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Original Contribution

Long-term Dietary Acrylamide Intake and Breast Cancer Risk in a Prospective Cohort of Swedish Women

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The association between dietary acrylamide intake and the incidence of invasive breast cancer was examined among 61,433 Swedish women who were cancer free and completed a food frequency questionnaire in 1987–1990 and again in 1997. During a mean follow-up of 17.4 years, a total of 2,952 incident cases of breast cancer were diagnosed in the cohort. In multivariate analyses controlling for breast cancer risk factors, no statistically significant association was observed between long-term acrylamide intake (assessed at baseline and in 1997) and the risk of breast cancer, overall or by estrogen receptor (ER) and progesterone receptor (PR) status. The multivariate rate ratios comparing extreme quartiles of acrylamide intake were 0.91 (95% confidence interval (CI): 0.80, 1.02) for overall breast cancer, 0.89 (95% CI: 0.74, 1.08) for ER+PR+ tumors, 1.17 (95% CI: 0.84, 1.64) for ER+PR– tumors, and 0.91 (95% CI: 0.61, 1.38) for ER–PR– tumors. The association between acrylamide intake and breast cancer risk did not differ by smoking status. These findings for Swedish women do not support the hypothesis that dietary acrylamide is positively associated with risk of breast cancer, at least not within the ranges of acrylamide consumed by this population.

acrylamide; breast neoplasms; cohort studies; diet; prospective studies

Abbreviations: ER, estrogen receptor; FFQ, food frequency questionnaire; PR, progesterone receptor.

The detection of acrylamide in several fried and baked carbohydrate-rich foods in 2002 (1) has caused worldwide concern because acrylamide has carcinogenic properties in experimental animals (2, 3). High levels of acrylamide have been found in foods such as potato crisps, French fries, fried potato, bread (especially crisp bread), breakfast cereals, cookies, and coffee (4). The average daily acrylamide intake has been estimated to be approximately 0.4 μg/kg of body weight in European countries (4). Besides heated foods, acrylamide exposure occurs through tobacco smoke and occupational exposure and, to a minor extent, through drinking water (4). Compared with nonsmokers, smokers have been found to have about 4 times higher levels of acrylamide-hemoglobin adducts (marker of internal dose of acrylamide) (5).

Studies in rodents have shown a positive dose-response relation between acrylamide exposure and cancer in multiple organs (3), especially in hormone-sensitive organs such as the mammary gland and the uterus (6, 7). Epidemiologic data are limited on the relation between dietary acrylamide intake (8–10) and the risk of breast cancer in humans, and the few data that do exist are inconsistent. Only one previous study has, to our knowledge, examined whether the association between acrylamide exposure and breast cancer risk differs according to hormone receptor status of the breast tumor (11). Given the paucity and inconsistent data, we investigated prospectively the association between acrylamide intake and the incidence of breast cancer, overall and by hormone receptor status, in a population-based cohort of Swedish women. We also evaluated whether the relation between acrylamide intake and breast cancer risk varied by smoking status.

MATERIALS AND METHODS

Study cohort

The Swedish Mammography Cohort was established in 1987–1989 in Västmanland County and in 1988–1990 in

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Uppsala County in central Sweden. All women born between 1917 and 1948 in Västmanland County and between 1914 and 1948 in Uppsala County received a mailed invitation to be screened by mammography. Enclosed with this invitation was a 6-page questionnaire regarding diet, body size, reproductive factors, family history of breast cancer, and other factors; a completed questionnaire was obtained from 66,651 women, representing 74% of the source population. In the late autumn of 1997, all cohort members who were still alive and residing in the study area ($n = 56{,}030$ women) received a new questionnaire that was expanded to include about 350 items concerning diet and other lifestyle factors (including cigarette smoking); 39,227 women (70%) completed the second questionnaire.

