Lung Cancer Risk in Relation to Dietary Acrylamide Intake

Janneke G. F. Hogervorst, Leo J. Schouten, Erik J. M. Konings, R. Alexandra Goldbohm, Piet A. van den Brandt

Background Acrylamide is a probable human carcinogen that is present in several heat-treated foods. In epidemiological studies, positive associations between dietary acrylamide intake and the risks of endometrial, ovarian, estrogen receptor–positive breast, and renal cell cancers have been observed. The association between dietary acrylamide intake and lung cancer risk is not known.

Methods We conducted a case–cohort study among 58 279 men and 62 573 women (aged 55–69 years) in the Netherlands Cohort Study on Diet and Cancer. Intakes of acrylamide-containing foods and risk factors for cancer were assessed with a self-administered questionnaire at baseline in 1986 and combined with acrylamide levels in relevant Dutch foods to assess total dietary acrylamide intake. The number of person-years at risk was estimated by using a random sample of participants from the total cohort that was chosen at baseline (n = 5000). Incident lung cancer cases in the total cohort were detected by computerized record linkages to the Netherlands Cancer Registry and the Netherlands Pathology Registry. Hazard ratios and 95% confidence intervals (CIs) for the risk of lung cancer associated with acrylamide intakes were estimated using Cox proportional hazards models that controlled for smoking (status, quantity, and duration) and other lung cancer risk factors. All statistical tests were two-sided.

Results After 13.3 years of follow-up (September 17, 1986 up to January 1, 2000) there were 2649 cases of primary, histologically verified lung cancer (International Classification of Diseases for Oncology-3 code: C34) when cases with prevalent cancer at baseline (other than skin cancer) were excluded. The multivariable-adjusted hazard ratio of lung cancer for a 10-μg/d increment of acrylamide intake was 1.03 (95% CI = 0.96 to 1.11) for men and 0.82 (95% CI = 0.69 to 0.96) for women. The hazard ratio of lung cancer for the highest (median intake [μg/d]: men = 37.6 and women = 36.8) vs the lowest (median intake [μg/d]: men = 10.8 and women = 9.5) quintile of acrylamide intake was 1.03 (95% CI = 0.77 to 1.39, P_{trend} = .85) for men and 0.45 (95% CI = 0.27 to 0.76, P_{trend} = .01) for women. The inverse association in women was strongest for adenocarcinoma (hazard ratio for highest vs lowest tertile of intake = 0.40, 95% CI = 0.21 to 0.78; P_{trend} = .01).

Conclusions Acrylamide intake was not associated with lung cancer risk in men but was inversely associated in women, most strongly for adenocarcinoma. This finding suggests that acrylamide is involved in human carcinogenesis through pathways other than genotoxicity.

J Natl Cancer Inst 2009;101:651–662

Acrylamide was found several years ago to be present in commonly consumed carbohydrate-rich heated foods (1) such as French fries and potato crisps and is classified as a probable human carcinogen based on results from animal studies (2). Recently, an advisory group of the International Agency for Research on Cancer (IARC) gave high priority to assessment of acrylamide as a human carcinogen in future IARC Monograph series (3), probably because of the outcomes of some recent epidemiological studies on acrylamide and cancer risk (4–6).

Animal studies have shown positive dose–response relationships between acrylamide exposure and cancer in multiple organs and tissues (7–10), including oral tissues, thyroid gland, and mammary gland, in the rat and lung and skin in the mouse. Recently, two prospective epidemiological studies have shown positive associations between acrylamide exposure and cancer risk. In one of those studies, we observed that increased dietary acrylamide exposure was positively associated with the risk of postmenopausal endometrial and ovarian cancers (but not with the risk of postmenopausal

Affiliations of authors: Department of Epidemiology, GROW–School for Oncology and Developmental Biology, Maastricht University, Maastricht, the Netherlands (JGFH, LJS, PAvdB); Food and Consumer Product Safety Authority, Region South, Department of Research & Development, Eindhoven, the Netherlands (EJMK); Department of Prevention and Health, Netherlands Organisation for Applied Scientific Research, Quality of Life, Leiden, the Netherlands (RAG).

Correspondence to: Janneke G. F. Hogervorst, MSc, Department of Epidemiology, GROW–School for Oncology and Developmental Biology, Maastricht University, PO Box 616, 6200 MD, Maastricht, the Netherlands (e-mail: jgf.hogervorst@epid.unimaas.nl).

See "Funding" and "Notes" following "References."

DOI: 10.1093/jnci/djp077

CONTEXT AND CAVEATS

Prior knowledge

Acrylamide, which is found in commonly consumed foods, had been shown to be a carcinogen in animal studies.

Study design

Prospective case–cohort study with cancer incidence determined from data from national registries. Intake of acrylamide-containing foods was estimated based on a self-administered questionnaire and government data on acrylamide content in foods. Cox proportional hazard regression models that adjusted for known or potential risk factors were used to assess the association of acrylamide intake with lung cancer.

Contribution

This study suggested that acrylamide intake does not increase the risk of lung cancer. The decreased risk of lung cancer with increasing intake of acrylamide in women observed in this study and previous studies on hormonal effects of acrylamide in animals raise the possibility that acrylamide may be involved in carcinogenesis via nongenotoxic effects.

Implications

Additional epidemiological studies on the association of acrylamide intake with cancer at various sites are warranted.

Limitations

Nondifferential misclassification of exposure may have obscured an association of acrylamide exposure with increased risk of lung cancer.

From the Editors

breast cancer) (4), as well as with the risk of renal cell cancer (but not with the risk of bladder or prostate cancer) (5). In the other study, a Danish group observed a positive association between acrylamide exposure and postmenopausal estrogen receptor–positive breast cancer risk using acrylamide–hemoglobin adducts for the assessment of acrylamide exposure (6). More prospective epidemiological studies on the association between acrylamide intake and cancer risk are needed, especially for cancer sites that have not yet been studied, such as the lung.

Here we report the first prospective epidemiological study to examine the association between dietary acrylamide intake and lung cancer risk.

Methods

Study Design and Participants

This study was conducted within the prospective Netherlands Cohort Study (NLCS) on Diet and Cancer, which started in September 1986 with the inclusion of 58 279 men and 62 573 women aged 55–69 years who were randomly sampled from Dutch municipal registries (11). At baseline, study participants were sent a questionnaire on diet and other risk factors for cancer, such as smoking and physical activity, that was designed to be self-administered. Participants were informed that by returning the completed questionnaire they would be giving their consent to participate in a study of the etiology of cancer in relation to diet. This procedure of informed consent was approved by the Medical Ethics Committees of the University Hospital Maastricht and the Netherlands Organisation for Applied Scientific Research.

A case–cohort approach (12) was used for data processing and analysis; case subjects were derived from the entire cohort, and the number of person-years at risk for the entire cohort was estimated from a subcohort of 5000 men and women who were randomly sampled from the full cohort at baseline. Incident lung cancer cases in the total cohort were detected by computerized record linkages to the Netherlands Cancer Registry and the Netherlands Pathology Registry. The completeness of cancer follow-up through linkage with these cancer registries is at least 96% (13), and follow-up of the subcohort at the end of the 13.3-year follow-up period (September 17, 1986, up to January 1, 2000) was nearly 100% complete (only two male subcohort members were lost to follow-up). Further details on the design of the study and methods of follow-up have been published previously (11,14,15).

Case subjects and subcohort members were excluded from this analysis if they had been diagnosed with any cancer (except skin cancer) at baseline and if their dietary data were incomplete or inconsistent. Figure 1 shows the selection and exclusion steps that resulted in the numbers of case subjects and subcohort members that were included in the analysis.

According to the formula of Cai and Zeng (16), the power was 80% to detect a statistically significant ($\alpha = .05$) association with a hazard ratio (HR) of 1.35 or higher (analyzing all male case subjects) or 1.90 or higher (for the smallest case group in men, those with large cell tumors), when comparing the highest with the lowest quintile of acrylamide intake. For women the power was 80% to detect a statistically significant ($\alpha = .05$) association with an HR of 1.65 or higher for overall lung cancer or 3.2 or higher for large cell tumors (the smallest case group in women), when comparing the highest with the lowest quintile of acrylamide intake.

