Dietary Acrylamide Intake and Brain Cancer Risk

Janneke G.F. Hogervorst,1 Leo J. Schouten,1 Erik J.M. Konings,2 R. Alexandra Goldbohm,3 and Piet A. van den Brandt1

1Department of Epidemiology, GROW-School for Oncology and Developmental Biology, Maastricht University, Maastricht, the Netherlands; 2Food and Consumer Product Safety Authority, Department of Research and Development, Eindhoven, the Netherlands; and 3Department of Prevention and Health, TNO Quality of Life, Leiden, the Netherlands

Abstract

Background: Acrylamide is a probable human carcinogen, which is present in several heat-treated foods. In epidemiologic studies, positive associations with endometrial, ovarian, and renal cell cancer risk have been observed. The incidence of central nervous system tumors was increased upon acrylamide administration in drinking water to rats. In the current study, the association between dietary acrylamide intake and human brain cancer risk was investigated for the first time.

Methods: In 1986, 120,852 persons (ages 55-69 years) were included in the Netherlands Cohort Study on diet and cancer. At baseline, a random subcohort of 5,000 participants was randomly selected from the total cohort for a case-cohort approach. Acrylamide intake was assessed with a food frequency questionnaire at baseline and based on acrylamide analyses in relevant Dutch foods. Hazard ratios (HR) were calculated using Cox proportional hazards analysis. Subgroup analyses were done for microscopically verified brain cancer, astrocytic gliomas, high-grade astrocytic gliomas, and never-smokers. The acrylamide risk estimates were adjusted for possible brain cancer risk factors.

Results: After 16.3 years of follow-up, 216 brain cancer cases were available for analysis. The multivariable-adjusted HR per 10 μg/d increment of acrylamide intake was 1.02 (95% confidence interval, 0.89-1.16). HRs were not significantly increased either when dietary acrylamide intake was analyzed as a categorical variable. Also, there was no association in the subgroups based on histology and smoking.

Conclusion: In this prospective cohort study, acrylamide intake was not associated with brain cancer risk.

Introduction

Acrylamide has been classified as a probable human carcinogen based on animal studies (1), and is since 2002 known to be present in several carbohydrate-rich heated foods, such as French fries and potato crisps. Recent epidemiologic studies on dietary acrylamide intake and cancer risk reported positive associations with endometrial, ovarian, and renal cell cancer risk (2, 3). An advisory group of the IARC recently gave high priority to acrylamide for assessment in future IARC Monograph series (4).

Because the acrylamide molecule is small and hydrophilic, it passively diffuses throughout the whole body, and for this reason, theoretically all tissues are targets for acrylamide carcinogenesis. The incidence of central nervous system tumors was increased upon acrylamide administration in drinking water to one of the two lifetime carcinogenicity studies with rats (5, 6). In this prospective cohort study, we investigated the association between dietary acrylamide intake and human brain cancer risk.
Acrylamide Intake Assessment. The Netherlands Cohort Study on diet and cancer food frequency questionnaire contained questions on habitual consumption of 150 food items during the year preceding the baseline. We used data on acrylamide levels in food on the Dutch market in order to obtain an intake estimate representative for the Dutch situation. The acrylamide intake was estimated from the mean acrylamide level of foods, and the frequency of consumption and portion size of the foods. For further details of the intake assessment, see ref. (2).

Statistical Analysis. Hazard ratios (HR) were obtained through Cox proportional hazards regression with STATA software (package 9.2). Smoking does not seem to be a clear risk factor for brain cancer in adults (8), but smokers have, on average, three to four times higher levels of acrylamide-hemoglobin adducts (a marker of internal doses of acrylamide) compared with non-smokers (9). Therefore, subgroup analyses were done for never-smokers. Other analyses were based on histologic subtype: astrocytic glioma (ICD-O morphology codes: M9384, M9400-9401, M9410-9411, M9420-9421, M9424, M9440-9442, and M9481; other case groups were too small for meaningful analysis), and astrocytic glioma with a high malignancy grade (M9400-9401, differentiation grade 3-4; M9410-9411, differentiation grade 3-4; M9420, differentiation grade 3-4; M9424, differentiation grade 3-4; M9440-9442, and M9481; ref. (10)). The HRs for acrylamide intake were adjusted for sex, age, and the a priori selected covariables smoking (status, quantity, and duration), body mass index, height, education level, and energy intake. The other variables from Table 1 were checked for confounding potential based on causing a change of >10% in the HR of acrylamide and incorporated as covariables if they fulfilled this criterion. We considered 100 cases as the minimum number needed for quintile analyses, 60 for tertile analyses, and 20 for analyses with acrylamide as a continuous variable.

