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Dietary Acrylamide Intake Is Not Associated with Gastrointestinal Cancer Risk[1–3]

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Abstract

Acrylamide is a probable human carcinogen that was detected in several heat-treated foods, such as French fries and crisps, in 2002. Prospective studies are needed on acrylamide and human cancer risk. We prospectively investigated the association between acrylamide and gastrointestinal cancer risk. In 1986, 120,852 men and women (aged 55–69 y) were included in the Netherlands Cohort Study on diet and cancer. At baseline, a random subcohort of 5000 participants was selected for a case-cohort approach. Acrylamide intake was assessed with a FFQ at baseline and was based on acrylamide analyses in relevant Dutch foods. After 13.3 y of follow-up, 2190, 563, 349, and 216 cases of colorectal, gastric, pancreatic, and esophageal cancer, respectively, were available for analysis. The daily acrylamide intake of the subcohort was (mean ± SD) 21.7 ± 12.1μg. A 10-μg/d increment of acrylamide intake was associated with multivariable-adjusted Cox proportional hazard rate ratios (HR) (95% CI) of 1.00 (0.96–1.06), 1.02 (0.94–1.10), 1.06 (0.96–1.17), and 0.96 (0.85–1.09) for colorectal, gastric, pancreatic, and esophageal cancer, respectively. For former or never-smokers, the corresponding HR were: 1.03 (0.94–1.12), 1.09 (0.98–1.22), 1.07 (0.93–1.24), and 0.92 (0.76–1.11). There were some significantly increased risks within subgroups stratified by obesity, nonoccupational physical activity, and age, factors that were a priori selected based on their capacity to modify cytochrome P4502E1 activity. Overall, acrylamide intake was not associated with colorectal, gastric, pancreatic, and esophageal cancer risk, but some subgroups deserve further attention. J. Nutr. 138: 2229–2236, 2008.

Introduction

In 2002, acrylamide was detected at high concentrations in heat-processed, carbohydrate-rich foods, such as French fries and potato crisps, and coffee (1). It is formed in Maillard browning reactions in which amino acids, particularly asparagine, react with reducing sugars at temperatures >120°C (2,3).

Recently, in epidemiological studies, positive associations have been observed for endometrial and ovarian cancer (4), renal cell cancer (5), and postmenopausal estrogen receptor-positive breast cancer risk (6). In a retrospective cohort study from 1986 on occupational acrylamide exposure, a positive association was observed between cumulative acrylamide exposure and pancreatic cancer risk (7,8). These findings, combined with the fact that acrylamide is present at high levels in many everyday foods, stress the need for more prospective studies on the association between dietary acrylamide and cancer risk.

In 1994, the International Agency for Research on Cancer classified the industrial chemical acrylamide as a probable human carcinogen based on its carcinogenic action in rodents (9). Animal studies have shown positive dose-response relationships between acrylamide exposure and cancer at multiple sites (10), e.g. oral tissues, thyroid gland, mammary gland, lung, and skin. Both genotoxic and nongenotoxic pathways have been suggested for the carcinogenic effect of acrylamide. Acrylamide itself and its epoxide metabolite glycidamide, which is generated by cytochrome P4502E1, are clastogenic and glycidamide forms DNA adducts. As for possible nongenotoxic pathways, acrylamide may influence the redox status of cells and thus gene transcription or it may interfere with DNA repair or hormonal balances (10).

Epidemiological studies on occupational acrylamide exposure have been negative, apart from the positive association with pancreatic cancer risk mentioned above (7,8,11–14). Despite the recommendation of the WHO to perform epidemiological studies on dietary acrylamide and cancer risk links (15), only a few case-control studies (16–18) and prospective cohort studies (4–6,19,20) have been published up to now. Most of these studies rendered no indications for a positive association, except for the 3 studies mentioned previously (4–6).

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Because the acrylamide molecule is small and hydrophilic, it reaches every organ and virtually every tissue in the body (21). For this reason, theoretically all tissues are targets for carcinogenesis. When acrylamide is taken orally, the gastrointestinal tract is exposed to considerable amounts of this substance. Gastric and pancreatic cancer have not been studied before, to our knowledge, in epidemiological studies on dietary acrylamide intake. Pancreatic cancer had our particular interest, because it was associated with acrylamide exposure in 1 study on occupational acrylamide exposure.

Subjects and Methods

Study participants. The Netherlands Cohort Study on diet and cancer (NLCS) started in September 1986 with the inclusion of 58,279 men and 62,573 women aged 55–69 y sampled from Dutch municipal registries (22). At baseline, the participants completed a self-administered questionnaire on diet and other cancer risk factors. The case-cohort approach was used; cases were enumerated for the entire cohort, whereas the accumulated person-years for the total cohort were estimated from a subcohort of 5000 participants randomly sampled from the full cohort at baseline. Since the start of the study, vital status information was obtained from the subcohort at regular time intervals. Incident cases in the total cohort were detected by annual record linkages to the regional cancer registries and the Netherlands Pathology Registry. The completeness of cancer follow-up was assessed to be at least 96% (23), whereas the follow-up of the subcohort at the end of follow-up was nearly 100% complete (only 2 male subcohort members were lost to follow-up). The study was approved by the Medical Ethics Committees of the University Hospital Maastricht and TNO Nutrition in February 1985 and July 1986, respectively. Further details on the design of the study and methods of follow-up are presented elsewhere (22,24–26).