From the baseline cohort of 66,651 women, we excluded those with an incorrect or missing national registration number as well as those whose questionnaire lacked the date, date of moving out of the study area, or date of death. After further exclusion of women with implausible values for total energy intake (i.e., 3 standard deviations from the mean value for $\log_e$-transformed energy intake) and women with a cancer diagnosis (other than nonmelanoma skin cancer) before baseline, the baseline cohort consisted of 61,433 women. For analyses using data from the second questionnaire, 36,664 women were eligible after we excluded those with an implausible energy intake on the second dietary questionnaire and those who had been diagnosed with cancer between baseline and January 1, 1998. The study was approved by the ethics committees at the Uppsala University Hospital (Uppsala, Sweden) and the Karolinska Institutet (Stockholm, Sweden).

Assessment of diet

A food frequency questionnaire (FFQ) with 67 and 96 food items was used to assess diet at baseline and in 1997, respectively. In these questionnaires, women were asked to report how often, on average, they had consumed each food item during the previous 6 months (1987–1990 FFQ) or the previous year (1997 FFQ). The questionnaires listed 8 mutually exclusive, predefined categories for frequency of consumption, ranging from ''never/seldom'' to ''3 or times per day'' (1997 FFQ) or ''4 or more times per day'' (1987–1990 FFQ).

Information on the acrylamide content of Swedish foods was obtained from the Swedish National Food Administration (12) and Svensson et al. (13). In 2002, more than 130 food samples were collected from supermarkets in Uppsala, Sweden (the study area), for analysis of acrylamide concentrations (13). Concentrations of acrylamide were available for such foods as coffee, cereal grain products, various types of potato products, snacks, cookies and biscuits, and minced meat products such as meatballs and hamburgers. Dietary acrylamide intake was calculated by multiplying the frequency of consumption of each food item by its acrylamide content per age-specific serving. The age-specific serving sizes were based on mean values obtained from 213 randomly selected women from the study area who weighed and recorded their food intake for an average of 27.8 days.

The validity of the baseline dietary questionnaire was assessed previously by comparing responses from the FFQ with responses from four 1-week dietary records among 129 women randomly chosen from the cohort (A. Wolk, unpublished data). Although the validity of values for acrylamide intake could not be directly tested, we examined correlations between the questionnaire and the dietary records for the major food sources of acrylamide. The corrected Pearson correlation coefficients were 0.6 for coffee, 0.5 for whole grain bread, and 0.6 for breakfast cereals/muesli.

Case ascertainment and follow-up

We ascertained histologically confirmed incident cases of invasive breast cancer by linkage of the study cohort with the national and regional Swedish Cancer registers. The completeness of cancer follow-up was estimated to be almost 100% (14). Information on estrogen receptor (ER) and progesterone receptor (PR) status of breast tumors was obtained by reviewing pathology laboratory work logs stored at Uppsala University Hospital (from 1987 to 1994) and by linkage with the clinical database (the Quality Register) at the Regional Oncology Centre in Uppsala (from January 1992 through December 2007), which was based on the patients' original medical records. ER and PR status was evaluated by using an Abbott immunoassay (Abbott Laboratories, Abbott Park, Illinois) until 1997 and an immunohistochemical method thereafter. Cases with $\geq$0.1 fmol/μg cytosol DNA were considered hormone receptor positive when the Abbott immunoassay was used. By the immunohistochemical method, cases were considered receptor positive when the percentage of positive cells was $\geq$10% and receptor negative when the percentage of positive cells was $<$10%. The Department of Pathology and Cytology at Uppsala University Hospital and Västerås Central Hospital were involved in this evaluation. Information on dates of death for deceased participants was obtained from the Swedish Death Registry.

Statistical analysis

Person-time of follow-up was calculated from the date of enrollment until the date of breast cancer diagnosis, death from any cause, or December 31, 2007, whichever occurred first. In analyses of ER/PR status, for women in Västmanland County, person-time of follow-up was counted from January 1998 because routine evaluation of ER and PR status was implemented in Västmanland County first in 1997. For analyses using data from the second questionnaire, follow-up of all women began on January 1, 1998. Dietary acrylamide intake was adjusted for total energy by using the residual method (15) and was categorized into quartiles.