Acrylamide Intake Assessment

The NLCS food-frequency questionnaire contained questions on 150 food items (14,15). It queried the habitual intake, in terms of frequency and, for most foods, portion size, of foods consumed by the participant during the year preceding baseline. The major dietary sources of acrylamide in the Netherlands in 1998 (determined through a National Food Consumption Survey) were estimated to be potato crisps (31% of the total), French fries (21%), Dutch spiced cake (16%), coffee (13%), bread (10%), and cookies (4%) (17). All of these foods were included as separate items in the NLCS food-frequency questionnaire. Thus, the most important sources of dietary acrylamide in the Netherlands were taken into account in the acrylamide exposure assessment.

We used data from the Dutch Food and Consumer Product Safety Authority on acrylamide levels in foods that were sampled from Dutch shops in 2002 and 2005 to obtain an intake estimate representative for our study population. Chemical acrylamide measurements in cookies were done in several types of cookies that are known to be eaten most frequently by a population comparable to the NLCS, according to information from the development phase of the questionnaire. The acrylamide level that was used for cookies in this acrylamide intake estimation was based on the acrylamide level of the specific types of cookies weighted by the relative frequency of consumption of the NLCS-comparable

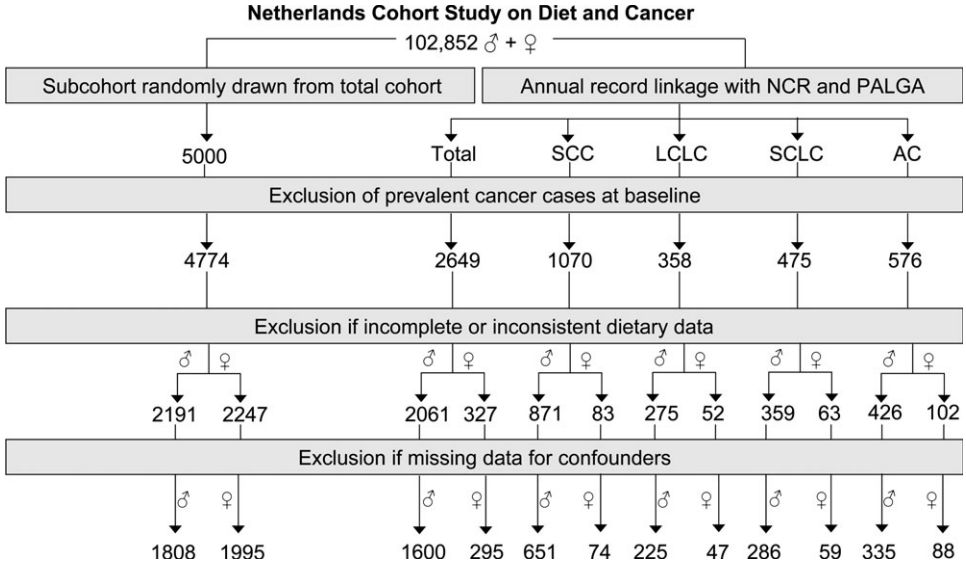

Figure 1. Flow diagram of subcohort members and case subjects on whom the analyses were based; LCLC = large cell lung carcinoma; SCLC = small cell lung carcinoma; NCR = Netherlands Cancer Registry; PALGA = Netherlands Pathology Registry; AC = adenocarcinoma; SCC = squamous cell carcinoma.

population. The same was done to estimate acrylamide levels for other composite food items, such as pies and chocolates.

We performed a validation study to investigate whether using mean acrylamide levels for foods that vary widely in their acrylamide content results in a sound estimate of total acrylamide intake (E. J. M. Konings, PhD, J. G. F. Hogervorst, MSc, L. van Rooij, MSc, L. J. Schouten, MD PhD, E. A. Sizoo, H. P. van Egmond, et al., MSc, unpublished observations 2008). For this validation study, we used 39 collected 24-hour duplicate diets that were collected by the Dutch National Institute for Public Health and the Environment in 2004. A 24-hour duplicate diet is the collection of duplicate portions of everything eaten and drunk during 24 hours by an individual. The 39 participants in the duplicate diet study were asked to keep a diary in which they reported the amounts of specific foods that they ate during the 24 hours; we used the information in those diaries to estimate the acrylamide content of the 24-hour diets as the amount of specific food multiplied by the mean acrylamide level of a specific food that was also used for the NLCS acrylamide intake assessment. Subsequently, the acrylamide levels of the duplicate diets were chemically analyzed by liquid chromatography-tandem mass spectrometry using the method of Rosén and Hellenas (18) and correlated to the acrylamide content estimated from the diaries, which rendered a Spearman correlation coefficient of .82 ($P < .001$). This good correlation indicates that it is feasible to make a reliable rank ordering of acrylamide intake via a 24-hour diet by using mean acrylamide levels for individual foods. Further details of the intake assessment, including levels of acrylamide in foods, are presented elsewhere (4).

Statistical Analysis

Confounders were selected in two steps: some were chosen a priori to be included in the models. Others were only included if they changed the age- and sex-adjusted hazard ratio of lung cancer for a 27-μg/d increment of acrylamide intake (27 μg/d is the difference between the 10th and 90th percentile of acrylamide intake of the subcohort) by more than 10% compared with the age- and sex-adjusted hazard ratio. The a priori–selected covariables were age (years); sex; family history of lung cancer (yes or no); smoking status (current or not current); number of cigarettes smoked per day; duration of smoking (years); body mass index (BMI, kg/m^2); energy intake (kcal/d); consumption of vegetables (g/d), fruits (g/d), and alcohol (g/d); educational level (primary school, lower vocational school, intermediate vocational/high school, or higher vocational school or university); and, for the analyses of men, pipe and cigar smoking (never or former or current, number smoked per day, and number of years of smoking for pipe and cigar separately). The following variables were checked for confounding with the 10% change criterion that was described above: height (cm); nonoccupational physical activity (min/d); consumption of dairy (g/d), meat (g/d), processed meat (g/d), and fish (g/d); intake of vitamins A (mg/d) and C (mg/d), α-carotene (μg/d), β-carotene (μg/d), selenium (μg/d), folate (μg/d), niacin (mg/d), total fat (g/d), saturated fat (g/d), trans-fatty acid (g/d), carbohydrates (g/d), and fiber (g/d); and use of vitamin A supplements (yes or no). In separate analyses, we additionally adjusted for the following passive smoking variables: smoking by the parents in the period that the participant lived with his or her parents (no, both, mother only, father only); smoking by the partner in the presence of the participant (never or former or current), and number of hours per day spent in a smoky room. In other separate analyses, we additionally adjusted separately for consumption of the five most important dietary sources of acrylamide in this cohort: coffee (g/d), Dutch spiced cake (g/d), cookies (g/d), potato crisps (g/d), and French fries (g/d) (4).

Compared with nonsmokers, smokers have, on average, three to four times higher levels of acrylamide–hemoglobin adducts, which are a biomarker for exposure to acrylamide (19). For this reason, and because smoking is such an important risk factor for lung cancer, subgroup analyses were performed for never smokers. For men, this subgroup included cigar and pipe smokers, and in those analyses, we adjusted for pipe and cigar smoking. There were virtually no female cigar or pipe smokers in this study population (five cigar smokers in the subcohort, and one cigar smoker and one pipe smoker among the large cell lung cancer case subjects), and therefore we did not adjust the hazard ratios for women for pipe and cigar smoking. Hazard ratios and 95% confidence intervals (CIs)

were obtained through Cox proportional hazards regression (20) using STATA software (release 9.2, 2005; STATA Corporation, College Station, TX) with person-years at risk as the time metric. Scaled Schoenfeld residuals were used to test the proportional hazards assumption (21). The assumption was not violated. 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, a method similar to the variance– covariance estimator of Barlow (12). Tests for dose–response trends were performed by fitting the median acrylamide intake per quintile or tertile as a continuous variable. We considered 100 and 60 case subjects as the minimum number needed to do analyses with acrylamide exposure categorized into quintiles and tertiles, respectively, and assumed that 20 case subjects were needed to analyze acrylamide exposure as a continuous variable.

