Null Results in Brief

Long-Term Dietary Acrylamide Intake and Risk of Epithelial Ovarian Cancer in a Prospective Cohort of Swedish Women

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Abstract

Background: **Acrylamide, a probable human carcinogen, can be formed in carbohydrate-rich foods cooked at high temperatures. Whether dietary acrylamide intake is associated with the risk of cancer in humans is uncertain. We aimed to assess the relation between dietary acrylamide intake and the incidence of epithelial ovarian cancer.**
Methods: **The Swedish Mammography Cohort is a population-based prospective study of 61,057 Swedish women. Diet was assessed with a food-frequency questionnaire at baseline in 1987-1990 and again in 1997.**
Results: **During a mean follow-up of 17.5 years, we ascertained 368 incident cases of ovarian cancer. We observed no association between acrylamide intake and the risk of ovarian cancer. Compared with the lowest quartile of acrylamide intake (mean intake, 16.9 μg/day), the multivariable rate ratios for the highest quartile (mean intake, 32.5 μg/day) were 0.86 (95% confidence interval, 0.63-1.16) for total ovarian cancer and 1.05 (95% confidence interval, 0.68-1.63) for serous ovarian cancer (n = 182 cases).**
Conclusions: **The results from this prospective study provide no evidence that dietary acrylamide in amounts typically consumed by Swedish women is associated with the risk of ovarian cancer.** (Cancer Epidemiol Biomarkers Prev 2009;18(3):994–7)

Introduction

Acrylamide is a small hydrophilic molecule that is classified by the IARC as a ''probable human carcinogen'' based on experiments in rodents (1). In 2002, Swedish researchers reported the presence of acrylamide in several heat-treated carbohydrate-rich foods, such as potato crisps, French fries, crisp bread, and cookies (2). Although studies in animals support a dose-response relationship between acrylamide given in drinking water and cancer in multiple organs (3), the potential health risks of dietary acrylamide in humans are uncertain. To date, only one cohort study (4) and one case-control study (5) have examined the association between acrylamide intake and ovarian cancer risk, with inconsistent results.

Given the limited and inconsistent epidemiologic data on the relation between acrylamide intake and ovarian cancer risk, we analyzed data from a population-based prospective cohort of Swedish women to assess whether long-term dietary acrylamide intake is associated with the incidence of epithelial ovarian cancer. We have previously reported no associations of acrylamide intake with the risk of breast and endometrial cancer in this cohort (6, 7).

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Materials and Methods

Study cohort. The Swedish Mammography Cohort was established in 1987-1990 when 66,651 women (74% of the source population) born from 1914 to 1948 and residing in central Sweden completed a questionnaire on diet, reproductive factors, and other factors (8). After excluding women with an erroneous or missing National Registration Number, those with implausible values for total energy intake (i.e., 3 SDs from the $\log_e$-transformed mean energy intake), those with a previous cancer diagnosis (except nonmelanoma skin cancer), and those who had undergone a bilateral oophorectomy, 61,057 women remained. In the late autumn of 1997, all participants who were still alive and living in the study area (n = 56,030 women) received a new questionnaire that included about 350 items concerning diet and other lifestyle factors (including smoking); 39,227 women (70%) completed the questionnaire. The study was approved by the ethics committees at the Uppsala University Hospital and the Karolinska Institutet in Sweden.

Dietary Assessment. A food-frequency questionnaire (FFQ) with 67 and 96 foods and beverages was used to assess diet at baseline and in 1997, respectively. Women were asked to report how often, on average, they had consumed each food item during the past 6 mo (baseline FFQ) or the previous year (second FFQ). Information on the acrylamide content in Swedish foods was obtained from the Swedish National Food Administration (9) and Svensson et al. (10). The estimated daily dietary intake of acrylamide was calculated based on the following food items (acrylamide concentration used in the calculation):

Table 1. Age-standardized characteristics of the Swedish Mammography Cohort (*n* = 61,057) by quartiles of energy-adjusted acrylamide intake in 1987-1990

