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Short Communication

Dietary acrylamide intake and risk of colorectal cancer in a prospective cohort of men

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ABSTRACT

Acrylamide is a probable human carcinogen that causes cancer at multiple sites in animal models. However, whether dietary acrylamide intake increases the risk of colorectal cancer in humans is unclear. We examined the association between dietary acrylamide intake and colorectal cancer incidence in the Cohort of Swedish Men, a population-based prospective cohort of 45,306 men who completed a food-frequency questionnaire at enrolment in 1997. During a mean follow-up of 9.3 years, we ascertained 676 incident colorectal cancer cases. Compared with the lowest quartile of acrylamide intake (<29.6 μg/d), the multivariate rate ratios for the highest quartile (⩾41.7 μg/d) were 0.95 (95% confidence interval (CI) 0.74–1.20) for colorectal cancer, 0.97 (95% CI 0.71–1.31) for colon cancer and 0.91 (95% CI 0.62–1.34) for rectal cancer. In conclusion, this study provides no evidence that dietary acrylamide in amounts typically consumed by Swedish men is associated with risk of colorectal cancer.

1. Introduction

Acrylamide is known as a carcinogen in experimental animal studies, and is classified by the International Agency for Research on Cancer (IARC) as a probable human carcinogen.[1] In 2002, Swedish researchers reported the presence of detectable levels of acrylamide in commonly consumed carbohydrate-rich foods cooked at high temperatures (>120 °C).[2] Acrylamide is formed in foods through a series of reactions, known as Maillard reactions, in which an amino acid, mainly asparagine, reacts with a reducing sugar such as glucose or fructose.[3,4] High levels of acrylamide have been found in fried and baked potato products and in cereal products such as crisp bread, breakfast cereals and cookies.[5]

Although studies in animals show that acrylamide exposure causes cancer in multiple organs,[6] it is unclear whether dietary acrylamide from foods is associated with cancer risk in humans. To date, only two case-control studies[7,8] and one cohort study[9] have examined the association between acrylamide intake and colorectal cancer risk. To examine further whether a high acrylamide intake is associated with the risk of colorectal cancer, we analysed data from a population-based prospective cohort of Swedish men.

2. Materials and methods

2.1. Study population

The Cohort of Swedish Men was initiated in the late autumn of 1997, when all men born between 1918 and 1952 and residing in central Sweden received a questionnaire including about 350 items concerning diet and other lifestyle factors.

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Of the 100,303 eligible men, 48,850 (49%) returned a completed questionnaire.

For the present analyses, we excluded men with an erroneous or missing national registration number, men with implausible values for total energy intake (i.e. 3 SDs from the $\log_e$-transformed mean energy intake) and men with a previous cancer diagnosis (except non-melanoma skin cancer) at baseline. After these exclusions, 45,306 men remained for the analyses. The study was approved by the ethics committee at the Karolinska Institutet (Stockholm, Sweden).

2.2. Assessment of diet

Diet was assessed at baseline with a food-frequency questionnaire, in which participants reported their average frequency of consumption of 96 foods and beverages over the past year. The questionnaire had eight mutually exclusive predefined categories for frequency of consumption, ranging from 'never/seldom' to '3 or times per day'. Information on the acrylamide content in Swedish foods was obtained from the Swedish National Food Administration[10] and Svensson et al.[5] Concentrations of acrylamide were available for foods such as coffee, cereal grain products, potato products, snacks, cookies, biscuits, and minced meat products such as meat balls and hamburgers. Acrylamide intake was calculated by multiplying the frequency of consumption of each food item by its acrylamide content per age-specific serving. Intakes of nutrients and acrylamide were adjusted for total energy intake using the residual method.[11]

2.3. Case ascertainment and follow-up

Incident cases of colorectal cancer were identified by computerised linkage of the study cohort to the national and regional Swedish Cancer registers. These registries have been estimated to be nearly 100% complete.[12] Proximal colon cancers were defined as tumours in the caecum, appendix, ascending colon and hepatic flexure, transverse colon and splenic flexure (C18.0–18.5; International Statistical Classification of Diseases, 10th Revision); distal colon cancers were defined as tumours in the descending and sigmoid colon (C18.6–C18.7). Analyses of total colon cancer included proximal and distal colon cancers as well as tumours that were overlapping or unspecified (C18.8 and C18.9). Cancer of the rectum included tumours occurring at the rectosigmoid junction (C19) and rectum (C20). Anal canal tumours were excluded. Information on dates of death for deceased men was obtained from the Swedish Death Registry.