The analyses are based on 13.3 y of follow-up (September 1986–January 2000). There were 2740 colorectal [1818 colon (ICD-O-3 C18), 278 rectosigmoid (ICD-O-3 C19), and 644 rectal (ICD-O-3 C20)] cancer cases. Among the 681 gastric cancer cases, 180 adenocarcinomas of the cardia (ICD-O-3 C16.0), 284 adenocarcinomas of the distant stomach (ICD-O-3 C16.1-C16.5), and 217 adenocarcinomas of the stomach with an unspecified localization (ICD-O-3 C16.6-C16.9) were detected. Of the 445 pancreatic cancer cases (ICD-O-3 C25, excluding C25.4), 289 cases were microscopically verified. Among the 267 esophageal cancer cases (ICD-O-3 C15), there were 142 adenocarcinomas (M8140–8141, 8190–8231, 8260–8263, 8310, 8430, 8480–8490, 8560, 8570–8572) and 108 squamous cell carcinomas (M8050–8076).

Cases and subcohort members were excluded from analysis if they had cancer (other than skin cancer) at baseline and if their dietary data were incomplete or inconsistent (25) (**Fig. 1**).

Acrylamide intake assessment. The 150-item FFQ queried the habitual intake of foods during the year preceding baseline (25). The acrylamide intake was estimated from the mean acrylamide level of food items and the frequency of consumption and portion size of foods. To be representative of our cohort, we used data on acrylamide levels in foods on the Dutch market only. Further details of the intake assessment, including levels of acrylamide in foods, are presented elsewhere (4).

Statistical analysis. Some confounders were chosen a priori and some were included in the models only if they changed age and sex-adjusted hazard rate ratios (HR) of acrylamide (expressed as the interval between the 10th and 90th percentiles of intake of the subcohort: 27 μg acrylamide/d) by >10% (**Supplemental Table 1**). Smoking status, quantity, and duration were always included in the models, because cigarette smoke is an important acrylamide source. Smokers have been shown to have on average 4 times higher levels of acrylamide-hemoglobin adducts, which is a marker of internal dose of acrylamide, than nonsmokers (27,28). For this reason, subgroup analyses were performed for never-smokers. For gastric, pancreatic, and esophageal cancers, the number of never-smokers was too small and therefore it was decided to combine never-smokers and ex-smokers who quit >10 y before the start of the study.

Scaled Schoenfeld residuals were used to test the proportional hazards assumption. HR were obtained through Cox proportional hazards regression with STATA software (package 9.2). Additional variance introduced by sampling a subcohort from the cohort was taken into account by estimation of standard errors using the robust Huber-White sandwich estimator. Tests for trend were performed by fitting the median acrylamide intake per quintile as a continuous variable.

To check for the influence of preclinical disease, the analyses were also performed excluding the first 2 y of follow-up.

Effect modification by other variables was tested using Wald chi-square tests. The variables that were tested for effect modification were selected based on their ability to modify the activity of cytochrome P4502E1 and are age, diabetes, obesity, smoking, alcohol consumption, and physical activity (29–32).

Results

The mean daily acrylamide intake of the subcohort was 21.7 ± 12.1 μg. The most important dietary source of acrylamide in the

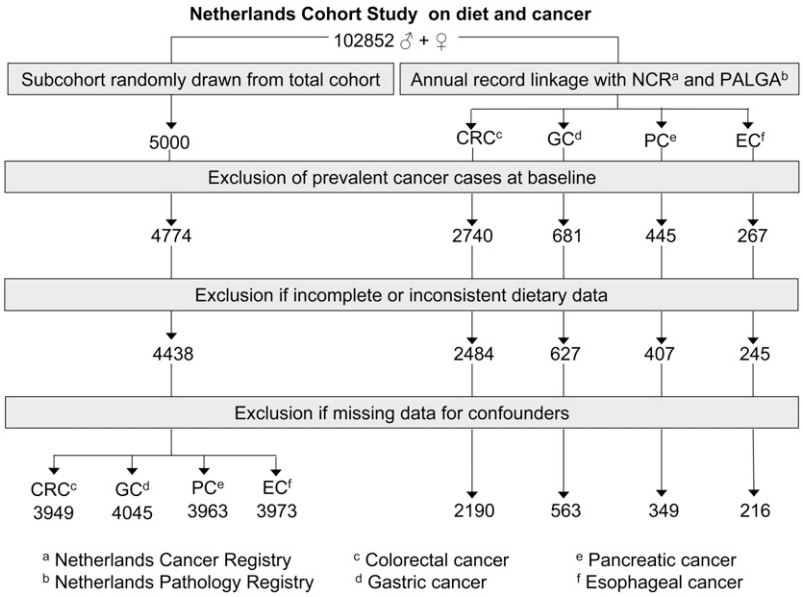

FIGURE 1 Flow diagram of subcohort members and cases on whom the analyses are based.

subcohort was coffee, which contributed on average 47% to the acrylamide intake, whereas Dutch spiced cake, cookies, French fries, and potato crisps contributed 15, 13, 8, and 2%, respectively (5). However, most of the variance of the acrylamide intake was explained by Dutch spiced cake (57%), followed by coffee (15%), French fries (14%), potato crisps (5%), and cookies (3%) (5).