Characteristics	Quartile of acrylamide intake, μg/d			
	<19.9 (16.9)*	19.9-24.2 (22.3)	24.3-28.8 (26.4)	≥28.9 (32.5)
Age (y)	56.4	54.5	52.9	50.9
Postsecondary education (%)	11.9	13.0	12.9	13.2
Nulliparous (%)	11.9	10.6	10.2	10.7
Number of children †	2.4	2.4	2.4	2.4
Age at first birth (y) †	23.9	24.1	24.2	24.2
Age at menarche (y)	13.3	13.2	13.2	13.2
Age at menopause (y)	50.6	50.7	50.7	50.7
Oral contraceptive use (%)	53.1	54.2	54.7	53.9
Postmenopausal hormone use (%)	41.9	44.4	44.6	46.8
Body mass index (kg/m^2)	24.9	24.8	24.6	24.6
Total energy (kcal/d)	1616	1609	1582	1535
Total fat (g/d)	55.3	54.6	54.3	53.7
Saturated fat (g/d)	24.7	24.2	23.9	23.4
Carbohydrate (g/d)	227	228	229	231
Fiber (g/d)	24.2	24.2	24.2	24.5

NOTE: All values are means if not otherwise indicated.
*Median values in parenthesis.
†Parous women only.

coffee (15 μg/kg), crisp bread (15-214 μg/kg), white bread (15-45 μg/kg), whole grain bread (45-162 μg/kg), porridge (15 μg/kg), breakfast cereals (31-1031 μg/kg), rice (15 μg/kg), pasta (15 μg/kg), pizza (15 μg/kg), pancakes (15 μg/kg), rusk (15 μg/kg), cookies/buns (15-98 μg/kg), wafers/crackers (15-642 μg/kg), cakes (0-98 μg/kg), boiled potato (15 μg/kg), fried potato (62-338 μg/kg), French fries (450 μg/kg), potato crisps/popcorn (150-980 μg/kg), meatballs and minced meat products containing breadcrumbs (64 μg/kg), fishfingers containing breadcrumbs (30 μg/kg), and scrambled eggs (15 μg/kg). Acrylamide intake was calculated by multiplying the intake of each food item by the mean concentration of acrylamide in the food item, and summed across all of the food items. Intakes of nutrients and acrylamide were energy-adjusted by using the residual method (11).

The validity of the baseline dietary questionnaire was assessed previously by comparing responses from the FFQ with responses from four 1-wk dietary records among 129 women randomly chosen from the study cohort.[1] The Pearson correlation coefficients between the FFQ and the diet records for major food sources of acrylamide were 0.6 for coffee, 0.5 for whole grain bread, and 0.6 for breakfast cereals.

Case Ascertainment and Follow-up. Incident cases of invasive epithelial ovarian cancer were identified by linkage of the cohort with the National Swedish Cancer Registry and the Regional Cancer Registry that recorded all cancer diagnoses in the study area. Follow-up for cancers is estimated to be almost 100% complete (12). Borderline invasive ovarian tumors were not included in the present analyses. 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 to the date of diagnosis of ovarian cancer, the date of a bilateral oophorectomy or a hysterectomy with unknown ovaries removed, the date of death, or December 31, 2007, whichever occurred first. Quartiles of acrylamide intake were derived based on the distribution in the cohort. To account for changes in diet during follow-up and to better represent long-term dietary intake, we used a cumulative average approach (13). Specifically, the incidence of ovarian cancer from baseline through 1997 was related to acrylamide intake at baseline, and ovarian cancer incidence from 1998 through December 2007 was related to the average acrylamide intake at baseline and in 1997. In sensitivity analyses, we also related baseline acrylamide intake to ovarian cancer incidence over the entire follow-up and acrylamide intake in 1997 to ovarian cancer incidence from 1998 through December 2007.

We used Cox proportional hazards models (14) to estimate rate ratios with 95% confidence intervals for the relation between acrylamide intake and ovarian cancer risk. To control as finely as possible for age and calendar time, and possible two-way interactions between these two time scales, we stratified the models by age in months at start of follow-up and the year of enrollment. In multivariable models, we additionally adjusted for education, body mass index, parity, age at first childbirth, age at menarche, age at menopause, use of oral contraceptives, use of postmenopausal hormones, and total energy intake (kcal/day). In a second multivariable model we further controlled for intakes of dietary fat, carbohydrate, and fiber. In analyses using data from the second questionnaire, we also adjusted for smoking status (never, past, and current smoker); information on smoking was not available at baseline.

Because cigarette smoke is an important source of acrylamide (15), we conducted analyses stratified by smoking status. We also conducted analyses stratified by alcohol intake and use of oral contraceptives and postmenopausal hormones. To test for trend, we assigned the median value to each quartile of acrylamide intake and modeled this value as a continuous variable. All statistical analyses were conducted by using SAS version 9.1 (SAS Institute Inc.). All *P* values were two-sided.

[1] Wolk A, unpublished data.