To examine the influence of preclinical disease on the results, the analyses were also performed with exclusion of case patients with cancer detected in the first 2 years of follow-up. We also performed subgroup analyses among participants who had no occupational exposure to biological dust, mineral dust, or gases or fumes [as defined according to the community-based job exposure matrix (ALOHA JEM) that was developed to translate occupation into none, low, or high exposure to biological dust, mineral dust, or gases or fumes (22)]. Effect modification of the association between acrylamide intake and lung cancer by other variables was tested using Wald χ^2 tests. The variables that were tested for effect modification were selected according to their ability to modify the activity of CYP2E1 (23–26), the enzyme that converts acrylamide to genotoxic glycidamide (27). These variables were age (55–59, 60–64, 65–69 years), diabetes (ever or never diagnosed of diabetes), obesity (BMI >30 kg/m^2), smoking (smoking status and both duration of smoking in years and number of cigarettes smoked per day), alcohol consumption (0, >0 to 5, >5 g/d), and physical activity (<30, 30 to <60, 60 to <90, ≥90 min/d). All reported *P* values were from two-sided tests. A *P* value less than .05 was considered to be statistically significant.

Results

After 13.3 years of follow-up (September 17, 1986, up to January 1, 2000), there were 2238 cases of primary, histologically verified lung cancer (International Classification of Diseases for Oncology-3 code: C34). The characteristics of the subcohort and the lung cancer case subjects by sex and by histological subtype are shown in Table 1. Apart from the expected higher frequency, quantity, and duration of smoking among case subjects than among subcohort members, there were clear differences in fruit and alcohol intake. Case subjects, regardless of the type of lung cancer that they had, consumed less fruit and had a higher alcohol intake than subcohort members. In addition, among the male participants, case subjects, regardless of lung cancer type, were older than subcohort members, whereas among the female participants this was not the case.

The interaction between acrylamide intake and sex was statistically significant or borderline statistically significant in most case subject groups ($P_{interaction}$ = .06, .08, and <.01 for all case subjects with any lung cancer, small cell carcinoma, and adenocarcinoma, respectively). Therefore, the hazard ratios for lung cancer according to histological subtype are shown separately for men (Table 2) and women (Table 3).

In men (smokers and nonsmokers combined), acrylamide intake was not associated with the risk of lung cancer overall. The multivariable-adjusted hazard ratio of lung cancer for a 10-μg/d increment of acrylamide intake was 1.03 (95% CI = 0.96 to 1.11), and there was no trend over the quintiles of acrylamide intake. Acrylamide was also not associated with the risk of any of the histological subtypes of lung cancer. For male never smokers, there were increased hazard ratios in the second and third tertiles of acrylamide intake, but the 95% confidence intervals were wide. When acrylamide intake was treated as a continuous variable, there was no evidence of an increased risk of lung cancer (HR = 0.93; 95% CI = 0.66 to 1.32). Because of the small number of male never smokers, it was not possible to investigate if the increased risks in this group were due to a particular subtype of lung cancer.

In women, there was a statistically significantly decreased risk of overall lung cancer associated with increasing acrylamide intake, both for the continuous acrylamide variable (multivariable-adjusted HR per 10-μg/d increment of acrylamide intake = 0.82; 95% CI = 0.69 to 0.96) and across the intake quintiles (multivariable-adjusted HR for highest vs lowest quintile = 0.45; 95% CI = 0.27 to 0.76; P_{trend} = .01). For never-smoking women, there was also an inverse association between acrylamide intake and overall lung cancer risk, with a borderline statistically significant multivariable-adjusted hazard ratio for the continuous acrylamide variable (HR = 0.78; 95% CI = 0.61 to 1.00) and an inverse trend across the tertiles of acrylamide intake with a statistically nonsignificant *P* for trend. Within the female subgroups based on histological subtypes, a statistically nonsignificant inverse trend across the tertiles of acrylamide intake was observed for squamous cell cancer (although the hazard ratio for the continuous acrylamide variable was not significantly decreased) and most strongly for adenocarcinoma, for which the hazard ratio in the third tertile compared with the first tertile was 0.40 (95% CI = 0.21 to 0.78; P_{trend} = .01).

The null associations for men and the inverse associations for women remained unchanged when we additionally adjusted for passive smoking by the parents and by the domestic partner and for the number of hours per day spent in a smoky room (data not shown). In addition, adjustment for intake of coffee, Dutch spiced cake, cookies, potato crisps, or French fries did not result in substantially different hazard ratios (data not shown).

The results for both men and women did not change substantially when we excluded case subjects who were diagnosed during the first 2 years of follow-up (data not shown). In addition, in subgroup analyses among participants who were never occupationally exposed to biological dust, mineral dust, or gases or fumes, the results were not substantially changed (data not shown).

In men, there were no statistically significant *P* values for interaction for any of the variables tested for total lung cancer (Table 4). However, men with the lowest alcohol intake had a statistically significantly increased acrylamide-associated risk of lung cancer when acrylamide intake was treated as a continuous variable (HR per 10-μg/d increment = 1.28; 95% CI = 1.06 to 1.56).

Table 1. Characteristics of lung cancer case subjects and subcohort members, the Netherlands Cohort Study on Diet and Cancer, 1986–1999*