Table 1. Characteristics of brain cancer cases and subcohort members; the Netherlands Cohort Study on diet and cancer (1986-2002)

| Variable | Subcohort | Total brain cancer | Mv brain cancer | Astrocytic glioma | High-grade astrocytic glioma |
|----------|-----------|--------------------|----------------|-------------------|-----------------------------|
| n | 4,438 | 238 | 191 | 168 | 148 |
| Dietary variables | | | | | |
| Acrylamide intake (µg/d) | 21.8 (12.1) | 22.1 (12.9) | 21.7 (12.1) | 21.7 (12.2) | 21.3 (12.0) |
| Acrylamide intake (µg/kg BW/d) | 0.30 (0.18) | 0.30 (0.19) | 0.29 (0.17) | 0.29 (0.17) | 0.29 (0.17) |
| Coffee (g/d) | 537 (271) | 546 (263) | 546 (266) | 544 (271) | 541 (275) |
| Dutch spiced cake (g/d) | 4.9 (9.0) | 5.4 (11.3) | 5.0 (10.8) | 5.0 (10.9) | 4.6 (10.5) |
| Cookies (g/d) | 13.6 (10.8) | 13.0 (9.6) | 13.4 (9.7) | 13.2 (9.8) | 13.4 (10.0) |
| Potato crisps (g/d) | 0.43 (1.83) | 0.27 (0.88) | 0.31 (0.97) | 0.34 (1.01) | 0.35 (1.05) |
| French fries (g/d) | 5.6 (12.6) | 5.2 (10.6) | 4.7 (9.1) | 4.8 (9.1) | 4.8 (9.0) |
| Total energy intake (kcal) | 1,923 (516) | 1,965 (457) | 1,985 (450) | 1,995 (451) | 2,015 (444) |
| Vegetables (g/d) | 194 (83) | 199 (91) | 202 (92) | 200 (90) | 198 (85) |
| Fruit (g/d) | 175 (120) | 171 (111) | 181 (115) | 177 (113) | 178 (115) |
| Alcohol (g/d) | 10.4 (14.4) | 12.7 (14.0) | 12.9 (13.7) | 13.1 (14.1) | 13.6 (14.3) |
| Non-dietary variables | | | | | |
| Age (y) | 61.4 (4.2) | 61.4 (4.1) | 60.9 (3.9) | 61.0 (4.0) | 60.9 (4.0) |
| BMI (kg/m²) | 25.0 (3.1) | 25.2 (2.8) | 25.2 (2.7) | 25.2 (2.7) | 25.2 (2.6) |
| Height (cm) | 171 (9) | 173 (8) | 173 (8) | 174 (8) | 174 (8) |
| Nonocc. phys. act. (min/d) | 72 (61) | 82 (72) | 81 (70) | 81 (68) | 81 (67) |
| Cigarette smoking (%) | | | | | |
| Never-smokers | 35.8 | 30.7 | 31.4 | 33.3 | 31.1 |
| Former smokers | 35.9 | 36.6 | 36.6 | 35.7 | 37.8 |
| Current smokers | 28.3 | 32.8 | 31.9 | 31.0 | 31.1 |
| n cigarettes/d | 9.5 (10.9) | 10.0 (10.8) | 10.1 (11.2) | 10.0 (11.2) | 10.3 (11.1) |
| n smoking years | 20.2 (18.2) | 23.4 (18.8) | 22.3 (18.5) | 21.9 (18.5) | 22.5 (18.2) |
| Education (%) | | | | | |
| Primary school | 29.1 | 29.0 | 27.2 | 27.4 | 28.4 |
| Lower vocational school | 21.9 | 16.0 | 15.2 | 13.7 | 13.5 |
| Intermediate vocational/high school | 34.8 | 38.7 | 39.3 | 39.9 | 38.5 |
| Higher vocational school/University | 13.6 | 14.7 | 16.2 | 17.3 | 17.6 |
| Family history of brain cancer (% yes) | 0.2 | 0.0 | 0.0 | 0.0 | 0.0 |

NOTE: Data represent means (SD), or percentages.

Mv, microscopically verified.

1 n represents the 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.

Nonoccupational physical activity.

Results

After 16.3 years of follow-up, there were 259 cases of primary brain cancer (ICD-O-3: C71), of which 205 were microscopically verified. One hundred and eighty cases were of the astrocytic glioma type, and there were 158 cases with high-grade astrocytic glioma. Table 1 shows the characteristics of the subcohort and the brain cancer cases. Cases consumed more alcohol, were more physically active, smoked more and longer, had a somewhat higher education level and body mass index, and were slightly taller than the subcohort members. There was no effect modification by sex, and therefore the association
between acrylamide intake and brain cancer risk is shown for both sexes combined. Acrylamide intake was not associated with brain cancer risk (Table 2), either adjusted only for sex and age or multivariable-adjusted. The same applied to microscopically verified brain cancer, astrocytic glioma, and high-grade astrocytic glioma. Also, in the never-smokers, no association was found. The most important acrylamide-contributing foods in this cohort (Dutch spiced cake and coffee) were by themselves also not associated with brain cancer risk (results not shown).