The characteristics of cases and subcohort are shown in **Table 1**. Cases were older at baseline than subcohort members. The BMI of gastric cardia cancer, microscopically verified pancreatic cancer, and esophageal adenocarcinoma cases was higher than that of the subcohort but lower for squamous cell esophageal cancer cases. Smoking was more prevalent among all cancer case groups (except colon cancer) than among subcohort members, and cases smoked more and for a longer period. For dietary factors, cases consumed more alcohol than the subcohort, especially squamous cell esophageal cancer cases. Fish consumption was higher in the gastric and squamous cell esophageal cancer cases than in the subcohort. Finally, gastric cardia cancer

TABLE 1 Baseline characteristics of cases and subcohort members: the NLCS, 1986–1999[1]

Variable	Subcohort	Colon	Rectum	Gastric cardia	Gastric noncardia	Pancreas total	Pancreas-mv[2]	E-AC[3]	E-SCC[4]
n[5]	4438	1696	591	163	264	407	268	132	98
Dietary variables									
Acrylamide intake, *μg/d*	21.8 ± 12.1	21.8 ± 12.1	21.6 ± 11.5	22.5 ± 11.1	21.9 ± 11.6	22.1 ± 12.7	22.0 ± 11.8	22.0 ± 11.3	20.4 ± 11.5
Acrylamide intake, *μg·kg body weight^{-1}·d^{-1}*	0.30 ± 0.18	0.30 ± 0.17	0.29 ± 0.16	0.29 ± 0.15	0.30 ± 0.17	0.30 ± 0.19	0.30 ± 0.17	0.28 ± 0.15	0.29 ± 0.16
Coffee, *g/d*	537 ± 271	526 ± 257	571 ± 269	627 ± 272	597 ± 284	572 ± 302	589 ± 319	613 ± 322	547 ± 258
Dutch spiced cake, *g/d*	4.9 ± 9.0	5.1 ± 9.4	4.1 ± 8.4	4.1 ± 7.7	3.9 ± 7.6	4.5 ± 8.9	4.1 ± 8.1	3.0 ± 6.2	4.8 ± 9.8
Cookies, *g/d*	13.6 ± 10.8	14.2 ± 10.6	13.4 ± 9.6	14.8 ± 11.8	13.7 ± 11.9	13.4 ± 12.4	13.1 ± 10.1	12.9 ± 9.5	9.4 ± 8.5
Potato crisps, *g/d*	0.43 ± 1.83	0.42 ± 1.73	0.41 ± 1.61	0.48 ± 1.30	0.56 ± 1.97	0.44 ± 1.66	0.37 ± 1.44	0.41 ± 1.31	0.14 ± 0.38
French fries, *g/d*	5.6 ± 12.6	5.3 ± 11.9	5.7 ± 11.1	5.0 ± 11.0	5.2 ± 12.3	5.7 ± 14.0	6.4 ± 14.7	7.9 ± 11.1	5.3 ± 10.4
Vegetables, *g/d*	194 ± 83	189 ± 82	201 ± 92	182 ± 78	185 ± 83	202 ± 87	204 ± 89	191 ± 85	187 ± 74
Fruit, *g/day*	175 ± 120	175 ± 118	173 ± 121	154 ± 115	155 ± 106	170 ± 116	163 ± 105	161 ± 133	141 ± 119
Dairy products, *g/d*	304 ± 203	291 ± 190	292 ± 198	317 ± 206	310 ± 199	301 ± 201	300 ± 183	324 ± 223	262 ± 229
Meat, *g/d*	99 ± 42	98 ± 40	102 ± 42	106 ± 45	101 ± 44	100 ± 40	99 ± 40	99 ± 41	106 ± 40
Fish, *g/d*	12.9 ± 15.4	12.5 ± 14.9	13.0 ± 14.6	16.1 ± 20.7	15.0 ± 20.3	13.1 ± 16.5	12.1 ± 14.6	13.8 ± 17.9	15.2 ± 14.5
Tea,[6] *cups/d*	2.8 ± 2.1	2.8 ± 2.0	2.6 ± 2.1	2.3 ± 2.0	2.7 ± 1.9	2.7 ± 2.2	2.7 ± 2.2	2.4 ± 2.5	2.7 ± 2.5
Total energy intake, *kJ/d*	8051 ± 2160	8018 ± 2114	8395 ± 2102	8642 ± 2357	8449 ± 2240	8127 ± 2093	8231 ± 2098	8541 ± 2110	8185 ± 2018
Carbohydrate, *g/d*	202 ± 62	200 ± 59	210 ± 62	214 ± 70	214 ± 64	201 ± 61	204 ± 58	210 ± 61	191 ± 55
Saturated fat, *g/d*	33.3 ± 11.5	33.2 ± 11.4	34.0 ± 11.0	35.3 ± 13.3	34.9 ± 12.2	33.5 ± 10.6	34.0 ± 10.5	34.6 ± 11.3	31.9 ± 10.8
Trans unsaturated fatty acid, *g/d*	2.9 ± 1.5	2.9 ± 1.5	2.9 ± 1.3	3.0 ± 1.7	3.1 ± 1.6	2.9 ± 1.6	3.1 ± 1.6	3.2 ± 1.6	2.6 ± 1.3
Fiber, *g/d*	27.0 ± 8.1	26.6 ± 8.0	27.9 ± 8.2	27.4 ± 7.4	26.6 ± 7.5	27.1 ± 7.9	27.4 ± 7.7	27.1 ± 8.1	24.7 ± 7.5
Vitamin B-6, *mg/d*	1.44 ± 0.36	1.42 ± 0.36	1.50 ± 0.38	1.50 ± 0.35	1.45 ± 0.35	1.45 ± 0.37	1.47 ± 0.35	1.45 ± 0.34	1.41 ± 0.37
Alcohol, *g/d*	10.4 ± 14.4	11.1 ± 14.7	13.4 ± 17.4	14.2 ± 15.7	11.6 ± 15.0	13.0 ± 16.8	12.8 ± 16.8	15.4 ± 18.5	23.4 ± 28.1
Nondietary variables									
Age, *y*	61.4 ± 4.2	62.5 ± 4.1	61.9 ± 4.0	61.6 ± 4.0	62.9 ± 4.1	62.3 ± 4.1	61.8 ± 4.0	61.9 ± 4.1	62.8 ± 4.0
BMI, *kg/m^2*	25.0 ± 3.1	25.2 ± 3.1	25.1 ± 3.0	25.8 ± 3.0	25.0 ± 3.2	25.4 ± 3.3	25.8 ± 3.2	26.2 ± 3.4	24.3 ± 3.6
Height, *cm*	171 ± 9	172 ± 9	173 ± 8	175 ± 7	172 ± 7	172 ± 8	172 ± 8	174 ± 7	171 ± 8
Current cigarette smoking, *% yes*	28.3	22.9	29.9	37.4	39.8	38.6	39.9	31.1	53.1
Cigarettes, *n/d*	9.5 ± 10.9	10.1 ± 11.4	11.9 ± 11.6	14.9 ± 12.3	12.2 ± 11.6	11.0 ± 11.5	11.0 ± 10.5	16.7 ± 13.9	14.7 ± 12.4
Years of smoking, *n*	20.2 ± 18.2	20.7 ± 18.0	24.2 ± 17.9	29.7 ± 16.0	27.9 ± 18.6	24.8 ± 18.4	25.1 ± 18.4	28.3 ± 16.3	29.4 ± 18.2
NOPA,[7] *min/d*	72 ± 61	72 ± 61	75 ± 71	82 ± 71	71 ± 58	68 ± 51	71 ± 55	79 ± 93	72 ± 71
Education, *%*									
Primary school	29.1	29.2	30.5	27.6	36.4	33.2	32.5	22.0	33.7
Lower vocational school	21.9	18.6	24.9	26.4	24.6	17.9	18.7	28.0	20.4
Intermediate vocational/high school	34.8	36.0	31.6	29.4	29.2	34.2	34.0	34.1	34.7
Higher vocational school/university	13.6	15.6	11.8	16.6	9.1	14.5	14.6	15.2	10.2
Family medical history, *% yes*									
Colorectal cancer	5.5	9.7	8.3	5.5	8.0	9.6	10.1	6.8	3.1
Gastric cancer	6.6	6.9	7.3	8.0	13.3	8.1	7.5	10.6	8.2
Pancreatic cancer	0.9	1.1	1.0	3.1	0.8	2.2	1.9	1.5	0.0
Esophageal cancer	0.9	1.3	0.5	1.2	0.4	0.7	0.4	2.3	2.0