Table 2. Rate ratios (95% confidence intervals) of invasive epithelial ovarian cancer by quartiles of long-term acrylamide intake among 61,057 women in the Swedish Mammography Cohort, 1987–2007

	Quartile of acrylamide intake, μg/d				
	<19.9	19.9-24.2	24.3-28.8	≥28.9	P_{trend}
Total ovarian cancer					
Cases, *n*	104	92	94	78	
Person-years	261,196	267,092	270,165	270,815	
Age-adjusted model	1.00	0.87 (0.65-1.17)	0.91 (0.68-1.20)	0.82 (0.61-1.11)	0.25
Multivariable model 1*	1.00	0.90 (0.68-1.20)	0.96 (0.72-1.28)	0.84 (0.62-1.14)	0.33
Multivariable model 2†	1.00	0.91 (0.68-1.21)	0.97 (0.73-1.29)	0.86 (0.63-1.16)	0.39
Serous ovarian cancer					
Cases, *n*	47	50	45	40	
Age-adjusted model	1.00	1.05 (0.70-1.57)	0.96 (0.63-1.46)	0.96 (0.62-1.49)	0.78
Multivariable model 1*	1.00	1.10 (0.73-1.66)	1.04 (0.68-1.59)	1.01 (0.65-1.56)	0.97
Multivariable model 2†	1.00	1.13 (0.75-1.70)	1.08 (0.70-1.65)	1.05 (0.68-1.63)	0.88

*Adjusted for age, education (primary school, high school, university), body mass index (<18.5, 18.5-24.9, 25-29.9, ≥30 kg/m^2), parity (nulliparous, 1-2, ≥3), age at first childbirth (nulliparous, <26, 26-30, ≥31 y), age at menarche (≤12, 13, ≥14 y), age at menopause (<51, ≥51 y), use of oral contraceptives (ever/never), use of postmenopausal hormones (ever/never), and total energy intake (kcal/d).
†Adjusted for the same variables as in model 1 and additionally for quartiles of intakes of dietary fat, carbohydrate, and fiber.

Results

The mean (± SD) daily intake of acrylamide in the study population at baseline was 24.6 ± 7.6 μg. Major contributors to the total acrylamide intake in 1997 were coffee (29%), whole grain bread (13%), crisp bread (8%), breakfast cereals (7.5%), wafers/crackers (7%), cookies/buns (6%), fried potato (5%), and boiled potato (4.5%). Minor sources were white bread (4%), meatballs and minced meat products containing breadcrumbs (3.5%), potato crisps/popcorn (2.5%), French fries (2%), and oatmeal porridge (2.5%). Compared with women with a low acrylamide intake, those with a high intake were, on average, younger and had a lower fat intake (Table 1).

During a mean follow-up of 17.5 years (1,069,268 person-years) of 61,057 women, we identified 368 incident cases of invasive epithelial ovarian cancer, including 182 serous, 60 endometroid, 25 mucinous, 9 clear cell, and 92 other or unknown histologic subtypes. The mean age at diagnosis of ovarian cancer was 65.8 years (range, 42-92 years); 48 cases were <55 years of age at diagnosis. We found no significant association between acrylamide intake and the risk of total or serous ovarian cancer after adjustment for age or in multivariable analyses adjusting for risk factors for ovarian cancer and dietary factors (Table 2). Excluding cases diagnosed during the first two years of follow-up did not change the results materially. The association between acrylamide intake and the risk of ovarian cancer was similar when we used data from the baseline FFQ only, without updating of exposures; the multivariable rate ratio of ovarian cancer comparing the highest with the lowest quartile of baseline acrylamide intake was 0.85 (95% confidence interval, 0.63-1.14). We observed no association between acrylamide intake and ovarian cancer risk across strata of alcohol intake, oral contraceptive use, or postmenopausal hormone use (data not shown). None of the major food sources of acrylamide was associated with ovarian cancer risk.