To account for changes in diet during follow-up and to better represent long-term dietary intake, we used a cumulative average approach (16). Specifically, the incidence of breast cancer from baseline through 1997 was related to acrylamide intake reported on the baseline dietary questionnaire, and breast cancer incidence from 1998 through December 2007 was related to average acrylamide intake at baseline and in 1997; for women who did not complete

Table 1. Age-standardized Characteristics of the Swedish Mammography Cohort ($n = 61,433$) by Quartiles of Acrylamide Intake in 1987–1990[a]

Characteristic	Quartile of Acrylamide Intake, μg/day (Median Value)			
	<19.9 (16.9)	19.9–24.2 (22.3)	24.3–28.8 (26.4)	≥28.9 (32.5)
Age, years	56.4	54.5	52.9	50.9
Postsecondary education, %	11.9	13.0	12.9	13.2
Body mass index, kg/m^2	24.9	24.8	24.6	24.6
Age at menarche, years	13.3	13.2	13.2	13.2
Age at menopause, years	50.6	50.7	50.7	50.7
Age at first birth, years[b]	23.9	24.1	24.2	24.2
No. of children[b]	2.4	2.4	2.4	2.4
Oral contraceptive use, %	53.1	54.2	54.7	53.9
Postmenopausal hormone use, %	41.9	44.4	44.6	46.8
Family history of breast cancer, %	6.9	7.2	7.2	7.6
Dietary intake				
Total energy, kcal/day	1,616	1,609	1,582	1,535
Alcohol, g/day	2.4	2.6	2.6	2.5
Coffee, cups/day	1.7	2.4	2.6	2.9
Cereal fiber, g/day	18.0	17.8	17.7	18.0

[a] All values are means if not otherwise indicated.
[b] Parous women only.

the second questionnaire, only those data from the baseline questionnaire were used for the entire follow-up. We also related dietary intake in 1997 to breast cancer incidence from 1998 through December 2007.

We used Cox proportional hazards regression models (17) to estimate incidence rate ratios and 95% confidence intervals for the relation between acrylamide intake and risk of breast cancer. To control as finely as possible for age and calendar time, and possible 2-way interactions between these 2 time scales, we stratified the models by age in months at the start of follow-up and the year of enrollment. In multivariate models, we further adjusted for education (primary school, high school, university) and potential risk factors for breast cancer, including body mass index ($<$18.5, 18.5–24.9, 25–29.9, $\geq$30 kg/m^2), height (in centimeters), parity (nulliparous, 1–2, $\geq$3), age at first birth (nulliparous, $<$26, 26–30, $\geq$31 years), age at menarche ($\leq$12, 13, $\geq$14 years), age at menopause ($<$51, $\geq$51 years), use of oral contraceptives (ever/never), use of postmenopausal hormones (ever/never), family history of breast cancer (yes/no), history of benign breast disease, and intakes of alcohol (nondrinkers, $<$3.4, 3.4–9.9, $\geq$10.0 g/day), coffee ($\leq$1, 2, 3, $\geq$4 cups/day), cereal fiber (in quartiles), and total energy (kcal/day). In analyses using exposure information from the second questionnaire, we further controlled for smoking status (never, past, current) and pack-years of smoking ($<$20, 20–39, $\geq$40 pack-years); information on smoking was not available at baseline. We tested the proportional hazards assumption by using the likelihood ratio test and found no departure from the assumption.

Because cigarette smoke is an important source of acrylamide (5), we conducted analyses stratified by smoking status (never/ever) by using data from the second questionnaire. To test for trend, we assigned the median value to each quartile of acrylamide intake and treated this value as a continuous variable in the Cox model. All statistical analyses were conducted with SAS version 9.1 software (SAS Institute, Inc., Cary, North Carolina). In this paper, all P values are based on 2-sided tests.

RESULTS

In this cohort of Swedish women, the mean daily intake of acrylamide at baseline was 24.6 μg (standard deviation, 7.6), which corresponds to 0.38 μg (standard deviation, 0.17) of acrylamide per kilogram of body weight per day. Major food sources of acrylamide were coffee (29%), whole-grain bread (13%), crisp bread (8%), breakfast cereals/muesli (7%), cookies/buns (6%), and fried potato (5%). The baseline distributions of risk factors for breast cancer by quartiles of dietary acrylamide intake are presented in Table 1. Compared with women with a low acrylamide intake, those with higher intakes were somewhat younger and consumed more coffee. Other characteristics did not vary appreciably across quartiles of acrylamide intake.