[1] Values are means ± SD, or percentages.
[2] mv, Microscopically verified.
[3] E-AC, Adenocarcinoma of the esophagus.
[4] E-SCC, Squamous cell carcinoma of the esophagus.
[5] *n* without missing values on any of the row variables. *n* varies across the rows due to varying numbers of missing values for the row variables.
[6] 1 cup = 125 mL.
[7] NOPA, Nonoccupational physical activity.

and esophageal adenocarcinoma cases drank less tea than the subcohort did. For the proportional hazards analysis, men and women were combined, because there was no significant effect modification by sex.

Overall, there were no indications for a positive association between acrylamide intake and colorectal cancer risk (**Table 2**). When the analyses were restricted to never-smokers, there was a significantly increased HR in the 3rd quintile for colon and rectal cancer combined and for colon cancer alone. There was no linear dose-response relationship over the quintiles. For rectal cancer, the HR for never-smokers were significantly increased in the 2nd and 4th quintile, but again there was no linear dose-response relationship. The results did not change when the first 2 y of follow-up were excluded (results not shown).

Acrylamide intake was not associated with total gastric cancer, gastric cardia adenocarcinoma, or noncardia gastric cancer risk overall (**Table 3**). When the analyses were restricted to nonsmokers, there were some indications ($P = 0.26$ and 0.19, respectively) for a positive linear trend, both for cardia and noncardia cancer risk. However, these associations weakened further when the first 2 y of follow-up were excluded.

Acrylamide intake was not associated with pancreatic (**Table 4**) or esophageal cancer risk (**Table 5**). The same applies to the group of nonsmokers and when the first 2 y of follow-up were excluded.

Reanalyzing the age- and sex-adjusted associations between acrylamide and cancer risk by excluding only observations with missing values on age and sex did not lead to other conclusions than excluding persons with missing values on any of the covariables in the multivariable-adjusted models. Therefore, bias due to nonrandomness of the missing values on the covariables is not likely.

There was no significant effect modification by any of the studied variables for colorectal or gastric cancer. For microscopically verified pancreatic cancer, there was significant effect modification by obesity, with obese people having an increased risk (95% CI) of 1.59 (0.87–2.89, $n = 14$) per 10-μg/d increment of acrylamide intake (P for effect modification = 0.04).

There was also effect modification ($P = 0.02$) by obesity for esophageal cancer, particularly adenocarcinoma ($P = 0.03$), with obese participants having a 55% (8–121%; $n = 20$) and 90% (15–214%; $n = 14$) increased risk, respectively, for every 10-μg/d increment of acrylamide intake. The acrylamide-associated cancer risk was significantly increased in the subgroup with the highest nonoccupational physical activity, although the test for effect modification was never significant. This was observed for colon cancer in never-smokers and for pancreatic cancer. There were significantly decreased acrylamide-associated risks for noncardia gastric cancer in nonsmokers and for squamous cell esophageal cancer in the group with the lowest nonoccupational physical activity.

