96 (0.78, 1.19)	0.97 (0.80, 1.17)	0.48
Popcorn						
Median intake, servings/week	0	0.5	0.7	1.0	3.0	
No. of cases	256	220	247	273	183	
Multivariable relative risk[b]	1.00	1.02 (0.85, 1.23)	1.09 (0.91, 1.31)	0.99 (0.83, 1.18)	0.78 (0.64, 0.95)	0.002
Muffins						
Median intake, servings/week	0	0.2	0.5	1.0	2.0	
No. of cases	216	155	324	212	272	
Multivariable relative risk[b]	1.00	1.01 (0.81, 1.24)	1.09 (0.92, 1.30)	0.98 (0.80, 1.19)	1.18 (0.98, 1.43)	0.10
Crackers						
Median intake, servings/week	0	0.5	0.7	1.2	3.0	
No. of cases	244	195	204	285	251	
Multivariable relative risk[b]	1.00	0.94 (0.77, 1.14)	0.96 (0.79, 1.16)	0.96 (0.81, 1.15)	1.10 (0.92, 1.33)	0.13

Table continues

RESULTS

During 14 years (945,764 person-years) of follow-up, we documented 1,179 cases of invasive breast cancer among 90,628 premenopausal women in the cohort. The age range of women in 1991 was 26–46 years. Ages at breast cancer diagnosis ranged from 26 to 56 years. We had information on estrogen receptor (ER)/progesterone receptor (PR) status for 916 (78%) cases. Of these, 597 were ER and PR positive (ER+/PR+), and 196 were ER and PR negative (ER−/PR−). Because of the small number of mixed ER/PR status tumors, we did not include these cases in our analysis by ER/PR status.

Table 1 shows the characteristics of the cohort in 1991 by quintile of energy-adjusted acrylamide intake. The mean acrylamide intake was 10.8 μg/day in the lowest quintile and 37.8 μg/day in the highest quintile. The major food contributors to acrylamide intake were French fries (23%), coffee (15%), cold breakfast cereal (12%), potato chips (9%), and other potatoes (baked, roasted, mashed; 5%). Those in the highest quintile of acrylamide consumption were more likely to be current smokers and were less likely to exercise than those in the lowest quintile.

Intake of acrylamide was not associated with risk of premenopausal breast cancer (Table 2). The multivariable relative risk of breast cancer was 0.92 (95% confidence interval (CI): 0.76, 1.11) in the highest quintile of intake compared with the lowest quintile. The *P* value for a linear trend across quintiles was 0.61. No association was found for ER+/PR+ or ER−/PR− cancers.

Table 3. Continued

	Intake of High-Acrylamide Foods					P_{trend}[a]
	Quintile 1, Low	Quintile 2	Quintile 3	Quintile 4	Quintile 5, High	
Dark bread						
Median intake, servings/week	0	1.0	3.0	4.7	10.2	
No. of cases	219	267	280	199	214	
Multivariable relative risk[b]	1.00	1.30 (1.08, 1.55)	1.11 (0.93, 1.33)	0.96 (0.79, 1.17)	0.96 (0.79, 1.17)	0.05
English muffins, bagels, rolls						
Median intake, servings/week	0	0.5	1.0	3.0	5.0	
No. of cases	149	279	270	268	213	
Multivariable relative risk[b]	1.00	1.04 (0.85, 1.28)	1.02 (0.83, 1.25)	0.93 (0.76, 1.15)	0.98 (0.78, 1.22)	0.38
Pizza						
Median intake, servings/week	0.2	0.5	0.7	1.0	2.0	
No. of cases	185	268	324	271	131	
Multivariable relative risk[b]	1.00	0.91 (0.75, 1.11)	1.10 (0.91, 1.33)	0.94 (0.76, 1.15)	0.93 (0.73, 1.18)	0.55
All potatoes[c]						
Median intake, servings/week	1.0	2.0	3.0	4.5	7.0	
No. of cases	246	225	250	239	219	
Multivariable relative risk[b]	1.00	0.90 (0.74, 1.08)	0.89 (0.74, 1.07)	0.95 (0.78, 1.15)	0.90 (0.73, 1.11)	0.59
Breads/starches[c]						
Median intake, servings/day	0.7	1.2	1.6	2.2	3.4	
No. of cases	253	223	228	258	217	
Multivariable relative risk[b]	1.00	0.86 (0.71, 1.03)	0.86 (0.71, 1.04)	0.95 (0.78, 1.16)	0.87 (0.70, 1.09)	0.59
Baked goods[c]						
Median intake, servings/week	0.9	2.0	3.3	5.2	9.9	
No. of cases	257	223	220	237	242	
Multivariable relative risk[b]	1.00	0.94 (0.78, 1.13)	0.85 (0.70, 1.02)	0.88 (0.73, 1.07)	0.91 (0.74, 1.11)	0.55

Abbreviation: MET, metabolic equivalent.