2.4. Statistical analysis

Participants contributed person-time from baseline until the date of diagnosis of colon or rectal cancer, death from any cause, or 31st December 2007, whichever occurred first. We categorised participants into quartiles of acrylamide intake based on the distribution in the entire cohort. We used Cox proportional hazards models[13] to estimate rate ratios (RRs) with their 95% confidence intervals (CIs) for the association between acrylamide intake and colorectal cancer. All models were adjusted for age. In multivariate analysis, we further controlled for education (less than high school, high school graduate or more than high school), family history of colorectal cancer (no or yes), body mass index (in kg/m^2; <23.0, 23.0–24.9, 25.0–29.9, or $\geqslant$30.0), exercise (<1 h/week, 1–2 h/week, or $\geqslant$3 h/week), history of diabetes (no or yes), cigarette smoking (never, past, or current), aspirin use (no or yes), total energy intake (in kcal/day; continuous), and quartiles of intakes of alcohol, calcium and dietary fiber. We tested the proportional hazard assumption using the likelihood ratio test and found no departure from the assumption.

Tests for trend were conducted by assigning the median value for acrylamide intake to each quartile and modelling this variable as a continuous variable. Because cigarette smoke is an important source of acrylamide exposure,[14] we conducted analyses stratified by smoking status (never, past and current smoker). All statistical analyses were conducted using SAS version 9.1 (SAS Institute Inc., Cary, NC). All *P*-values were two sided.

3. Results

The mean (±SD) daily intake of acrylamide in the study population was 36.1 ± 9.6 μg. The major food sources of acrylamide were coffee (23%), whole grain bread (17%), crisp bread (8%), white bread (7%), cookies/buns (7%), wafers/crackers/rusks (6%), breakfast cereals/muesli (6%) and fried potato (6%). Compared with men with a low acrylamide intake, those with a high intake were, on average, younger and less likely to have a postsecondary education and a family history of colorectal cancer (Table 1). Moreover, they were more likely to have diabetes and had lower intakes of alcohol and calcium but higher fiber intake.

A total of 676 incident cases of colorectal adenocarcinomas were ascertained during 421,000 person-years of follow-up (mean, 9.3 years). Among these, 410 were located in the colon (180 proximal colon, 153 distal colon and 77 unspecified), and 266 in the rectum. We observed no statistically significant association between acrylamide intake and the risk of colorectal, colon or rectal cancer after adjustment for age only or after further adjustment for colorectal cancer risk factors (Table 2). Acrylamide intake was not associated with risk of proximal or distal colon cancer. Excluding all cases diagnosed during the first two years of follow-up did not change the results materially.

The association between acrylamide intake and colorectal cancer risk did not vary by smoking status. The multivariate RRs of colorectal cancer comparing the highest with the lowest quartile of acrylamide intake were 0.97 (95% CI 0.64–1.50) in never smokers, 0.84 (95% CI, 0.57–1.25) in past smokers and 1.17 (95% CI 0.72–1.89) in current smokers.

4. Discussion

In this prospective cohort of Swedish men, we observed no association between dietary acrylamide intake and risk of colon or rectal cancer. The lack of association persisted in subgroups of never, past and current smokers.

Our findings are consistent with those from the Swedish Mammography Cohort[9] and an Italian and Swiss hospital-based case-control study,[7] where no relation between

Table 1 – Baseline characteristics according to quartiles of acrylamide intake in the Cohort of Swedish Men[a].