Although there was no significant effect modification by age, the oldest participants had a significantly decreased risk of rectal cancer per 10-μg/d acrylamide intake, whereas the youngest

TABLE 2 Association between dietary acrylamide intake and colorectal cancer risk: the NLCS, 1986–1999

	Overall				Never-smokers			
	Cases, *n*	PY,[1] *n*	HR (95% CI)[2]	HR (95% CI)[3]	Cases, *n*	PY,[1] *n*	HR (95% CI)[2]	HR (95% CI)[4]
Colorectal cancer								
Acrylamide intake (10 μg/d)	2190	47,417	1.00 (0.95–1.04)	1.00 (0.96–1.06)	717	17,944	1.01 (0.93–1.09)	1.03 (0.94–1.12)
Q1	465	9308	Ref (1.00)	Ref (1.00)	140	3870	Ref (1.00)	Ref (1.00)
Q2	425	9364	0.94 (0.80–1.12)	0.96 (0.81–1.15)	156	3597	1.24 (0.93–1.64)	1.25 (0.93–1.68)
Q3	450	9462	1.03 (0.87–1.22)	1.06 (0.89–1.27)	139	3283	1.32 (0.99–1.78)	1.37 (1.01–1.86)
Q4	407	9662	0.92 (0.77–1.09)	0.96 (0.80–1.14)	139	3595	1.18 (0.88–1.57)	1.22 (0.90–1.67)
Q5	443	9621	0.96 (0.82–1.14)	1.00 (0.84–1.20)	143	3599	1.13 (0.85–1.51)	1.19 (0.88–1.63)
P-trend			0.62	0.94			0.80	0.57
Colon cancer								
Acrylamide intake (10 μg/d)	1505	47,524	1.01 (0.96–1.06)	1.03 (0.98–1.09)	529	17,980	1.02 (0.93–1.11)	1.04 (0.94–1.14)
Q1	315	9322	Ref (1.00)	Ref (1.00)	105	3877	Ref (1.00)	Ref (1.00)
Q2	283	9384	0.93 (0.77–1.12)	0.95 (0.78–1.15)	108	3604	1.14 (0.83–1.57)	1.13 (0.82–1.57)
Q3	313	9504	1.06 (0.88–1.28)	1.11 (0.91–1.35)	107	3283	1.37 (0.99–1.89)	1.42 (1.01–1.98)
Q4	275	9685	0.92 (0.76–1.12)	0.98 (0.80–1.20)	100	3615	1.13 (0.82–1.56)	1.18 (0.83–1.66)
Q5	319	9629	1.03 (0.85–1.24)	1.09 (0.89–1.33)	109	3602	1.15 (0.84–1.58)	1.21 (0.86–1.69)
P-trend			0.75	0.37			0.63	0.45
Rectal cancer								
Acrylamide intake (10 μg/d)	510	47,707	0.97 (0.90–1.05)	0.97 (0.89–1.05)	141	18,064	0.97 (0.84–1.12)	1.02 (0.86–1.20)
Q1	94	9375	Ref (1.00)	Ref (1.00)	21	3880	Ref (1.00)	Ref (1.00)
Q2	117	9462	1.27 (0.95–1.70)	1.29 (0.96–1.74)	42	3638	2.20 (1.27–3.81)	2.34 (1.32–4.13)
Q3	105	9508	1.16 (0.86–1.57)	1.18 (0.86–1.61)	23	3299	1.45 (0.78–2.71)	1.56 (0.82–2.97)
Q4	106	9701	1.16 (0.86–1.57)	1.16 (0.85–1.60)	31	3626	1.74 (0.97–3.11)	1.90 (1.03–3.51)
Q5	88	9661	0.94 (0.69–1.28)	0.94 (0.67–1.31)	24	3620	1.26 (0.69–2.32)	1.48 (0.77–2.84)
P-trend			0.28	0.27			0.82	0.79

[1] PY, Person years.
[2] Adjusted for age and sex, same data set as multivariable-adjusted data set.
[3] Adjusted for: age, sex, BMI, height, energy, fiber and vitamin B-6 intake, consumption of vegetables, fruits, dairy, meat, and alcohol, nonoccupational physical activity, smoking status (current vs. not current), number of cigarettes per day, number of years of smoking, and family history of colorectal cancer.
[4] Adjusted for: age, sex, BMI, height, energy, fiber and vitamin B-6 intake, consumption of vegetables, fruits, dairy, meat, and alcohol, nonoccupational physical activity, and family history of colorectal cancer.