[a] Test for trend calculated by using the median intake in each quintile as a continuous variable.

[b] Multivariable models are stratified by age in months and calendar year and adjusted for the following: body mass index (<18.5, 18.5–19.9, 20.0–22.4, 22.5–24.9, 25.0–29.9, and ≥30 kg/m^2), height (<62, 62–<65, 65–<68, and ≥68 inches; 1 inch = 2.54 cm), oral contraceptive use (never, former use <4 years, former use ≥4 years, current use <8 years, and current use ≥8 years), parity and age at first birth (nulliparous, parity 1–2 and age at first birth <25 years, parity 1–2 and age at first birth 25–<30 years, parity 1–2 and age at first birth ≥30 years, parity ≥3 and age at first birth <25 years, parity ≥3 and age at first birth ≥25 years), age at menarche (<12, 12, 13, or ≥14 years), family history of breast cancer (yes/no), history of benign breast disease (yes/no), smoking (never, former smoker <25 cigarettes/day, former smoker ≥25 cigarettes/day, current smoker <25 cigarettes/day, and current smoker ≥25 cigarettes/day), physical activity (≤18 and >18 MET-hours/week), animal fat (quintiles), glycemic load (quintiles), alcohol intake (continuous), and total energy intake (continuous).

[c] All potatoes include French fries, potato chips, and potatoes (baked, roasted, and mashed). Breads/starches include white bread, dark bread, English muffins/rolls/bagels, muffins, tortillas, pancakes, crackers, and pizza. Baked goods include cookies, brownies, donuts, cake, pie, and sweet rolls.

Because tobacco use is a major source of acrylamide exposure, we examined the association among never smokers, former smokers, and current smokers separately (Table 2). There was no indication of increased risk of breast cancer for higher acrylamide intakes in any of these groups.

We found no significant differences in the association between dietary acrylamide intake and breast cancer risk when we stratified the population by age, body mass index, alcohol intake, glycemic index, or glycemic load (data not shown).

We repeated the analysis measuring acrylamide exposure relative to body weight (i.e., μg/kg of body weight/day), as this is the exposure measurement used in toxicology studies, and again found similar results. The relative risk for the highest versus the lowest quintile of acrylamide by body weight was 1.00 (95% CI: 0.82, 1.22), with a P value for linear trend of 0.95. Baseline acrylamide intake through diet was also not associated with breast cancer risk. The relative risks relative to the lowest quintile of baseline acrylamide intake were 0.96 (95% CI: 0.79, 1.15) for quintile 2, 1.05 (95% CI: 0.88, 1.26) for quintile 3, 1.01 (95% CI: 0.84, 1.21) for quintile 4, and 1.03 (95% CI: 0.86, 1.24) for quintile 5 ($P_{trend} = 0.62$).

Table 3 shows the association between consumption of the major acrylamide-contributing foods and

premenopausal breast cancer risk. We examined all individual foods that contributed at least 2% to the total estimated acrylamide intake in our population, and none was positively associated with breast cancer risk. We also examined several food groups that are major sources of acrylamide: all potatoes (French fries, potato chips, and baked/mashed/roasted potatoes), breads (white and dark bread, English muffins/bagels/rolls, tortillas, pancakes, pizza, and crackers), and baked goods (cookies, brownies, donuts, cake, pie, and sweet rolls). None of these food groups was associated with breast cancer risk.

DISCUSSION

We found no association between acrylamide intake and premenopausal breast cancer risk in this cohort. There was no association for ER/PR-positive or -negative cancers or by smoking status. In addition, there was no association between intake of any major acrylamide-contributing foods and breast cancer risk.