	Men					Women				
Variable	**Subcohort**	**SCC**	**LCLC**	**SCLC**	**AC**	**Subcohort**	**SCC**	**LCLC**	**SCLC**	**AC**
Number of persons	2191	871	275	359	426	2247	83	52	63	102
Dietary variables										
Acrylamide intake, μg/d	22.6 (12.2)	22.9 (11.9)	22.7 (11.4)	22.8 (12.6)	22.4 (11.6)	21.0 (11.9)	21.5 (16.1)	22.8 (13.5)	20.7 (10.3)	17.7 (9.1)
Acrylamide intake, μg/kg body weight per day	0.29 (0.16)	0.30 (0.16)	0.30 (0.15)	0.30 (0.19)	0.30 (0.16)	0.32 (0.19)	0.34 (0.27)	0.36 (0.23)	0.31 (0.15)	0.27 (0.15)
Coffee, g/d	578 (290)	685 (334)	648 (295)	677 (321)	641 (322)	497 (245)	623 (349)	671 (481)	643 (355)	527 (351)
Dutch spiced cake, g/d	4.1 (8.6)	3.3 (7.4)	3.2 (7.2)	3.8 (9.4)	4.0 (1.3)	5.7 (9.4)	4.8 (10.6)	4.6 (7.6)	3.8 (7.8)	3.1 (6.1)
Cookies, g/d	13.5 (10.6)	11.9 (10.9)	12.7 (10.2)	11.8 (11.1)	11.5 (11.5)	13.7 (11.0)	9.3 (10.4)	9.6 (9.2)	9.7 (9.2)	9.2 (8.8)
Potato crisps, g/d	0.47 (1.72)	0.37 (1.51)	0.48 (2.09)	0.44 (2.16)	0.41 (1.87)	0.40 (1.93)	0.29 (1.17)	0.93 (2.91)	0.43 (1.92)	0.40 (1.70)
French fries, g/d	7.2 (15.4)	6.9 (15.1)	6.5 (15.3)	6.1 (10.9)	6.5 (14.7)	4.0 (8.7)	4.8 (8.6)	3.7 (9.6)	4.0 (6.3)	3.5 (7.6)
Total energy intake, kcal/d	2166 (511)	2181 (517)	2161 (472)	2150 (477)	2175 (509)	1686 (398)	1726 (415)	1686 (469)	1666 (437)	1731 (393)
Carbohydrate, g/d	227 (66)	224 (65)	223 (62)	221 (63)	224 (60)	179 (48)	178 (50)	184 (62)	172 (50)	174 (45)
Saturated fat, g/d	36.9 (12.0)	36.7 (12.2)	36.4 (12.0)	36.3 (11.0)	36.7 (12.4)	29.8 (9.8)	31.7 (12.0)	29.0 (10.3)	29.0 (9.6)	32.3 (10.6)
Trans-fatty acid, g/d	3.3 (1.7)	3.3 (1.7)	3.3 (1.7)	3.2 (1.4)	3.4 (1.8)	2.5 (1.2)	2.8 (1.4)	2.5 (1.6)	2.5 (1.2)	2.7 (1.5)
Fiber, g/d	28.7 (8.7)	27.3 (8.3)	26.9 (8.6)	27.6 (8.3)	27.2 (8.1)	25.3 (7.0)	23.1 (7.6)	24.8 (7.9)	22.8 (7.9)	23.9 (6.8)
Niacin, mg/d	15.3 (4.8)	16.2 (5.5)	15.5 (5.3)	15.7 (4.6)	15.7 (5.1)	12.4 (3.4)	13.3 (4.1)	14.2 (4.7)	13.2 (3.9)	12.5 (4.3)
Vegetables, g/d	192 (85)	184 (87)	176 (86)	183 (80)	182 (75)	196 (81)	202 (82)	212 (88)	178 (83)	183 (70)
Fruit, g/d	154 (114)	132 (110)	140 (109)	131 (97)	136 (114)	196 (121)	143 (111)	179 (132)	161 (146)	186 (120)
Alcohol, g/d	15.0 (16.8)	18.9 (20.0)	19.0 (20.4)	19.0 (19.4)	18.1 (18.3)	5.9 (9.5)	9.2 (14.2)	7.4 (12.5)	9.0 (13.7)	9.1 (13.5)
Nondietary variables										
Age, y	61.3 (4.2)	62.3 (4.3)	62.6 (4.2)	62.2 (4.0)	62.0 (4.0)	61.4 (4.3)	61.0 (4.2)	61.6 (4.2)	60.7 (4.0)	61.7 (4.4)
BMI, kg/m^2	25.0 (2.6)	24.8 (2.7)	24.6 (2.8)	25.0 (2.6)	24.6 (2.8)	25.1 (3.6)	24.4 (3.5)	23.3 (3.4)	24.9 (3.5)	24.2 (3.2)
Height, cm	176 (7)	176 (7)	176 (7)	176 (7)	176 (7)	165 (6)	165 (7)	165 (5)	166 (7)	166 (6)
Nonoccupational physical activity, min/d	80 (68)	75 (69)	81 (72)	78 (73)	73 (65)	64 (53)	78 (74)	58 (49)	61 (53)	59 (61)
No. cigarettes smoked/d	14.7 (11.4)	19.2 (10.7)	17.6 (9.2)	20.3 (12.0)	19.6 (12.3)	4.6 (7.7)	18.1 (12.7)	11.6 (8.3)	16.2 (9.0)	10.5 (11.7)
No. years smoked	29.4 (15.8)	39.4 (12.0)	39.3 (12.4)	40.1 (11.2)	39.2 (11.6)	11.4 (15.8)	33.1 (15.9)	31.8 (16.4)	32.4 (13.2)	22.8 (19.2)
Cigarette smoking status, %										
Never smokers	12.7	3.8	4.4	3.3	3.1	58.4	15.7	15.4	7.9	35.3
Former smokers	51.6	30.2	35.6	26.7	38.5	20.6	13.3	19.2	11.1	20.6
Current smokers	35.7	66.0	60.0	69.9	58.5	21.0	71.1	65.4	81.0	44.1
Pipe smoking status, %										
Never smokers	84.5	82.3	86.2	86.1	83.8	100	100	98.1	100	100
Former smokers	9.2	5.7	7.6	2.8	5.6	0	0	0.0	0	0
Current smokers	6.3	11.9	6.2	11.1	10.6	0	0	1.9	0	0

(Table continues)

Table 1 (continued).

Variable	Men					Women				
	Subcohort	SCC	LCLC	SCLC	AC	Subcohort	SCC	LCLC	SCLC	AC
Cigar smoking status, %										
Never smokers	74.0	70.4	74.5	71.9	77.5	99.8	100	98.1	100	100
Former smokers	12.6	9.3	10.5	5.8	8.5	0	0	0.0	0	0
Current smokers	13.4	20.3	14.9	22.3	14.1	0.2	0	1.9	0	0
Education level, %										
Primary school	24.9	31.3	36.7	32.0	28.9	33.3	41.0	38.5	33.3	33.3
Lower vocational school	20.6	26.4	20.0	26.7	19.5	23.1	20.5	25.0	30.2	18.6
Intermediate vocational/high school	35.4	31.3	31.3	29.0	33.3	34.3	33.7	30.8	30.2	36.3
Higher vocational school/university	18.6	10.1	11.6	12.0	17.4	8.8	4.8	5.8	6.3	9.8
Family history of lung cancer, % yes	9.4	14.5	13.8	12.5	7.7	10.1	13.3	9.6	9.5	12.7

* Data represent mean values (SD) or percentages unless otherwise indicated; n represents number of subcohort members or cases after exclusion of participants with prevalent cancer at baseline and/or with incomplete or inconsistent dietary data. The number of missing values varies for the variables in this table. SCC = squamous cell carcinoma; LCLC = large cell lung carcinoma; SCLC = small cell lung carcinoma; AC = adenocarcinoma; BMI = body mass index.

For women, the *P* value for interaction between nonoccupational physical activity and acrylamide was statistically significant both for the total group of women and for the never-smoking women, but the acrylamide-associated risk of lung cancer did not increase or decrease linearly over the categories of nonoccupational physical activity but instead followed a U-shaped curve. Furthermore, among never-smoking women, those in the lowest category of alcohol intake had a lower acrylamide-associated risk of lung cancer risk than those in the higher categories of alcohol intake, with a borderline statistically significant *P* for interaction ($P = .08$).

Discussion

This prospective cohort study did not provide evidence of a positive association between dietary acrylamide intake and lung cancer risk in men.

For women we observed a statistically significant inverse association between acrylamide intake and lung cancer risk; this association was strongest for adenocarcinoma. The inverse association for women was robust in that it remained unchanged after exclusion of cases diagnosed during the first 2 years of follow-up and after adjustment for exposure to passive smoke or for consumption of foods that are important sources of dietary acrylamide in this cohort. Furthermore, after multivariable adjustment, the hazard ratios were more decreased than the age-adjusted hazard ratios, which implies that residual confounding by any of the included covariables (eg, smoking) is unlikely. In never-smoking women, the hazard ratios were decreased as well.

Our results are not in line with two mouse studies. In two strains of mice (male and female A/J mice and female Swiss-ICR mice), an increased incidence of lung cancer was observed after administration of acrylamide by gavage or intraperitoneal injection (8,9). To our knowledge, this is the first time that dietary acrylamide intake has been studied in relation to human lung cancer risk. Epidemiological studies on occupational acrylamide exposure have observed an increased risk of respiratory tract cancer (28–30), but this finding was ascribed to concurrent exposure to organic dyes. In addition, there was no evidence of a dose–response relationship, a negative finding that does not support a causal association between acrylamide exposure and respiratory tract cancer risk. Furthermore, these epidemiological studies lacked appropriate control for confounders, such as smoking, and the study populations included virtually only men.