TABLE 3 Association between dietary acrylamide intake and gastric cancer risk: the NLCS, 1986–1999

	Overall				Never and former smokers			
	Cases, *n*	PY,[1] *n*	HR (95% CI)[2]	HR (95% CI)[3]	Cases, *n*	PY,[1] *n*	HR (95% CI)[2]	HR (95% CI)[4]
Gastric cancer								
Acrylamide intake (10 μg/d)	563	49,317	1.03 (0.96–1.11)	1.02 (0.94–1.10)	250	29,586	1.08 (0.98–1.20)	1.09 (0.98–1.22)
Q1	104	9774	Ref (1.00)	Ref (1.00)	20	6224	Ref (1.00)	Ref (1.00)
Q2	114	9819	1.15 (0.86–1.54)	1.09 (0.81–1.47)	22	6213	1.19 (0.78–1.83)	1.16 (0.74–1.80)
Q3	113	9759	1.20 (0.89–1.60)	1.09 (0.81–1.48)	28	5240	1.44 (0.93–2.24)	1.50 (0.95–2.38)
Q4	120	10,024	1.27 (0.95–1.70)	1.18 (0.87–1.60)	25	5865	1.23 (0.79–1.91)	1.24 (0.78–1.98)
Q5	112	9941	1.13 (0.84–1.51)	1.06 (0.78–1.45)	25	6045	1.42 (0.94–2.15)	1.43 (0.92–2.24)
P-trend			0.49	0.77			0.14	0.16
Gastric cardia adenocarcinoma								
Acrylamide intake (10 μg/d)	143	49,383	1.03 (0.90–1.16)	1.05 (0.91–1.20)	66	29,591	1.14 (0.96–1.34)	1.16 (0.97–1.39)
Q1	24	9782	Ref (1.00)	Ref (1.00)	10	6224	Ref (1.00)	Ref (1.00)
Q2	29	9845	1.24 (0.71–2.17)	1.25 (0.71–2.21)	14	6214	1.51 (0.65–3.47)	1.54 (0.65–3.68)
Q3	34	9770	1.45 (0.84–2.51)	1.44 (0.82–2.52)	13	5243	1.71 (0.72–4.07)	1.85 (0.72–4.72)
Q4	27	10,045	1.16 (0.66–2.06)	1.21 (0.66–2.20)	12	5865	1.47 (0.61–3.53)	1.61 (0.63–4.11)
Q5	29	9942	1.21 (0.70–2.12)	1.28 (0.70–2.35)	17	6045	1.77 (0.78–3.98)	1.85 (0.76–4.52)
P-trend			0.77	0.66			0.26	0.26
Distant (noncardia) gastric cancer								
Acrylamide intake (10 μg/d)	238	49,332	1.01 (0.91–1.12)	0.99 (0.88–1.11)	104	29,591	1.04 (0.90–1.20)	1.06 (0.91–1.24)
Q1	50	9774	Ref (1.00)	Ref (1.00)	21	6224	Ref (1.00)	Ref (1.00)
Q2	43	9822	0.91 (0.60–1.39)	0.83 (0.54–1.30)	20	6214	1.03 (0.55–1.93)	1.00 (0.52–1.92)
Q3	43	9767	0.98 (0.64–1.51)	0.88 (0.57–1.38)	17	5243	1.15 (0.59–2.21)	1.26 (0.63–2.51)
Q4	58	10,027	1.33 (0.89–1.97)	1.19 (0.79–1.80)	21	5865	1.27 (0.68–2.36)	1.35 (0.70–2.60)
Q5	44	9941	0.94 (0.62–1.43)	0.88 (0.56–1.38)	25	6045	1.32 (0.73–2.39)	1.42 (0.75–2.67)
P-trend			0.81	0.99			0.28	0.19

[1] PY, Person years.
[2] Adjusted for age and sex, same data set as multivariable-adjusted data set.
[3] Adjusted for: age, sex, BMI, energy intake, consumption of tea, vegetables, fruits, and fish, socioeconomic status, smoking status (current vs. not current), number of cigarettes per day, number of years of smoking, and family history of gastric cancer.
[4] Adjusted for: age, sex, BMI, energy intake, consumption of tea, vegetables, fruits, and fish, socioeconomic status, number of cigarettes per day, number of years of smoking, and family history of gastric cancer.

participants had a significantly increased acrylamide-associated pancreatic cancer risk.

Discussion

Overall, this prospective cohort study does not give strong support for the hypothesis that dietary acrylamide intake is positively associated with gastrointestinal cancer risk.

The association between dietary acrylamide and colorectal cancer risk was studied in 2 case-control studies and 1 prospective cohort study (16,17,19). These studies found no indications of a positive association either. In our study, the HR across the quintiles for colorectal cancer in never-smokers did not increase linearly (or follow any other clear dose-response relationship) and, thus, the significant HR in some of the quintiles are most likely due to chance.

The association between acrylamide intake and gastric cancer risk has not been studied before. In the present study, no clear indications for a positive overall association were found. We found no association between dietary acrylamide intake and overall pancreatic cancer risk, contrary to a study on occupational acrylamide exposure (8,11). However, the analyses were poorly adjusted for smoking and other risk factors in that study, which may have biased the results. Furthermore, in an update of this study with longer follow-up and better adjustment for smoking, the acrylamide-associated risk was much reduced and no longer significant (13).

There was no overall association between acrylamide intake and esophageal cancer risk. This was also observed in the only other study on it, which was a case-control study (16).

The genotoxic action of glycidamide (10) is often noted as the predominant mechanism of carcinogenic action in acrylamide cancer risk assessments. The fact that we did not observe an overall association between acrylamide intake and the risk of gastrointestinal tumors, but did observe positive associations between acrylamide intake and endometrial and ovarian cancer risk in a previous study, indicates that disturbance of hormonal balances may also be at the basis of acrylamide carcinogenesis. If acrylamide does indeed exert its carcinogenic effects through a hormonal mechanism, that would explain why no clear overall associations between acrylamide intake and gastrointestinal cancer risk were observed in this study, because sex hormones do not play as clear a role in the etiology of these tumors as they do in the etiology of, e.g. endometrial and ovarian cancer.

The fact that a Danish study observed a positive association between acrylamide hemoglobin adducts in the blood and postmenopausal estrogen receptor-positive breast cancer (6) also points toward an effect of acrylamide on hormonal pathways.

