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Citation for published version (APA):

Lipunova, N., Schouten, L. J., van den Brandt, P. A., & Hogervorst, J. G. F. (2017). A prospective cohort study on dietary acrylamide intake and the risk for cutaneous malignant melanoma. *European Journal of Cancer Prevention*, 26(6), 528-531. <https://doi.org/10.1097/CEJ.0000000000000268>

**Document status and date:**

Published: 01/11/2017

**DOI:**

[10.1097/CEJ.0000000000000268](https://doi.org/10.1097/CEJ.0000000000000268)

**Document Version:**

Publisher's PDF, also known as Version of record

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# A prospective cohort study on dietary acrylamide intake and the risk for cutaneous malignant melanoma

Nadezda Lipunova<sup>a</sup>, Leo J. Schouten<sup>a</sup>, Piet A. van den Brandt<sup>a</sup> and Janneke G.F. Hogervorst<sup>a,b</sup>

Epidemiological studies have shown inconsistent associations between dietary acrylamide exposure and the risk for various malignancies. This is the first epidemiological study on the association between acrylamide intake and the risk for cutaneous malignant melanoma (CMM). A case-cohort analysis was carried out within the prospective Netherlands Cohort Study on diet and cancer. Acrylamide intake was estimated from a food frequency questionnaire combined with acrylamide data for Dutch foods. After 17.3 years of follow-up, 501 microscopically confirmed cases of CMM were identified. There was an increased risk for CMM when dietary acrylamide was modeled as a continuous variable [hazard ratio: 1.13 (95% confidence interval: 1.01–1.26)] per 10 µg increment among men but there was no clear linear trend over the quintiles ( $P_{\text{trend}} = 0.12$ ). No associations were observed for women. Our study provides some indications

that dietary acrylamide may increase the risk for CMM in men. *European Journal of Cancer Prevention* 26:528–531 Copyright © 2017 Wolters Kluwer Health, Inc. All rights reserved.

*European Journal of Cancer Prevention* 2017, 26:528–531

**Keywords:** cutaneous malignant melanoma, dietary acrylamide, prospective cohort study

<sup>a</sup>Department of Epidemiology, GROW – School for Oncology and Developmental Biology, Maastricht University Medical Center +, Maastricht, The Netherlands and

<sup>b</sup>Department of Environmental Biology, Center for Environmental Sciences, Hasselt University, Diepenbeek, Belgium

Correspondence to Janneke G.F. Hogervorst, PhD, Center for Environmental Sciences, Hasselt University, Agoralaan gebouw D, 3590 Diepenbeek, Belgium Tel: +32 11 268224; fax: +32 11 268301; e-mail: janneke.hogervorst@uhasselt.be

Received 9 February 2016 Accepted 6 April 2016

## Introduction

Acrylamide is classified as a probable human carcinogen based on its observed carcinogenicity in rodent studies (Pelucchi *et al.*, 2015). Acrylamide forms in heat-treated starchy foods, such as coffee, French fries, and cookies (Pelucchi *et al.*, 2015).

Results from epidemiological studies indicate that dietary acrylamide might be associated with the risk for kidney, endometrial, and ovarian cancers but the results were inconsistent (Pelucchi *et al.*, 2015). Every tissue is a potential target for acrylamide-induced carcinogenesis because acrylamide is distributed throughout the whole body.

Our objective was to investigate, for the first time, the association between dietary acrylamide intake and the risk for cutaneous malignant melanoma (CMM).

## Materials and methods

The association between acrylamide intake and CMM risk was investigated in the Netherlands Cohort Study on diet and cancer (NLCS) (van den Brandt *et al.*, 1990), a case-cohort study. CMM cases from the whole cohort were identified during follow-up, and a random sample of 5000 men and women sampled at baseline served as a subcohort from which accumulated person-years for the

entire cohort (120 852 participants) were estimated. There were 1951 male subcohort members and 224 male CMM cases, and 2101 female subcohort members and 224 female CMM cases available for analysis (Supplemental Fig. 1, Supplemental digital content 1, <http://links.lww.com/EJCP/A66>).