Our study has some limitations that should be described. First, an important component of any epidemiological study on the association between dietary acrylamide intake and cancer risk is the validity and reliability of the exposure assessment. A number of sources of nondifferential misclassification of the acrylamide intake may have occurred in this study. For example, we measured acrylamide sampled in Dutch shops in 2002 and 2005, but the study participants consumed foods that were on the market before those dates. We did not ask participants whether the foods they consumed were purchased preprepared or were prepared by 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 contributed relatively little to the

Table 2. Association between dietary acrylamide intake and lung cancer risk in men, the Netherlands Cohort Study on Diet and Cancer, 1986–1999*

Case group and analysis	Quantile of intake†						
	Per 10 μg/d acrylamide	Q1 or T1 (lowest)	Q2	Q3 or T2	Q4	Q5 or T3 (highest)	P_{trend}
Overall lung cancer							
All men							
No. of case subjects/No. of person-years in subcohort	1600/21 145	310/4372	321/4009	302/4257	339/4197	328/4310	
Age-adjusted HR (95% CI)	1.04 (0.98 to 1.10)	1.00 (Referent)	1.15 (0.93 to 1.44)	1.11 (0.89 to 1.39)	1.27 (1.02 to 1.58)	1.14 (0.91 to 1.41)	.29
Multivariable-adjusted HR (95% CI)	1.03 (0.96 to 1.11)	1.00 (Referent)	1.05 (0.81 to 1.38)	0.94 (0.71 to 1.26)	1.00 (0.75 to 1.34)	1.03 (0.77 to 1.39)	.85
Never smokers							
No. of case subjects/No. of person-years in subcohort	61/3071	18/1099		21/997		22/975	
Age-adjusted HR (95% CI)	1.11 (0.87 to 1.42)	1.00 (Referent)		1.71 (0.81 to 3.62)		1.64 (0.80 to 3.39)	.23
Multivariable-adjusted HR (95% CI)	0.93 (0.66 to 1.32)	1.00 (Referent)		2.84 (0.77 to 10.46)		2.18 (0.61 to 7.82)	.37
SCC							
All men							
No. of case subjects/No. of person-years in subcohort	651/21 145	113/4372	129/4009	132/4257	138/4197	139/4310	
Age-adjusted HR (95% CI)	1.06 (0.99 to 1.14)	1.00 (Referent)	1.27 (0.94 to 1.71)	1.33 (0.99 to 1.78)	1.41 (1.05 to 1.88)	1.32 (0.98 to 1.76)	.11
Multivariable-adjusted HR (95% CI)	1.05 (0.95 to 1.15)	1.00 (Referent)	1.17 (0.82 to 1.66)	1.12 (0.77 to 1.64)	1.07 (0.73 to 1.57)	1.18 (0.80 to 1.74)	.59
Never smokers							
No. of case subjects/No. of person-years in subcohort	26/3071						
Age-adjusted HR (95% CI)	1.20 (0.81 to 1.79)	—	—	—	—	—	—
Multivariable-adjusted HR (95% CI)	0.88 (0.40 to 1.92)	—	—	—	—	—	—
LCLC							
No. of case subjects/No. of person-years in subcohort	225/21 145	47/4372	42/4009	40/4257	46/4197	50/4310	
Age-adjusted HR (95% CI)	1.05 (0.95 to 1.16)	1.00 (Referent)	1.01 (0.65 to 1.58)	0.99 (0.63 to 1.57)	1.16 (0.75 to 1.80)	1.15 (0.75 to 1.77)	.40
Multivariable-adjusted HR (95% CI)	1.07 (0.94 to 1.21)	1.00 (Referent)	0.89 (0.55 to 1.44)	0.83 (0.49 to 1.40)	0.95 (0.57 to 1.59)	1.08 (0.65 to 1.79)	.50
SCLC							
No. of case subjects/No. of person-years in subcohort	286/21 145	52/4372	64/4009	57/4257	54/4197	59/4310	
Age-adjusted HR (95% CI)	1.04 (0.94 to 1.15)	1.00 (Referent)	1.37 (0.92 to 2.04)	1.25 (0.83 to 1.88)	1.20 (0.79 to 1.81)	1.22 (0.81 to 1.82)	.67
Multivariable-adjusted HR (95% CI)	1.07 (0.94 to 1.23)	1.00 (Referent)	1.32 (0.84 to 2.07)	1.14 (0.69 to 1.90)	1.08 (0.65 to 1.78)	1.23 (0.74 to 2.06)	.71
AC							
No. of case subjects/No. of person-years in subcohort	335/21 145	69/4372	71/4009	57/4257	77/4197	61/4310	
Age-adjusted HR (95% CI)	0.99 (0.91 to 1.09)	1.00 (Referent)	1.15 (0.80 to 1.65)	0.93 (0.63 to 1.37)	1.27 (0.89 to 1.83)	0.94 (0.65 to 1.37)	.81
Multivariable-adjusted HR (95% CI)	0.97 (0.86 to 1.10)	1.00 (Referent)	1.04 (0.69 to 1.56)	0.80 (0.51 to 1.26)	1.01 (0.64 to 1.58)	0.85 (0.53 to 1.36)	.53

* HR for all men adjusted for age, body mass index, energy intake, alcohol intake, vegetable consumption, fruit consumption, lung cancer in the family, nonoccupational physical activity, education level, niacin intake, cigarette smoking status, number of cigarettes per day, number of years of smoking cigarettes, pipe smoking status, number of pipes per day, number of years of smoking pipes, cigar smoking status, number of cigars per day, number of years of smoking cigars. HR for never smokers adjusted for age, body mass index, energy intake, alcohol intake, vegetable consumption, fruit consumption, lung cancer in the family, nonoccupational physical activity, education level, niacin intake, number of cigarettes per day, number of years of smoking cigarettes (and for total and men: pipe smoking status, number of pipes per day, number of years of smoking pipes, cigar smoking status, number of cigars per day, number of years of smoking cigars). Q = quintile; T = tertile; HR = hazard ratio; CI = confidence interval; SCC = squamous cell carcinoma; LCLC = large cell lung carcinoma; SCLC = small cell lung carcinoma; AC = adenocarcinoma; – = insufficient number of cases.

† The median acrylamide intake of the male subcohort in the quintiles was 10.8, 15.6, 19.6, 25.4, and 37.6 μg/d and in the tertiles: 12.8, 19.6, and 32.8 μg/day.

Table 3. Association between dietary acrylamide intake and lung cancer risk in women, the Netherlands Cohort Study on Diet and Cancer, 1986–1999*

		Quantile of intake†					
Case group and analysis	**Per 10 μg/d acrylamide**	**Q1 or T1 (lowest)**	**Q2**	**Q3 or T2**	**Q4**	**Q5 or T3 (highest)**	P_{trend}
Overall lung cancer							
All women							
No. of case subjects/No. of person-years in subcohort	295/24928	66/4788	54/5057	62/4909	62/5168	51/5006	
Age-adjusted HR (95% CI)	0.94 (0.84 to 1.06)	1.00 (Referent)	0.78 (0.53 to 1.15)	0.92 (0.63 to 1.34)	0.87 (0.60 to 1.27)	0.74 (0.50 to 1.10)	.23
Multivariable-adjusted HR (95% CI)	0.82 (0.69 to 0.96)	1.00 (Referent)	0.66 (0.42 to 1.04)	0.60 (0.38 to 0.96)	0.58 (0.36 to 0.95)	0.45 (0.27 to 0.76)	.01
Never smokers							
No. of case subjects/No. of person-years in subcohort	73/14835	35/5061		20/4846		18/4927	
Age-adjusted HR (95% CI)	0.80 (0.64 to 1.01)	1.00 (Referent)		0.70 (0.40 to 1.25)		0.65 (0.36 to 1.16)	.18
Multivariable-adjusted HR (95% CI)	0.78 (0.61 to 1.00)	1.00 (Referent)		0.70 (0.38 to 1.30)		0.62 (0.33 to 1.16)	.18
SCC							
No. of case subjects/No. of person-years in subcohort	74/24928	27/8129		23/8390		24/8408	
Age-adjusted HR (95% CI)	1.07 (0.85 to 1.35)	1.00 (Referent)		0.77 (0.43 to 1.40)		0.97 (0.56 to 1.69)	.91
Multivariable-adjusted HR (95% CI)	0.95 (0.66 to 1.35)	1.00 (Referent)		0.50 (0.24 to 1.03)		0.56 (0.27 to 1.16)	.32
LCLC							
No. of case subjects/No. of person–years	47/24928						
Age-adjusted HR (95% CI)	1.11 (0.88 to 1.40)	—	—	—	—	—	—
Multivariable-adjusted HR (95% CI)	0.93 (0.73 to 1.20)	—	—	—	—	—	—
SCLC							
No. of case subjects/No. of person-years in subcohort	59/24928						
Age-adjusted HR (95% CI)	0.89 (0.73 to 1.10)	—	—	—	—	—	—
Multivariable-adjusted HR (95% CI)	0.75 (0.54 to 1.06)	—	—	—	—	—	—
AC							
All women							
No. of case subjects/No. of person-years in subcohort	88/24928	45/8129		26/8390		17/8408	
Age-adjusted HR (95% CI)	0.71 (0.57 to 0.88)	1.00 (Referent)		0.67 (0.41 to 1.10)		0.51 (0.30 to 0.88)	.02
Multivariable-adjusted HR (95% CI)	0.61 (0.45 to 0.81)	1.00 (Referent)		0.62 (0.35 to 1.10)		0.40 (0.21 to 0.78)	.01
Never smokers							
No. of case subjects/No. of person-years in subcohort	34/14835						
Age-adjusted HR (95% CI)	0.71 (0.48 to 1.06)	—	—	—	—	—	—
Multivariable-adjusted HR (95% CI)	0.77 (0.54 to 1.12)	—	—	—	—	—	—