During 1,071,164 person-years of follow-up (mean, 17.4 years) of 61,433 women, 2,952 incident cases of invasive breast cancer were diagnosed. Information on ER and PR status was available for 2,062 cases (information on ER/PR status was available for women in Västmanland County first in 1997). Among them, 1,286 cases (62.4%) were ER+PR+, 417 (20.2%) were ER+PR–, 266 (12.9%) were ER–PR–, and 93 (4.5%) were ER–PR+. The association between dietary acrylamide intake and incidence of breast

Table 2. Rate Ratios and 95% Confidence Intervals of Breast Cancer by Quartiles of Long-term Acrylamide Intake (in 1987–1990 and 1997) Among 61,433 Women in the Swedish Mammography Cohort, 1987–2007

	Quartile of Acrylamide Intake, μg/day				P_{trend}
	<19.9	19.9–24.2	24.3–28.8	≥28.9	
All invasive tumors					
No. of cases	766	784	730	672	
No. of person-years	260,898	267,482	271,029	271,755	
Age-adjusted RR (95% CI)	1.00 (referent)	1.01 (0.91, 1.11)	0.93 (0.83, 1.03)	0.89 (0.80, 1.00)	0.01
Multivariate RR (95% CI)[a]	1.00 (referent)	1.02 (0.92, 1.14)	0.95 (0.85, 1.06)	0.91 (0.80, 1.02)	0.06
ER+PR+ tumors					
No. of cases	312	352	351	271	
Age-adjusted RR (95% CI)	1.00 (referent)	1.03 (0.88, 1.20)	1.00 (0.85, 1.17)	0.84 (0.71, 0.99)	0.03
Multivariate RR (95% CI)[a]	1.00 (referent)	1.08 (0.91, 1.27)	1.07 (0.90, 1.26)	0.89 (0.74, 1.08)	0.22
ER+PR– tumors					
No. of cases	81	129	94	113	
Age-adjusted RR (95% CI)	1.00 (referent)	1.34 (1.01, 1.77)	0.94 (0.70, 1.27)	1.20 (0.90, 1.61)	0.65
Multivariate RR (95% CI)[a]	1.00 (referent)	1.29 (0.97, 1.74)	0.91 (0.66, 1.27)	1.17 (0.84, 1.64)	0.76
ER–PR– tumors					
No. of cases	65	70	69	62	
Age-adjusted RR (95% CI)	1.00 (referent)	1.02 (0.72, 1.43)	0.97 (0.69, 1.37)	0.89 (0.62, 1.28)	0.49
Multivariate RR (95% CI)[a]	1.00 (referent)	0.99 (0.69, 1.42)	0.96 (0.66, 1.41)	0.91 (0.61, 1.38)	0.64

Abbreviations: CI, confidence interval; ER, estrogen receptor; PR, progesterone receptor; RR, rate ratio.

[a] Multivariate rate ratios were adjusted for age, education, body mass index, height, parity, age at first birth, age at menarche, age at menopause, use of oral contraceptives, use of postmenopausal hormones, family history of breast cancer, history of benign breast disease, and intakes of alcohol, coffee, energy-adjusted cereal fiber, and total energy.

cancer, overall and by ER and PR status, is shown in Table 2. Acrylamide intake was weakly, inversely associated with risk of total and ER+PR+ breast cancer in the age-adjusted model. However, the associations were attenuated and not statistically significant after further adjustment for dietary and nondietary risk factors for breast cancer. The results remained essentially unchanged after additional adjustment for intakes of carbohydrate, saturated fat, folate, and calcium (rate ratio of total breast cancer for the highest vs. lowest quartile = 0.91, 95% confidence interval: 0.80, 1.03). Excluding cases diagnosed during the first 2 years of follow-up did not alter the results materially (rate ratio of total breast cancer for the highest vs. lowest quartile = 0.92, 95% confidence interval: 0.80, 1.06).