Characteristic	Acrylamide intake, μg/d			
	<29.6 (24.7)[b]	29.6–35.3 (32.6)	35.4–41.6 (38.4)	⩾41.7 (48.5)
Number of men	11,326	11,324	11,335	11,321
Age, mean (year)	63.3	61.5	59.3	57.0
Body-mass index, mean (kg/m^2)	26.0	25.7	25.7	25.8
Postsecondary education (%)	16.7	16.6	16.8	14.5
Family history of colorectal cancer (%)	7.8	7.0	7.4	6.3
History of diabetes (%)	5.7	5.6	5.7	8.3
Exercise ⩾2 h/week (%)	57.2	60.4	59.6	58.7
Current smokers (%)	25.5	23.6	23.2	27.0
Aspirin use (%)	36.2	36.5	36.2	36.8
Dietary intake, mean				
Alcohol (g/d)	11.1	10.2	9.6	8.4
Calcium (g/d)	1325	1245	1193	1129
Total fiber (g/d)	22.7	25.3	26.8	28.6
Fruits (servings/d)	1.5	1.5	1.5	1.4
Vegetables (servings/d)	2.5	2.6	2.6	2.4
Red meat as a main dish (servings/d)	0.5	0.5	0.5	0.5

a Standardised to the age distribution of the study population at baseline.
b Median value in parentheses.

Table 2 – Rate ratios and 95% confidence intervals of colorectal cancer by quartiles of acrylamide intake in the Cohort of Swedish Men, 1998–2007.

	Acrylamide intake, μg/d				P for trend
	<29.6	29.6–35.3	35.4–41.6	⩾41.7	
Colorectal cancer					
Cases, *n*	203	182	162	129	
Person-years	101,643	104,675	106,705	107,977	
Age-adjusted RR (95% CI)	1.00	0.98 (0.81–1.20)	1.00 (0.81–1.23)	0.95 (0.76–1.20)	0.71
Multivariate RR (95% CI)[a]	1.00	1.02 (0.83–1.25)	1.03 (0.83–1.28)	0.95 (0.74–1.20)	0.69
Colon cancer					
Cases, *n*	125	112	93	80	
Multivariate RR (95% CI)[a]	1.00	1.00 (0.77–1.30)	0.96 (0.72–1.27)	0.97 (0.71–1.31)	0.78
Proximal colon cancer					
Cases, *n*	55	48	47	30	
Multivariate RR (95% CI)[a]	1.00	0.94 (0.63–1.40)	1.10 (0.73–1.65)	0.84 (0.52–1.35)	0.63
Distal colon cancer					
Cases, *n*	47	42	28	36	
Multivariate RR (95% CI)[a]	1.00	1.05 (0.68–1.60)	0.77 (0.47–1.25)	1.13 (0.70–1.81)	0.84
Rectal cancer					
Cases, *n*	78	70	69	49	
Multivariate RR (95% CI)[a]	1.00	1.05 (0.76–1.46)	1.15 (0.82–1.61)	0.91 (0.62–1.34)	0.78

a Multivariate models were adjusted for age (in mo), education (less than high school, high school graduate or more than high school), family history of colorectal cancer (no or yes), body mass index (in kg/m^2; <23.0, 23.0–24.9, 25.0–29.9, or ⩾30.0), exercise (<1 h/week, 1–2 h/week, or ⩾3 h/week), history of diabetes (no or yes), cigarette smoking (never, past or current), aspirin use (no or yes), total energy intake (in kcal/day; continuous) and quartiles of intakes of alcohol, calcium and dietary fiber.

acrylamide intake and colorectal cancer risk was observed. However, in a population-based Swedish case-control study, acrylamide intake was unexpectedly inversely associated with the risk of colorectal cancer.[8] The observed inverse association in this study[8] may be due to residual confounding from other factors in acrylamide-rich foods.

The classification of acrylamide as a probable human carcinogen by IARC in 1994 was based primarily on evidence for carcinogenicity in experimental animals and mechanistic considerations.[1] Studies in rodents, which were given acrylamide in drinking water, show an increased incidence of cancer of the lung, mammary gland, uterus, thyroid, oral cavity and central nervous system.[15–17] In the experimental animal studies, the dose of exposure was 1000–100,000 times higher than what humans are exposed to through diet. Thus, both the dose and the source of acrylamide exposure differ between animal and epidemiologic studies, and may explain the null finding in case-control and cohort studies.