The current prospective cohort study has some limitations. FFQ have limitations, as discussed elsewhere (33), but they are the only feasible way to assess dietary intake over a long time period in large-scale epidemiological studies. The NLCS FFQ has proven to be both valid (25) and reproducible (26) with regard to nutrients that correlate with acrylamide, such as carbohydrates and fiber.

TABLE 4 Association between dietary acrylamide intake and pancreatic cancer risk: the NLCS, 1986–1999

	Overall				Never and former smokers			
	Cases, *n*	PY,[1] *n*	HR (95% CI)[2]	HR (95% CI)[3]	Cases, *n*	PY,[1] *n*	HR (95% CI)[2]	HR (95% CI)[4]
Pancreatic cancer								
Acrylamide intake (10 μg/d)	349	48,283	1.05 (0.95–1.15)	1.06 (0.96–1.17)	166	28,680	1.07 (0.94–1.23)	1.07 (0.93–1.24)
Q1	72	9498	Ref (1.00)	Ref (1.00)	40	5979	Ref (1.00)	Ref (1.00)
Q2	76	9581	1.08 (0.77–1.51)	1.02 (0.72–1.44)	29	6013	0.74 (0.45–1.22)	0.72 (0.43–1.20)
Q3	69	9647	1.01 (0.71–1.43)	0.96 (0.66–1.38)	36	5157	1.15 (0.71–1.85)	1.07 (0.65–1.76)
Q4	63	9800	0.91 (0.64–1.30)	0.87 (0.60–1.27)	29	5645	0.83 (0.51–1.37)	0.73 (0.43–1.26)
Q5	69	9756	0.97 (0.69–1.37)	0.98 (0.68–1.40)	32	5885	0.84 (0.52–1.37)	0.80 (0.48–1.32)
P-trend			0.60	0.75			0.60	0.45
Microscopically verified pancreatic cancer								
Acrylamide intake (10 μg/d)	233	48,286	1.02 (0.92–1.13)	1.03 (0.92–1.15)	105	28,683	0.99 (0.84–1.18)	0.99 (0.83–1.19)
Q1	43	9498	Ref (1.00)	Ref (1.00)	25	5979	Ref (1.00)	Ref (1.00)
Q2	55	9584	1.28 (0.85–1.94)	1.19 (0.78–1.81)	22	6015	0.88 (0.49–1.58)	0.87 (0.47–1.59)
Q3	44	9647	1.03 (0.66–1.59)	0.94 (0.60–1.47)	20	5157	0.93 (0.51–1.71)	0.87 (0.46–1.62)
Q4	45	9801	1.04 (0.67–1.60)	0.98 (0.62–1.54)	20	5646	0.85 (0.47–1.56)	0.76 (0.40–1.45)
Q5	46	9756	1.05 (0.69–1.61)	1.03 (0.66–1.61)	18	5885	0.73 (0.39–1.35)	0.70 (0.37–1.32)
P-trend			0.78	0.84			0.31	0.24

[1] PY, Person years.
[2] Adjusted for age and sex, same data set as multivariable-adjusted data set.
[3] Adjusted for: age, sex, BMI, height, energy intake, consumption of vegetables, fruits, and alcohol, smoking status (current vs. not current), number of cigarettes per day, number of years of smoking, diabetes, and family history of pancreatic cancer.
[4] Adjusted for: age, sex, BMI, height, energy intake, consumption of vegetables, fruits, and alcohol, number of cigarettes per day, number of years of smoking, diabetes, and family history of pancreatic cancer.

Within foods, acrylamide levels vary greatly, which leads to nondifferential misclassification of acrylamide intake, which biases risk estimates toward null. To investigate the extent of misclassification, we estimated the acrylamide content (by using mean acrylamide levels of individual reported foods) of 39 Dutch duplicate 24-h meals, which were collected by the Dutch National Institute for Public Health and the Environment in 2004, and correlated this to the analytically measured content, and that rendered a Spearman correlation coefficient of 0.78 (E.J.M. Konings, J.G.F. Hogervorst, L.J. Schouten, R.A. Goldbohm, and P.A. van den Brandt, unpublished results). This indicates that it is feasible to make a sound rank ordering of the acrylamide intake via a 24-h meal using these mean acrylamide levels for foods. The acrylamide values in our food database were derived from foods that were sampled in 2002 and 2005. They may not be completely representative of the foods that were on the market in 1986. This will have resulted in nondifferential misclassification of the intake of our cohort, which will then have led to some underestimation of the true associations. We did not query whether the participants bought their foods or prepared them at home. Of the important acrylamide-containing foods, French fries were most likely to be prepared at home in the NLCS population. However, French fries contribute relatively little to the acrylamide intake and to the variance in acrylamide intake in this cohort. Dutch spiced cake, which is an important acrylamide source in this cohort, was not prepared at home. The misclassification that may have arisen from this is probably also nondifferential and would also have biased the risk estimates toward null. Despite these potential sources of nondifferential misclassification, acrylamide intake was associated with endometrial, ovarian, and renal cell cancer risk in this cohort (4,5). From this, we infer that if in reality acrylamide intake is positively associated with gastrointestinal cancers, the associations will probably be weaker than for endometrial, ovarian, and renal cell cancer.

It has to be borne in mind that the variation in acrylamide intake was to a large extent due to Dutch spiced cake and that coffee was overall the largest dietary source of acrylamide in our study. However, adjustment for Dutch spiced cake and coffee intake in the multivariable-adjusted models did not change the conclusions on the associations between acrylamide intake and colorectal, gastric, pancreatic, and esophageal cancer risk.