Histologically confirmed CMM cases were identified through linkage with the Dutch Pathology Registry (PALGA) and the National Dutch Cancer Registry. Completeness of follow-up of these registries is estimated to be at least 96% (Schouten *et al.*, 1993). Follow-up for vital status in the NLCS, as assessed through linkage with the Municipal Personal Records Database (GBA), at the end of the follow-up period (17.3 years) was nearly 100%; only one male subcohort member was lost to follow-up.

The NLCS has been approved by the Medical Ethics Committee of Maastricht University (Maastricht, the Netherlands).

Acrylamide intake was assessed using a self-administered food frequency questionnaire (FFQ) on 150 food items, and from this FFQ acrylamide intake was estimated as described elsewhere (Hogervorst *et al.*, 2007).

The NLCS questionnaire did not contain direct questions on UV exposure. To adjust for nonoccupational UV exposure, proxies using open-ended questions on hobbies and sports were constructed. The women's version of the NLCS

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questionnaire did not contain a question concerning hobbies, and hence for women we only constructed a proxy based on sports. A maximum of three hobbies and sports could be entered by the participants. Three variables were created for UV exposure through hobbies and three similar variables for UV exposure through sports: exposure to UV of limbs only (men and women combined) and exposure to UV of both limbs and trunk (sex-specific). Variables were coded as 1 (exposure to UV likely) and 0 (exposure to UV unlikely) (Supplemental Table 1, Supplemental digital content 2, <http://links.lww.com/EJCP/A67> and 2, Supplemental digital content 3, <http://links.lww.com/EJCP/A68>). Coding was carried out independently by two researchers (N.L. and J.G.F.H.). Divergent codings were discussed until consensus was reached. To adjust for occupational UV exposure, information from the Finnish job-exposure matrix (FINJEM) was used (Kauppinen et al., 2009). Exposure estimates in FINJEM are provided for the period between 1960 and 2003 and are presented as a proportion of workers exposed ( $P$ ) multiplied by the level of exposure ( $L$ ). Job codes assigned in the NLCS based on data on occupation were translated into those compatible with FINJEM (Koeman et al., 2013).

Hazard ratios (HR) were obtained using Cox proportional hazards models for men and women separately. SEs were

estimated using the robust Huber–White sandwich estimator. The proportional hazards assumption was tested using scaled Schoenfeld residuals. HRs were adjusted for covariates: age, smoking status, smoking frequency and duration, body mass index, and education level. The proxies for UV exposure did not change the HRs of acrylamide and were therefore not included in the models.

Subgroup analyses were carried out separately for histological subtypes [nodular (NM) and superficial spreading melanoma (SSM)] and for never-smokers (or for men: never-smokers and those who quit smoking at least 10 years before baseline) because smoking causes substantial acrylamide exposure (Hagmar et al., 2005).

A result was considered statistically significant if the  $P$ -value was 0.05 or less (two sided). STATA software (StataCorp 2011, Stata Statistical Software: Release 12; StataCorp LP, College Station, Texas, USA) was used for all statistical analyses.

## Results

For most variables there were no striking differences between CMM, NM, and SSM cases and subcohort members (Table 1). However, cases were more highly

**Table 1 Characteristics of total cutaneous malignant, superficial spreading, and nodular melanoma cases and subcohort members: the Netherlands cohort study on diet and cancer, 1986–2003<sup>a,b</sup>**