* HR whole group adjusted for age, body mass index, energy intake, alcohol intake, vegetable consumption, fruit consumption, lung cancer in the family, nonoccupational physical activity, education level, niacin intake, cigarette smoking status, number of cigarettes per day, number of years of smoking cigarettes. HR never smokers adjusted for age, body mass index, energy intake, alcohol intake, vegetable consumption, fruit consumption, lung cancer in the family, nonoccupational physical activity, education level, niacin intake. Q = quintile; T = tertile; SCC = squamous cell carcinoma; LCLC = large cell lung carcinoma; SCLC = small cell lung carcinoma; AC = adenocarcinoma; – = insufficient number of cases.

† The median acrylamide intake of the female subcohort in the quintiles was 9.5, 14.0, 17.9, 24.3, and 36.8 μg/d and in the tertiles: 11.4, 17.9 and 32.1 μg/day.

Table 4. Hazard ratios (per 10-μg/d increment of acrylamide intake) of lung cancer for strata of several covariables and tests for interaction, the Netherlands Cohort Study on Diet and Cancer, 1986–1999*

	Categories				
Variable and HRs	**I**	**II**	**III**	**IV**	$P_{interaction}$
Men					
Age at baseline, years	55–59	60–64	65–69		
HR (95% CI)	1.11 (0.98 to 1.26), n = 503	1.00 (0.87 to 1.16), n = 568	0.94 (0.81 to 1.09), n = 529		.31
HR never smokers (95% CI)	0.70 (0.27 to 1.80), n = 12	1.06 (0.58 to 1.96), n = 18	0.88 (0.59 to 1.31), n = 36		.26
Smoking status	Never	Ex	Current		.55
HR (95% CI)	0.93 (0.66 to 1.30), n = 61	0.98 (0.87 to 1.11), n = 522	1.06 (0.95 to 1.18), n = 1017		
No. cigarettes smoked/d	0	0 to <15	≥15		
HR (95% CI)	0.93 (0.66 to 1.30), n = 61	1.03 (0.91 to 1.16), n = 400	1.04 (0.94 to 1.16), n = 1139		.86
No. years smoked	0	0 to <30	≥30		
HR (95% CI)	0.93 (0.66 to 1.30), n = 61	0.98 (0.82 to 1.18), n = 146	1.03 (0.95 to 1.12), n = 1393		.67
BMI >30 kg/m^2	No	Yes			
HR (95% CI)	1.03 (0.96 to 1.11), n = 1540	0.76 (0.37 to 1.55), n = 60			
HR never smokers (95% CI)	0.92 (0.64 to 1.32), n = 58	n = 3†			.80
Diabetes	No	Yes			†
HR (95% CI)	1.04 (0.97 to 1.13), n = 1548	0.71 (0.32 to 1.59), n = 52			.33
HR never smokers (95% CI)	0.90 (0.63 to 1.30), n = 59	n = 2†			†
Nonoccupational physical activity, min/d	<30	30–60	60–90	>90	
HR (95% CI)	0.99 (0.87 to 1.13), n = 350	1.07 (0.90 to 1.27), n = 460	0.95 (0.76 to 1.18), n = 295	1.09 (0.94 to 1.27), n = 495	.20
HR never smokers (95% CI)	0.86 (0.40 to 1.84), n = 17	1.68 (0.97 to 2.92), n = 21	0.93 (0.39 to 2.20), n = 11	0.78 (0.36 to 1.71), n = 17	.10
Alcohol intake, g/d	0	>0 to 5	>5		
HR (95% CI)	1.28 (1.06 to 1.56), n = 199	1.04 (0.88 to 1.23), n = 278	0.97 (0.88 to 1.07), n = 1123		.11
HR never smokers (95% CI)	n = 9†	0.58 (0.15 to 2.19), n = 12	0.62 (0.39 to 0.98), n = 40		†
Women					
Age at baseline, years	55–59	60–64	65–69		
HR (95% CI)	0.89 (0.68 to 1.17), n = 116	0.64 (0.44 to 0.93), n = 100	0.85 (0.66 to 1.09), n = 79		.51
HR never smokers (95% CI)	0.56 (0.30 to 1.07), n = 15	0.59 (0.34 to 1.03), n = 28	0.98 (0.72 to 1.33), n = 30		.56
Smoking status	Never	Ex	Current		.19
HR (95% CI)	0.78 (0.61 to 1.00), n = 73	0.83 (0.58 to 1.18), n = 47	0.77 (0.57 to 1.05), n = 175		
No. cigarettes smoked/d	0	0 to <15	≥15		
HR (95% CI)	0.78 (0.61 to 1.00), n = 73	0.86 (0.68 to 1.08), n = 75	0.85 (0.63 to 1.14), n = 147		.49
No. years smoked	0	0 to <30	≥30		
HR (95% CI)	0.78 (0.61 to 1.00), n = 73	0.80 (0.58 to 1.11), n = 40	0.82 (0.62 to 1.09), n = 182		.71
BMI >30 kg/m^2	No	Yes			
HR (95% CI)	0.79 (0.66 to 0.94), n = 277	1.03 (0.64 to 1.67), n = 18			
HR never smokers (95% CI)	0.78 (0.60 to 1.01), n = 68	n = 5†			.30

(Table continues)

Table 4 (continued).

Variable and HRs	Categories				$P_{interaction}$
	I	II	III	IV	
Diabetes	No	Yes			†
HR (95% CI)	0.82 (0.69 to 0.97), n = 282	n = 13†			
HR never smokers (95% CI)	0.78 (0.60 to 1.01), n = 70	n = 3†			†
Nonoccupational physical activity, min/d	<30	30–60	60–90	>90	
HR (95% CI)	0.85 (0.64 to 1.12), n = 94	0.54 (0.34 to 0.83), n = 80	0.57 (0.36 to 0.90), n = 56	1.14 (0.83 to 1.56), n = 65	.01
HR never smokers (95% CI)	0.98 (0.63 to 1.51), n = 23	0.60 (0.40 to 0.90), n = 22	0.48 (0.19 to 1.21), n = 12	1.10 (0.61 to 1.99), n = 16	.03
Alcohol intake, g/d	0	>0 to 5	>5		
HR (95% CI)	0.74 (0.55 to 1.00), n = 102	0.94 (0.68 to 1.29), n = 73	0.76 (0.56 to 1.02), n = 120		.97
HR never smokers (95% CI)	0.55 (0.33 to 0.91), n = 30	0.95 (0.64 to 1.41), n = 27	0.91 (0.52 to 1.59), n = 16		.08

* HR for whole group adjusted for age, body mass index, energy intake, alcohol intake, vegetable consumption, fruit consumption, lung cancer in the family, nonoccupational physical activity, education level, niacin intake, cigarette smoking status, number of cigarettes per day, number of years of smoking cigarettes (and for men: pipe smoking status, number of pipes per day, number of years of smoking pipes, cigar smoking status, number of cigars per day, number of years of smoking cigars). HR for never smokers adjusted for age, body mass index, energy intake, alcohol intake, vegetable consumption, fruit consumption, lung cancer in the family, nonoccupational physical activity, education level, niacin intake, number of cigarettes per day, number of years of smoking cigarettes (and for men: pipe smoking status, number of pipes per day, number of years of smoking pipes, cigar smoking status, number of cigars per day, number of years of smoking cigars). HR = hazard ratio; CI = confidence interval; n = number of cases in analysis; BMI = body mass index.