These findings are in line with both previous prospective studies of acrylamide intake and breast cancer risk using FFQs. Mucci et al. (7) found no significant association between acrylamide intake and breast cancer risk among mostly premenopausal Swedish women. Hogervorst et al. (8) found no significant association among postmenopausal Dutch women. The mean acrylamide intake and the contrast in intakes between high and low quintiles were quite similar across the 3 studies. However, the main sources of acrylamide vary between populations. French fries, coffee, cold breakfast cereal, and potato chips contribute the most to intake in our US population. Coffee is a larger contributor to acrylamide intake in both the Swedish and Dutch cohorts (7, 8). Fried potatoes and crisp bread are other major contributors in the Swedish women (7), and Dutch spice cake and cookies are major contributors in the Dutch women (8). In addition, Pelucchi et al. found no association between acrylamide intake (15) or fried potato intake (16) and breast cancer risk in a hospital-based, case-control study in Italy and Switzerland.

In a nested case-control study, Olesen et al. (9) studied the association between acrylamide adducts to hemoglobin, a biomarker of acrylamide exposure, and postmenopausal breast cancer risk. Current smokers with higher levels of acrylamide adducts to hemoglobin at baseline had a significantly increased risk of breast cancer (for a 10-fold increase in adducts, relative risk (RR) = 3.1, 95% CI: 1.0, 9.7). Tobacco use is an important source of acrylamide exposure, and smokers have acrylamide adduct levels 3–5 times higher than do nonsmokers. Therefore, adduct levels among smokers reflect both tobacco use and dietary intake of acrylamide. Among nonsmoking women, whose adduct levels are thought primarily to represent dietary acrylamide exposure, Olesen et al. found no statistically significant association between adduct levels and breast cancer risk (for a 10-fold increase in adducts, RR = 1.5, 95% CI: 0.6, 3.6). The meaning of the positive association with adduct levels among smokers is not clear; however, their results among nonsmokers seem in line with our finding that acrylamide exposure in the range of dietary intakes is not clearly associated with breast cancer risk. Olesen et al. also found a significantly increased risk of ER+ cancers among those with higher adduct levels (for a 10-fold increase in adducts, RR = 2.7, 95% CI: 1.1, 6.6). This result was among smokers and nonsmokers combined, with multivariable adjustment for smoking behavior; however, given the relative contributions of smoking and diet to adduct levels, it is not clear that such adjustment provides adequate control of confounding by smoking. In our analysis of food frequency questionnaire-assessed acrylamide and ER+ cancers, we found no significant association.

Strengths of our study include its prospective design, large number of premenopausal cases, and high rates of follow-up. In addition, we are the first to study acrylamide intake and cancer risk using multiple FFQs administered to collect updated dietary data throughout the follow-up period, rather than a single point in time. This improves our assessment of long-term diet and reduces measurement error (17). Our study also uses an extensive acrylamide database with 42 acrylamide-contributing foods, approximately twice as many as used in previous studies.

We have previously found that FFQ acrylamide intake is significantly correlated with hemoglobin adducts of acrylamide and its metabolite glycidamide in this population (10). However, misclassification of acrylamide intake remains a limitation of our study, as acrylamide poses unique challenges for FFQ assessment. Acrylamide formation is affected by many parameters (for review, refer to Stadler and Scholz (18)), such as cooking temperature and even the length and temperature of storage of ingredients such as potatoes, which implies that acrylamide content varies widely among different brands of prepared foods, and depends on the cooking methods used at home. Therefore, the assignment of a single acrylamide value for each food likely results in nondifferential misclassification of acrylamide intake, which would bias our observed relative risks toward the null. As a result, we may have missed modest associations between acrylamide intake and cancer risk. We also found no association between breast cancer risk and intake of any of the top 11 acrylamide-contributing foods, which are well measured by the FFQ within the similar Nurses' Health Study cohort (11).

Residual confounding is also a concern in observational studies. Adjustment for known breast cancer risk factors had very little effect on the relative risk estimates, suggesting that it is unlikely that confounding was a source of substantial bias. Finally, it is not clear that adult diet is the most relevant period of exposure. It is possible that high acrylamide intake in childhood or adolescence may increase breast cancer risk later in life, and our study cannot address this question.

In conclusion, we found no association between acrylamide intake from the diet and risk of premenopausal breast cancer risk. Combined with the results of other prospective cohort studies, this suggests that intake of foods high in acrylamide is not a major risk factor for breast cancer. However, a modest association could have been missed, because the substantial variation in the acrylamide content of foods makes measurement of intake difficult.

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