### Discussion

This prospective cohort study does not give support for an association between dietary acrylamide intake and human brain cancer risk, which was not studied before. Although the route of exposure differs, these results are in line with studies on occupational acrylamide exposure, which did not show excess brain cancer incidence in association with acrylamide exposure (11, 12). The number of cases in the analyses was modest, especially in the subgroups based on histology. According to the formula of Cai and Zeng (13) for case-cohort studies, the power was 80% to detect a statistically significant (significance level of 0.05) association between acrylamide intake (highest versus lowest quintile) and brain cancer risk of 1.85 or higher. The strengths of this prospective study include the absence of recall bias and selection bias, and the fact that only acrylamide data for foods from the Dutch market were used (2). Also, assigning mean acrylamide concentrations to individual foods that are known to have considerable variation in acrylamide concentrations was shown to result in a reasonable rank ordering of the acrylamide intake of the participants in a 24-hour duplicate diet study (2).

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### Table 2. Association between dietary acrylamide intake (continuous and quintiles or tertiles) and brain cancer risk; the Netherlands Cohort Study on diet and cancer (1986-2002)

| Overall | Never cigarette-smokers |
|---------|-------------------------|
| Cases (n) | Person-years (n) | HR (95% CI)* | HR (95% CI) ¹ |
| Total brain cancer | | | |
| AA (10 μg/d) | 216 | 58,473 | 0.99 (0.88-1.12) | 1.02 (0.89-1.16) |
| Q1 or T1 | 44 | 11,535 | Reference | Reference |
| Q2 | 40 | 11,619 | 0.92 (0.59-1.44) | 0.92 (0.59-1.44) |
| Q3 or T2 | 51 | 11,591 | 1.18 (0.78-1.79) | 1.20 (0.78-1.83) |
| Q4 | 45 | 11,915 | 1.03 (0.67-1.58) | 1.07 (0.68-1.68) |
| Q5 or T3 | 36 | 11,813 | 0.81 (0.52-1.29) | 0.87 (0.54-1.41) |
| P trend ¹ | | | 0.37 | 0.61 |
| Microscopically verified brain cancer | | | |
| AA (10 μg/d) | 170 | 58,473 | 0.95 (0.82-1.09) | 0.97 (0.83-1.13) |
| Q1 | 29 | 11,535 | Reference | Reference |
| Q2 | 28 | 11,619 | 1.03 (0.63-1.70) | 1.04 (0.63-1.72) |
| Q3 | 36 | 11,591 | 1.27 (0.79-2.04) | 1.32 (0.82-2.13) |
| Q4 | 36 | 11,915 | 1.14 (0.70-1.85) | 1.20 (0.73-1.99) |
| Q5 | 22 | 11,813 | 0.75 (0.44-1.28) | 0.81 (0.46-1.43) |
| P trend ¹ | | | 0.22 | 0.39 |
| Astrocytic gliomas | | | |
| AA (10 μg/d) | 151 | 58,473 | 0.97 (0.83-1.12) | 0.99 (0.84-1.16) |
| Q1 | 29 | 11,535 | Reference | Reference |
| Q2 | 28 | 11,619 | 0.97 (0.57-1.64) | 0.97 (0.57-1.65) |
| Q3 | 36 | 11,591 | 1.20 (0.73-1.98) | 1.24 (0.74-2.06) |
| Q4 | 36 | 11,915 | 1.19 (0.72-1.97) | 1.24 (0.74-2.10) |
| Q5 | 22 | 11,813 | 0.73 (0.41-1.28) | 0.78 (0.43-1.42) |
| P trend ¹ | | | 0.28 | 0.44 |
| High-grade astrocytic glioma | | | |
| AA (10 μg/d) | 152 | 58,473 | 0.95 (0.81-1.12) | 0.96 (0.80-1.15) |
| Q1 | 24 | 11,535 | Reference | Reference |
| Q2 | 26 | 11,619 | 1.08 (0.62-1.91) | 1.06 (0.60-1.88) |
| Q3 | 33 | 11,591 | 1.32 (0.77-2.26) | 1.33 (0.76-2.30) |
| Q4 | 33 | 11,915 | 1.31 (0.76-2.26) | 1.34 (0.75-2.37) |
| Q5 | 16 | 11,813 | 0.64 (0.33-1.22) | 0.66 (0.33-1.31) |
| P trend ¹ | | | 0.13 | 0.20 |

*Age-adjusted and sex-adjusted.

¹ Adjusted for age (y), sex, educational level (primary school, lower vocational school, intermediate vocational/high school, higher vocational school/university), body mass index (kg/m²), height (cm), energy intake (kcal/d), cigarette smoking status (current vs not current), number of cigarettes per day, number of years of smoking cigarettes.

¹ Adjusted for age (y), sex, educational level (primary school, lower vocational school, intermediate vocational/high school, higher vocational school/university), body mass index (kg/m²), height (cm), energy intake (kcal/d).

¹ P value for trend was calculated by modeling the median acrylamide intake value in each quintile or tertile as a continuous variable.
prospective study does not give support for an association between dietary acrylamide intake and brain cancer risk.

**Disclosure of Potential Conflicts of Interest**
No potential conflicts of interest were disclosed.

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