† Insufficient number of cases.

acrylamide intake and to the variance in acrylamide intake in this cohort (4). Furthermore, acrylamide levels vary considerably within food items, such as French fries. However, all of these sources of nondifferential misclassification would bias the true association toward the null, so that the inverse association for women that we observed might be even stronger. On the other hand, our acrylamide intake assessment also has an important strength in that we only used acrylamide levels in foods sampled from Dutch shops and specifically sampled and analyzed foods that were relevant for the NLCS population.

Second, although we checked extensively for variables that confounded the association between acrylamide intake and lung cancer risk, confounding by unknown confounders might be an alternative explanation for the observed associations.

Finally, for the interaction analyses, the fact that we calculated hazard ratios for many small subgroups makes it likely that some of the observed statistically significant *P* values for interaction or hazard ratios in subgroups did not represent true associations and should therefore be interpreted with caution. The observations reported here need confirmation or refutation from other epidemiological studies in independent cohorts.

It is assumed that genotoxic compounds have no threshold below which exposure to this compound does not entail a risk of cancer. There are several indications that acrylamide is genotoxic in vitro and in vivo, mainly after it is metabolized to glycidamide. Acrylamide causes clastogenic effects (chromosome aberrations, micronuclei, or sister chromatid exchanges); glycidamide induces the same effects at lower doses and forms DNA adducts, which can lead to point mutations (31). Because of this presumed genotoxicity, linear extrapolation from high chronic doses in rats to low chronic doses in humans is applied in acrylamide risk assessment. The outcome of these extrapolations is that an acrylamide intake of 1 μg/kg body weight per day in humans corresponds to a relative risk of cancer in humans of between 1.006 and 1.05 (32) (in the Netherlands, the mean intake is approximately 0.5 μg/kg body weight per day) (17). The increased relative risks of endometrial, ovarian, renal cell, and estrogen receptor–positive breast cancer observed in recent epidemiological studies of acrylamide exposure (4–6) are at least 10- to 100-fold higher than what would have been expected from the animal studies. Although these epidemiological results need to be confirmed, they raise the possibility that risk extrapolation based on animal results might underestimate human cancer risk associated with acrylamide exposure instead of rendering conservative risk estimates, as is often presumed to be the case when using linear dose extrapolation. This underestimation might be due to a steeper dose–response relationship at lower doses than at higher doses or to entirely different mechanisms that operate at different dose levels or in different species. Epidemiological studies are important because they investigate the risks in the relevant species at the relevant doses.

The inverse association between dietary acrylamide intake and the risk of lung cancer that we observed for women may indicate that acrylamide is involved in human carcinogenesis through another pathway besides genotoxicity. The theory of a hormonal pathway of acrylamide carcinogenicity was first suggested because of the predominantly hormone-sensitive sites at which cancer occurred after administration of acrylamide in animal studies

(7,10). Furthermore, the frequency distribution of glycidamide DNA adducts across different tissues did not match the frequency with which cancers arose in particular tissues in animals (33), suggesting that genotoxicity may not be the only relevant cancer-causing characteristic of acrylamide. Consistent with the possibility that hormonal factors might be at the basis of the carcinogenic action of acrylamide, we observed positive associations between acrylamide intake and endometrial and ovarian cancer risk (4), and a Danish study observed a positive association between acrylamide–hemoglobin adducts in the blood and the risk of estrogen receptor–positive breast cancer (6). The established risk factors for these cancers are predominantly related to hormonal levels.

Studies in rats have produced conflicting evidence for the role of acrylamide in the disruption of endocrine systems. Acrylamide was shown to influence levels of prolactin, testosterone, estrogen, and progesterone (34–36), but in a study of male rats, no clear influence of acrylamide on the hypothalamus–pituitary–thyroid axis was observed (37). In the latter study, however, no sex steroid hormones were studied. A recent in vitro study on glycidamide-induced gene expression in human breast and colon cancer cells showed increased expression of genes that catalyze the conversion of inactive androgen and estrogen precursors to active forms, such as testosterone and 17β-estradiol (38).

Several lines of evidence indicate the involvement of sex hormones in lung cancer etiology. Normal human lung tissue and lung tumor tissue contain estrogen [especially estrogen receptor-β (ER-β) in contrast to, for instance, endometrial tissues, which contain mainly ER-α (39)], progesterone, and androgen receptors, and the expression of the receptors differs between men and women and among lung cancer subtypes (40–42). Adenocarcinomas, for example, express ER-β to a higher extent than squamous cell carcinomas (42). Several epidemiological studies have looked at the association between postmenopausal hormone treatment and female lung cancer risk, and some of these studies showed a decreased risk of postmenopausal hormone treatment (43,44). It is interesting that within the NLCS the associations between postmenopausal hormone treatment, oral contraceptive use, and BMI and lung cancer risk were opposite to those with endometrial and ovarian cancer, for which we observed positive associations with acrylamide exposure (4). On the basis of the above-mentioned, albeit still fragmented observations (sex hormone level changes in rats, increased expression of sex hormone precursor genes, estrogen receptors in lung tissue, and associations between reproductive factors and lung cancer risk), we hypothesize that acrylamide may alter hormonal balances in such a way that it decreases lung cancer risk in women but increases endometrial and ovarian cancer risk. We strongly encourage other research groups to examine the association between dietary acrylamide intake and the risk of lung cancer, separately among men and women and stratified by smoking status and alcohol consumption.