This study has several strengths including a large sample size, the population-based and prospective design, and the completeness of case ascertainment through linkage to various Swedish population-based registries. The prospective design precluded recall bias and the virtually complete follow-up of the study cohort[12] minimised the concern that our results have been affected by differential loss to follow-up. We cannot exclude measurement error, and resulting misclassification, due to self-reported diet as a contributor to the lack of observed association of acrylamide intake with colorectal cancer risk. Furthermore, large variations in acrylamide levels have been found between brands of a given food and in different food categories.[5] However, estimated acrylamide intake has been found to significantly correlate with haemoglobin acrylamide adduct levels in Swedish men and women.[18] Although we cannot rule out the possibility that we may have overlooked a weak association between acrylamide intake and colorectal cancer risk, acrylamide in foods is unlikely to be a strong risk factor.

In conclusion, we found no evidence that dietary exposure to acrylamide in amounts typically ingested by Swedish men is associated with risk of cancer of the colon or rectum.

Conflict of interest statement

None declared.

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REFERENCES

1. IARC. *Monographs on the evaluation of carcinogenic risks to humans: some industrial chemicals*. Lyon: International Agency for Research on Cancer; 1994.
2. Tareke E, Rydberg P, Karlsson P, Eriksson S, Tornqvist M. Analysis of acrylamide, a carcinogen formed in heated foodstuffs. *J Agric Food Chem* 2002;**50**:4998–5006.
3. Mottram DS, Wedzicha BL, Dodson AT. Acrylamide is formed in the Maillard reaction. *Nature* 2002;**419**:448–9.
4. Stadler RH, Blank I, Varga N, et al. Acrylamide from Maillard reaction products. *Nature* 2002;**419**:449–50.
5. Svensson K, Abramsson L, Becker W, et al. Dietary intake of acrylamide in Sweden. *Food Chem Toxicol* 2003;**41**:1581–6.
6. Rice JM. The carcinogenicity of acrylamide. *Mutat Res* 2005;**580**:3–20.
7. Pelucchi C, Galeone C, Levi F, et al. Dietary acrylamide and human cancer. *Int J Cancer* 2006;**118**:467–71.
8. Mucci LA, Dickman PW, Steineck G, Adami HO, Augustsson K. Dietary acrylamide and cancer of the large bowel, kidney, and bladder: absence of an association in a population-based study in Sweden. *Br J Cancer* 2003;**88**:84–9.
9. Mucci LA, Adami HO, Wolk A. Prospective study of dietary acrylamide and risk of colorectal cancer among women. *Int J Cancer* 2006;**118**:169–73.
10. Bergström L, Kylberg E, Hagman U, Erikson H, Bruce Å. The food composition database KOST: the National Food Administration's Information System for nutritive values of food. *Vår Föda* 1991;**43**:439–47.
11. Willett W, Stampfer MJ. Total energy intake: implications for epidemiologic analyses. *Am J Epidemiol* 1986;**124**:17–27.
12. Mattsson B, Wallgren A. Completeness of the Swedish Cancer Register. Non-notified cancer cases recorded on death certificates in 1978. *Acta Radiol Oncol* 1984;**23**:305–313.
13. Cox DR, Oakes D. *Analysis of survival data*. London: Chapman and Hall; 1984.
14. Schettgen T, Rossbach B, Kutting B, Letzel S, Drexler H, Angerer J. Determination of haemoglobin adducts of acrylamide and glycidamide in smoking and non-smoking persons of the general population. *Int J Hyg Environ Health* 2004;**207**:531–9.
15. Bull RJ, Robinson M, Laurie RD, et al. Carcinogenic effects of acrylamide in Sencar and A/J mice. *Cancer Res* 1984;**44**:107–11.
16. Friedman MA, Dulak LH, Stedham MA. A lifetime oncogenicity study in rats with acrylamide. *Fundam Appl Toxicol* 1995;**27**:95–105.
17. Johnson KA, Gorzinski SJ, Bodner KM, et al. Chronic toxicity and oncogenicity study on acrylamide incorporated in the drinking water of Fischer 344 rats. *Toxicol Appl Pharmacol* 1986;**85**:154–68.
18. Wirfält E, Paulsson B, Törnqvist M, Axmon A, Hagmar L. Associations between estimated acrylamide intakes, and hemoglobin AA adducts in a sample from the Malmö Diet and cancer cohort. *Eur J Clin Nutr* 2008;**62**:314–23.