We examined whether any of the major food sources of acrylamide were associated with breast cancer risk but found no significant relation. For total breast cancer, no association was observed for coffee (P_{trend} = 0.32), whole-grain bread (P_{trend} = 0.98), crisp bread (P_{trend} = 0.85), breakfast cereals/muesli (P_{trend} = 0.67), cookies/buns (P_{trend} = 0.09), fried potato (P_{trend} = 0.94), French fries (P_{trend} = 0.61), or potato crisps (P_{trend} = 0.39).

We used information from the second questionnaire to examine whether the association between acrylamide intake and breast cancer risk was modified by smoking status. During a mean follow-up of 9.4 years (346,163 person-years), 1,008 incident cases of invasive breast cancer were diagnosed among 36,664 women. Information on ER and PR status was available for 925 cases (91.8% of the total cases). Among them, 562 cases (60.8%) were ER+PR+, 244 (26.4%) were ER+PR–, 110 (11.9%) were ER–PR–, and 9 (1.0%) were ER–PR +. We observed no overall association between acrylamide intake and breast cancer after adjustment for breast cancer risk factors (Table 3). The association did not vary materially by smoking status.

DISCUSSION

In this prospective study of Swedish women, we observed no significant association between long-term dietary acrylamide intake and the incidence of breast cancer, overall or by hormone receptor status, after adjustment for risk factors for breast cancer. Furthermore, we found no significant association between acrylamide intake and breast cancer for never smokers or ever smokers.

Our findings are consistent with results from previous epidemiologic studies in which no significant association between acrylamide intake and total breast cancer risk was observed in a cohort of premenopausal Swedish women (9), in a cohort of Dutch postmenopausal women (10), or in an Italian and Swiss hospital-based case-control study (8). Mean acrylamide intake in those studies ranged from 21 μg/day in the Netherlands Cohort Study (10) to 23–29 μg/day in the case-control study (8), which is similar to the intake in our population (24.6 μg/day). In a nested case-control study within a prospective cohort of Danish postmenopausal women (11), levels of acrylamide-hemoglobin adducts (biomarkers of internal acrylamide exposure during the

Table 3. Rate Ratios and 95% Confidence Intervals of Breast Cancer by Quartiles of Acrylamide Intake (in 1997) Among 36,664 Women in the Swedish Mammography Cohort, 1998–2007

Tumor and Quartile of Acrylamide Intake	Overall					Never Smokers		Ever Smokers	
	No. of Cases[a]	Age-adjusted RR	95% CI	Multivariate RR[b]	95% CI	Multivariate RR[b]	95% CI	Multivariate RR[b]	95% CI
All invasive tumors									
Q1	263	1.00 (referent)		1.00 (referent)		1.00 (referent)		1.00 (referent)	
Q2	283	1.07	0.90, 1.26	1.12	0.93, 1.35	1.18	0.92, 1.51	1.03	0.78, 1.36
Q3	243	0.91	0.77, 1.09	0.98	0.80, 1.21	1.03	0.78, 1.37	0.92	0.67, 1.25
Q4	219	0.82	0.68, 0.98	0.90	0.71, 1.14	0.91	0.65, 1.27	0.88	0.62, 1.24
P_{trend}			0.01		0.22		0.43		0.37
ER+PR+ tumors									
Q1	152	1.00 (referent)		1.00 (referent)		1.00 (referent)		1.00 (referent)	
Q2	154	1.01	0.80, 1.26	1.02	0.80, 1.30	1.17	0.84, 1.64	0.85	0.59, 1.23
Q3	139	0.91	0.72, 1.14	0.93	0.71, 1.23	1.07	0.73, 1.56	0.79	0.52, 1.19
Q4	117	0.76	0.60, 0.97	0.81	0.59, 1.12	0.78	0.49, 1.24	0.82	0.52, 1.29
P_{trend}			0.02		0.16		0.25		0.42
ER+PR– tumors									
Q1	59	1.00 (referent)		1.00 (referent)		1.00 (referent)		1.00 (referent)	
Q2	66	1.10	0.78, 1.57	1.12	0.76, 1.65	1.18	0.68, 2.05	1.02	0.59, 1.74
Q3	64	1.06	0.75, 1.52	1.08	0.70, 1.65	1.19	0.65, 2.20	0.96	0.53, 1.75
Q4	55	0.90	0.62, 1.30	0.87	0.53, 1.42	1.12	0.56, 2.27	0.67	0.33, 1.36
P_{trend}			0.51		0.49		0.79		0.24
ER–PR– tumors									
Q1	28	1.00 (referent)		1.00 (referent)		1.00 (referent)		1.00 (referent)	
Q2	38	1.35	0.83, 2.20	1.48	0.87, 2.53	1.16	0.58, 2.32	1.94	0.79, 4.72
Q3	20	0.71	0.40, 1.26	0.82	0.42, 1.59	0.67	0.28, 1.63	1.03	0.35, 2.98
Q4	24	0.85	0.49, 1.47	0.98	0.48, 2.02	1.12	0.45, 2.76	0.86	0.26, 2.87
P_{trend}			0.23		0.62		0.99		0.45