References

1. 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(17):4998–5006.
2. International Agency for Research on Cancer. *Monographs on the Evaluation of Carcinogen Risk to Humans: Some Industrial Chemicals.* Lyon, France: International Agency for Research on Cancer; 1994.
3. Cogliano V, Baan R, Straif K, et al. Future priorities for IARC Monographs. *Lancet Oncol.* 2008;9(8):708.
4. Hogervorst JG, Schouten LJ, Konings EJ, Goldbohm RA, van den Brandt PA. A prospective study of dietary acrylamide intake and the risk of endometrial, ovarian, and breast cancer. *Cancer Epidemiol Biomarkers Prev.* 2007;16(11):2304–2313.
5. Hogervorst JG, Schouten LJ, Konings EJ, Goldbohm RA, van den Brandt PA. Dietary acrylamide intake and the risk of renal cell, bladder, and prostate cancer. *Am J Clin Nutr.* 2008;87(5):1428–1438.
6. Olesen PT, Olsen A, Frandsen H, Frederiksen K, Overvad K, Tjonneland A. Acrylamide exposure and incidence of breast cancer among postmenopausal women in the Danish Diet, Cancer and Health Study. *Int J Cancer.* 2008;122(9):2094–2100.
7. 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(2):154–168.
8. Bull RJ, Robinson M, Laurie RD, et al. Carcinogenic effects of acrylamide in Sencar and A/J mice. *Cancer Res.* 1984;44(1):107–111.
9. Bull RJ, Robinson M, Stober JA. Carcinogenic activity of acrylamide in the skin and lung of Swiss-ICR mice. *Cancer Lett.* 1984;24(2):209–212.
10. Friedman MA, Dulak LH, Stedham MA. A lifetime oncogenicity study in rats with acrylamide. *Fundam Appl Toxicol.* 1995;27(1):95–105.
11. van den Brandt PA, Goldbohm RA, van 't Veer P, Volovics A, Hermus RJ, Sturmans F. A large-scale prospective cohort study on diet and cancer in the Netherlands. *J Clin Epidemiol.* 1990;43(3):285–295.
12. Barlow WE. Robust variance estimation for the case-cohort design. *Biometrics.* 1994;50(4):1064–1072.
13. Goldbohm RA, van den Brandt PA, Dorant E. Estimation of the coverage of Dutch municipalities by cancer registries and PALGA based on hospital discharge data. *Tijdschr Soc Gezondheidsz.* 1994;72(2):80–84.
14. Goldbohm RA, van den Brandt PA, Brants HA, et al. Validation of a dietary questionnaire used in a large-scale prospective cohort study on diet and cancer. *Eur J Clin Nutr.* 1994;48(4):253–265.
15. Goldbohm RA, van 't Veer P, van den Brandt PA, et al. Reproducibility of a food frequency questionnaire and stability of dietary habits determined from five annually repeated measurements. *Eur J Clin Nutr.* 1995;49(6):420–429.
16. Cai J, Zeng D. Sample size/power calculation for case-cohort studies. *Biometrics.* 2004;60(4):1015–1024.
17 Konings EJ, Baars AJ, van Klaveren JD, et al. Acrylamide exposure from foods of the Dutch population and an assessment of the consequent risks. *Food Chem Toxicol.* 2003;41(11):1569–1579.
18. Rosén J, Hellenas KE. Analysis of acrylamide in cooked foods by liquid chromatography tandem mass spectrometry. *Analyst.* 2002;127(7):880–882.
19. 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(6):531–539.
20. Cox DR. Regression models and life-tables (with discussion). *J R Stat Soc B.* 1972;34(2):187–220.
21. Schoenfeld D. Partial residual for the proportional hazards regression model. *Biometrika.* 1982;69(1):239–241.
22. Sunyer J, Kogevinas M, Kromhout H, et al. Pulmonary ventilatory defects and occupational exposures in a population-based study in Spain. Spanish Group of the European Community Respiratory Health Survey. *Am J Respir Crit Care Med.* 1998;157(2):512–517.
23. Ardies CM, Smith TJ, Kim S, Yang CS. Induction of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) activation in rat lung microsomes by chronic ethanol consumption and repeated running exercise. *Cancer Lett.* 1996;103(2):209–218.
24. Howard LA, Micu AL, Sellers EM, Tyndale RF. Low doses of nicotine and ethanol induce CYP2E1 and chlorzoxazone metabolism in rat liver. *J Pharmacol Exp Ther.* 2001;299(2):542–550.
25. Wang Z, Hall SD, Maya JF, Li L, Asghar A, Gorski JC. Diabetes mellitus increases the in vivo activity of cytochrome P450 2E1 in humans. *Br J Clin Pharmacol.* 2003;55(1):77–85.

26. Wauthier V, Verbeeck RK, Buc Calderon P. Age-related changes in the protein and mRNA levels of CYP2E1 and CYP3A isoforms as well as in their hepatic activities in Wistar rats. What role for oxidative stress? *Arch Toxicol.* 2004;78(3):131–138.
27. Ghanayem BI, Witt KL, Kissling GE, Tice RR, Recio L. Absence of acrylamide-induced genotoxicity in CYP2E1-null mice: evidence consistent with a glycidamide-mediated effect. *Mutat Res.* 2005;578(1–2): 284–297.
28. Sobel W, Bond GG, Parsons TW, Brenner FE. Acrylamide cohort mortality study. *Br J Ind Med.* 1986;43(11):785–788.
29. Marsh GM, Youk AO, Buchanich JM, Kant IJ, Swaen G. Mortality patterns among workers exposed to acrylamide: updated follow up. *J Occup Environ Med.* 2007;49(1):82–95.
30. Marsh GM, Lucas LJ, Youk AO, Schall LC. Mortality patterns among workers exposed to acrylamide: 1994 follow up. *Occup Environ Med.* 1999; 56(3):181–190.
31. Exon JH. A review of the toxicology of acrylamide. *J Toxicol Environ Health B Crit Rev.* 2006;9(5):397–412.
32. Mucci LA, Adami HO. The role of epidemiology in understanding the relationship between dietary acrylamide and cancer risk in humans. *Adv Exp Med Biol.* 2005;561:39–47.
33. Segerback D, Calleman CJ, Schroeder JL, Costa LG, Faustman EM. Formation of N-7-(2-carbamoyl-2-hydroxyethyl)guanine in DNA of the mouse and the rat following intraperitoneal administration of [14C]acrylamide. *Carcinogenesis.* 1995;16(5):1161–1165.
34. Ali SF, Hong JS, Wilson WE, Uphouse LL, Bondy SC. Effect of acrylamide on neurotransmitter metabolism and neuropeptide levels in several brain regions and upon circulating hormones. *Arch Toxicol.* 1983;52(1):35–43.
35. Mannaa F, Abdel-Wahhab MA, Ahmed HH, Park MH. Protective role of Panax ginseng extract standardized with ginsenoside Rg3 against acrylamide-induced neurotoxicity in rats. *J Appl Toxicol.* 2006;26(3):198–206.
36. Uphouse LL, Nemeroff CB, Mason G, Prange AJ, Bondy SC. Interactions between "handling" and acrylamide on endocrine responses in rats. *Neurotoxicology.* 1982;3(1):121–125.
37. Bowyer JF, Latendresse JR, Delongchamp RR, et al. The effects of subchronic acrylamide exposure on gene expression, neurochemistry, hormones, and histopathology in the hypothalamus-pituitary-thyroid axis of male Fischer 344 rats. *Toxicol Appl Pharmacol.* 2008;230(2): 208–215.
38. Clement FC, Dip R, Naegeli H. Expression profile of human cells in culture exposed to glycidamide, a reactive metabolite of the heat-induced food carcinogen acrylamide. *Toxicology.* 2007;240(1–2):111–124.
39. Harris HA, Katzenellenbogen JA, Katzenellenbogen BS. Characterization of the biological roles of the estrogen receptors, ERalpha and ERbeta, in estrogen target tissues in vivo through the use of an ERalpha-selective ligand. *Endocrinology.* 2002;143(11):4172–4177.
40. Ishibashi H, Suzuki T, Suzuki S, et al. Progesterone receptor in non-small cell lung cancer—a potent prognostic factor and possible target for endocrine therapy. *Cancer Res.* 2005;65(14):6450–6458.
41. Lin P, Chang JT, Ko JL, Liao SH, Lo WS. Reduction of androgen receptor expression by benzo[alpha]pyrene and 7,8-dihydro-9,10-epoxy-7, 8,9,10-tetrahydrobenzo[alpha]pyrene in human lung cells. *Biochem Pharmacol.* 2004;67(8):1523–1530.
42. Omoto Y, Kobayashi Y, Nishida K, et al. Expression, function, and clinical implications of the estrogen receptor beta in human lung cancers. *Biochem Biophys Res Commun.* 2001;285(2):340–347.
43. Rodriguez C, Spencer Feigelson H, Deka A, et al. Postmenopausal hormone therapy and lung cancer risk in the cancer prevention study II nutrition cohort. *Cancer Epidemiol Biomarkers Prev.* 2008;17(3):655–660.
44. Kabat GC, Miller AB, Rohan TE. Reproductive and hormonal factors and risk of lung cancer in women: a prospective cohort study. *Int J Cancer.* 2007;120(10):2214–2220.

Funding

This work was supported by the Dutch Food and Consumer Product Safety Authority (VWA). The Netherlands Cohort Study was established with funding from the Dutch Cancer Society (KWF).

Notes

Erik Konings is an employee of the governmental Dutch Food and Consumer Product Safety Authority (VWA). As such, the sponsor had a role in the collection, analysis, and interpretation of the data and the writing of the manuscript. It had no role in the design of the study and the decision to submit the manuscript for publication.

The authors thank the participants of this study, the Netherlands Cancer Registry, and the Netherlands nationwide registry of pathology (PALGA). We thank Sacha van de Crommert, Jolanda Nelissen, Conny de Zwart, Annemie Pisters from Maastricht University and Henny Brants from the Dutch National Institute for Public Health for data management assistance; Linda van den Bosch from Netherlands Organisation for Applied Scientific Research (TNO) Quality of Life and Jack Berben and Harry van Montfort from Maastricht University for programming assistance.

Manuscript received August 25, 2008; revised February 13, 2009; accepted March 5, 2009.