We examined more extreme intakes of acrylamide by categorizing participants into deciles of their acrylamide intake. Compared with women in the lowest decile of

Table 3. Rate ratios (95% confidence intervals) of invasive epithelial ovarian cancer by quartiles of acrylamide intake in 1997 among 36,442 women in the Swedish Mammography Cohort, 1998–2007

	Quartile of acrylamide intake, μg/d				
	<20.5	20.5-24.6	24.7-29.1	≥29.2	P_{trend}
All women					
Cases, *n*	32	34	32	36	
Person-years	86,192	86,854	87,002	87,528	
Age-adjusted model	1.00	1.06 (0.65-1.71)	0.99 (0.61-1.62)	1.11 (0.69-1.79)	0.71
Multivariable model 1*	1.00	1.10 (0.68-1.78)	1.04 (0.63-1.69)	1.18 (0.73-1.90)	0.56
Multivariable model 2†	1.00	1.09 (0.67-1.77)	1.03 (0.63-1.69)	1.17 (0.72-1.89)	0.56
Never smokers					
Cases, *n*	18	23	19	15	
Multivariable model 1*	1.00	1.32 (0.71-2.45)	1.10 (0.57-2.09)	0.97 (0.49-1.93)	0.80
Ever smokers					
Cases, *n*	14	11	13	21	
Multivariable model 1*	1.00	0.83 (0.38-1.84)	0.90 (0.42-1.96)	1.42 (0.71-2.82)	0.24

*Adjusted for age, education (primary school, high school, university), body mass index (<18.5, 18.5-24.9, 25-29.9, ≥30 kg/m^2), parity (nulliparous, 1-2, ≥3), age at first childbirth (nulliparous, <26, 26-30, ≥31 y), age at menarche (≤12, 13, ≥14 y), age at menopause (<51, ≥51 y), use of oral contraceptives (ever/never), use of postmenopausal hormones (ever/never), and total energy intake (kcal/d).
†Adjusted for the same variables as in model 1 and additionally for smoking status (never, past, and current smoker).

acrylamide intake (mean, 12.8 μg/day), the multivariable rate ratio of ovarian cancer was 1.21 (95% confidence interval, 0.74-1.97) for women in the highest decile of acrylamide intake (mean, 38.4 μg/day).

To examine whether the relation between acrylamide intake and ovarian cancer risk was modified by smoking status we used exposure data from the second questionnaire. Among 36,442 women followed up for a mean of 9.5 years, from January 1998 through December 2007, 134 incident invasive epithelial ovarian cancer cases were diagnosed. As in the analyses using updated or baseline acrylamide intake, there was no association between acrylamide intake in 1997 and ovarian cancer risk (Table 3). The relation between acrylamide intake and ovarian cancer did not vary by smoking status.

Discussion

In this prospective cohort of Swedish women, we observed no association between long-term dietary acrylamide intake and the incidence of epithelial ovarian cancer. The lack of association persisted across strata of smoking status, alcohol intake, and use of oral contraceptives and postmenopausal hormones.

Our findings are consistent with those of an Italian-Swiss case-control study in which no association between acrylamide intake and ovarian cancer risk was observed (5). However, in the Netherlands Cohort Study of 62,573 women, with 11.3 years of follow-up and 300 cases of ovarian cancer, women in the highest quintile of acrylamide intake (mean, 40.2 μg/day) had a 78% increased risk of ovarian cancer compared with those in the lowest quintile of intake (mean, 8.9 μg/day; ref. 4). The acrylamide exposure range in the Netherlands Cohort Study was wider than in our Swedish cohort, thus increasing the possibility of detecting an association if one exists. When we examined more extreme intakes of acrylamide by comparing the highest with the lowest decile of acrylamide intake, we still did not observe a statistically significant association between acrylamide intake and ovarian cancer risk.

The strengths of this study include its prospective and population-based design, a large sample size, and the completeness of follow-up through linkage to various population-based Swedish registers. Furthermore, exposure information was updated during follow-up, which would reduce measurement error and provide a better estimate of long-term dietary intake. Although the number of food items differed between the baseline FFQ (67 items) and the second FFQ (96 items), the major food sources of acrylamide in this study population were the same in both FFQs.

We cannot exclude measurement error due to self-reported diet as a contributor to the lack of observed association between acrylamide intake and the risk of ovarian cancer. In addition, large variations in acrylamide levels have been found between single foodstuffs (different brands) within food categories as well as in different food categories (10). The estimated dietary acrylamide intake was found to significantly correlate with hemoglobin acrylamide adduct levels in Swedish smoking women and men, and in nonsmoking men, but not in nonsmoking women (16). In a study of 50 Norwegian women and men, the intake of crisps/snacks and crisp bread, but not total dietary acrylamide intake, was significantly positively correlated with hemoglobin acrylamide adduct levels (17).

In conclusion, the findings from this cohort study provide no evidence that dietary acrylamide in amounts typically consumed by Swedish women is associated with the risk of ovarian cancer. Prospective studies of the association between biomarkers of total acrylamide exposure, such as the concentration of hemoglobin adducts of acrylamide, and ovarian cancer incidence are warranted.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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