Abbreviations: CI, confidence interval; ER, estrogen receptor; PR, progesterone receptor; Q, quartile; RR, rate ratio.

[a] Person-years of follow-up across quartiles of acrylamide intake were 85,699 (Q1), 86,442 (Q2), 86,661 (Q3), and 87,361 (Q4).

[b] Multivariate rate ratios were adjusted for age, education, body mass index, height, parity, age at first birth, age at menarche, age at menopause, use of oral contraceptives, use of postmenopausal hormones, family history of breast cancer, history of benign breast disease, smoking status, pack-years of smoking, and intakes of alcohol, coffee, energy-adjusted cereal fiber, and total energy. Smoking was not adjusted for in the subgroup analyses stratified by smoking status.

preceding 120 days (4)) were not associated with overall breast cancer risk. However, there was a statistically significant positive association between acrylamide-hemoglobin levels and ER+ breast cancer, with a 2.7-fold increase in risk for a 10-fold increment in acrylamide-hemoglobin levels (11).

The lack of positive association between dietary acrylamide intake and breast cancer risk in epidemiologic studies may be due to the low levels of exposure to acrylamide from foods. In our study population, mean acrylamide intake was about 0.4 μg per kilogram of body weight per day, which is much lower than the doses that cause cancer in rodents. In studies in animals, increased cancer incidence has been observed in the mammary gland of female rats receiving 1.0 mg or 2.0 mg of acrylamide per kilogram of body weight per day but not in rats given lower acrylamide dosages (6, 7).

This study has several strengths, including its prospective and population-based design, a large sample size, detailed information on diet, and information about hormone receptor status of the breast tumor. The prospective design precluded recall bias, and virtually complete follow-up of the study population through linkage with various

population-based registers (14) minimizes the concern that our findings were affected by differential loss to follow-up. Another strength is that exposure information was updated during follow-up, which reduces measurement error and provides a better estimate of long-term diet. Although the number of food items differed between the baseline (67 items) and second (96 items) FFQs, foods that are major sources of acrylamide in this study population were the same in both FFQs.

Several limitations were also present in this study. First, dietary intake was assessed with a self-administered FFQ, which will inevitably lead to some error in the measurement of dietary acrylamide intake. Moreover, large variations in acrylamide levels have been found between single foodstuffs (different brands) within food categories as well as in different food categories (13). However, estimated acrylamide intake from foods has been found to significantly correlate with hemoglobin acrylamide adduct levels in Swedish women and men (18). Another limitation is the relatively limited range of acrylamide intake in this study population, which reduces the possibility of detecting an association if one exists. Finally, although we controlled for breast cancer risk factors, we cannot rule out the possibility of residual confounding from these variables or from other dietary factors correlated with acrylamide intake.

In conclusion, findings from this prospective cohort of Swedish women do not support the hypothesis that dietary acrylamide intake is positively associated with risk of breast cancer, at least not within the ranges of acrylamide consumed by the population studied.

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