For the effect modification analyses, HR in many small subgroups were calculated. This makes it likely that some of the observed significant *P*-values for effect modification or significantly increased HR in subgroups were spurious. Therefore, they should be interpreted cautiously but deserve further investigation in other studies. A high level of nonoccupational physical activity was associated with an increased acrylamide-associated risk of colorectal and pancreatic cancer, whereas obese persons had a significantly increased acrylamide-associated risk of pancreatic and esophageal cancer, although this was based on few obese cases. These factors thus quite consistently modified the risk of some gastrointestinal cancers. This could give support for the hypothesis of glycidamide-mediated gastrointestinal carcinogenesis, but physical activity and obesity are also known to influence hormone levels and may thus modify the putative hormonal influences of acrylamide.

This study has some clear strengths, apart from the already mentioned validity and reproducibility of the NLCS FFQ. The acrylamide intake assessment is an important asset of the present study. We used acrylamide levels of foods from the Dutch market only and specifically analyzed foods that were relevant for the NLCS population.

Due to its prospective nature, selection bias is unlikely and differential recall bias is absent. Furthermore, the association with acrylamide intake was studied for various subgroups of tumors that are known to differ with respect to etiology and risk factors.

In conclusion, overall, we found no indications for a positive association between dietary acrylamide intake and gastrointesti-

TABLE 5 Association between dietary acrylamide intake and esophageal cancer risk: the NLCS, 1986–1999

	Overall				Never and former smokers			
	Cases, *n*	PY,[1] *n*	HR (95% CI)[2]	HR (95% CI)[3]	Cases, *n*	PY,[1] *n*	HR (95% CI)[2]	HR (95% CI)[4]
Esophageal cancer								
Acrylamide intake (10 μg/d)	216	48,288	0.97 (0.86–1.09)	0.96 (0.85–1.09)	83	28,684	0.92 (0.76–1.10)	0.92 (0.76–1.11)
Q1	50	9493	Ref (1.00)	Ref (1.00)	23	5974	Ref (1.00)	Ref (1.00)
Q2	36	9591	0.75 (0.48–1.16)	0.73 (0.47–1.15)	14	6021	0.65 (0.33–1.27)	0.66 (0.33–1.35)
Q3	45	9647	0.96 (0.63–1.45)	0.86 (0.56–1.33)	15	5158	0.86 (0.44–1.70)	0.90 (0.44–1.82)
Q4	42	9800	0.90 (0.59–1.38)	0.83 (0.54–1.28)	15	5644	0.80 (0.41–1.56)	0.81 (0.41–1.60)
Q5	43	9756	0.88 (0.58–1.35)	0.83 (0.54–1.30)	16	5885	0.73 (0.38–1.42)	0.73 (0.36–1.47)
P-trend			0.85	0.68			0.56	0.54
Esophageal adenocarcinoma								
Acrylamide intake (10 μg/d)	115	48,289	1.01 (0.88–1.17)	1.00 (0.85–1.17)	48	28,684	0.93 (0.75–1.14)	0.91 (0.73–1.14)
Q1	24	9493	Ref (1.00)	Ref (1.00)			Ref (1.00)	Ref (1.00)
Q2	17	9591	0.73 (0.39–1.38)	0.72 (0.38–1.36)			[5]	[5]
Q3	29	9647	1.23 (0.71–2.14)	1.12 (0.64–1.98)			[5]	[5]
Q4	22	9801	0.95 (0.53–1.71)	0.89 (0.49–1.63)			[5]	[5]
Q5	23	9756	0.96 (0.53–1.72)	0.88 (0.47–1.63)			[5]	[5]
P-trend			0.95	0.85			[5]	[5]
Esophageal squamous cell carcinoma								
Acrylamide intake (10 μg/d)	90	48,296	0.93 (0.77–1.13)	0.95 (0.78–1.16)	33	28,691	0.89 (0.63–1.26)	0.93 (0.66–1.31)
Q1	23	9499	Ref (1.00)	Ref (1.00)			Ref (1.00)	Ref (1.00)
Q2	17	9592	0.77 (0.41–1.46)	0.75 (0.38–1.47)			[5]	[5]
Q3	15	9648	0.73 (0.37–1.40)	0.69 (0.35–1.38)			[5]	[5]
Q4	16	9802	0.77 (0.40–1.46)	0.72 (0.37–1.38)			[5]	[5]
Q5	19	9756	0.87 (0.47–1.61)	0.92 (0.49–1.71)			[5]	[5]
P-trend			0.83	0.96			[5]	[5]

[1] PY, Person years.
[2] Adjusted for age and sex, same data set as multivariable-adjusted data set.
[3] Adjusted for: age, sex, BMI, consumption of tea, vegetables, fruits, dairy, and alcohol, smoking status (current vs. not current), number of cigarettes per day, number of years of smoking, and family history of esophageal cancer.
[4] Adjusted for: age, sex, BMI, consumption of tea, vegetables, fruits, dairy, and alcohol, number of cigarettes per day, number of years of smoking, and family history of esophageal cancer.
[5] Too few cases.

nal cancer risk. We encourage other researchers to prospectively investigate the association between dietary acrylamide intake and colorectal, gastric, esophageal, and pancreatic cancer risk; to perform subgroup analyses for nonsmokers; and to study effect modification by factors such as obesity, physical activity, and age.

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