|   | Men         |            |             |             | Women       |             |             |             |
|---|-------------|------------|-------------|-------------|-------------|-------------|-------------|-------------|
|   | Subcohort   | CMM        | SSM         | NM          | Subcohort   | CMM         | SSM         | NM          |
| <i>N</i>  | 2191        | 241        | 94          | 40          | 2247        | 236         | 102         | 30          |
| Acrylamide (μg/day)   | 22.6 (12.2) | 23.9 (13)  | 24.1 (12.4) | 27.5 (15.4) | 21.1 (11.9) | 21.2 (11.7) | 20.5 (10.9) | 21.5 (12.6) |
| Age (years)   | 61.3 (4.2)  | 61.7 (4.3) | 61.2 (4.3)  | 62.8 (4.5)  | 61.4 (4.3)  | 61.9 (4.1)  | 61.6 (4.1)  | 61.4 (4.2)  |
| BMI (kg/m <sup>2</sup> )                                    | 25 (2.6)    | 25.4 (2.7) | 25.3 (3)    | 25.1 (2.1)  | 25.1 (3.6)  | 24.8 (3.4)  | 24.5 (3.1)  | 25.0 (4.3)  |
| Smoking status (%)  |             |            |             |             |             |             |             |             |
| Never-smokers   | 12.7        | 17.8       | 20.2        | 12.5        | 58.4        | 54.2        | 53.9        | 50          |
| Former smokers  | 51.6        | 59.8       | 59.6        | 65          | 20.6        | 28          | 32.4        | 26.7        |
| Current smokers   | 35.7        | 22.4       | 20.2        | 22.5        | 21          | 17.8        | 13.7        | 23.3        |
| Smoking [years (former and current smokers only)]           | 33.7 (11.8) | 29.8 (13)  | 28.4 (13.8) | 30.9 (12.7) | 27.8 (12.5) | 26.8 (12.4) | 25.7 (12.4) | 25.7 (13)   |
| Smoking [cigarettes/day (former and current smokers only)]  | 17 (10.6)   | 15 (10.5)  | 14.4 (9.3)  | 17.2 (12.1) | 11.4 (8.3)  | 12.2 (11.2) | 12.7 (9.5)  | 19.2 (20.2) |
| Education (%)   |             |            |             |             |             |             |             |             |
| Primary school  | 25          | 16.6       | 13.8        | 15          | 33.5        | 27.7        | 26.7        | 23.3        |
| Lower vocational school                                     | 20.7        | 13.7       | 11.7        | 7.5         | 23.2        | 23.4        | 25.7        | 16.7        |
| Intermediate vocational school/high school                  | 35.6        | 4.7        | 42.6        | 50          | 34.5        | 37          | 36.6        | 46.7        |
| Higher vocational school/university                         | 18.7        | 29.1       | 31.9        | 27.5        | 8.8         | 11.9        | 10.9        | 13.3        |
| Occupational UV exposure (%)                                |             |            |             |             |             |             |             |             |
| Never   | 72.9        | 78.0       | 77.7        | 80.0        | 97          | 95.8        | 97.1        | 90          |
| Ever  | 12.8        | 10.4       | 11.7        | 10.0        | 1.5         | 2.5         | 0.0         | 0.0         |
| High  | 14.3        | 11.6       | 10.6        | 10.0        | 1.5         | 1.7         | 2.9         | 10.0        |
| Cumulative exposure ( $P \times L/100$ )                    | 761 (1951)  | 673 (1770) | 697 (1708)  | 434 (1234)  | 57.3 (472)  | 80.1 (589)  | 126 (820)   | 36.0 (121)  |
| Nonoccupational UV exposure to the limbs from (%)           |             |            |             |             |             |             |             |             |
| Hobbies (yes)   | 41.5        | 36.5       | 35.1        | 42.5        | c           | c           | c           | c           |
| Sports (yes)  | 45.1        | 49.8       | 45.4        | 55.0        | 23.1        | 27.5        | 26.5        | 40.0        |
| Nonoccupational UV exposure to the limbs and trunk from (%) |             |            |             |             |             |             |             |             |
| Hobbies (yes)   | 30.8        | 27.8       | 29.8        | 22.5        | c           | c           | c           | c           |
| Sports (yes)  | 16.0        | 18.3       | 18.1        | 20.0        | 16.6        | 22.5        | 20.6        | 30.0        |

*P*, prevalence of exposure (%); *L*, level of exposure (J/m<sup>2</sup>) (Kauppinen et al., 2009).

CMM, cutaneous malignant melanoma; NM, nodular melanoma; NLCS, the Netherlands cohort study on diet and cancer; SSM, superficial spreading melanoma.

<sup>a</sup>Data represent means (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.

<sup>b</sup>The number of missing values varies.

<sup>c</sup>The NLCS questionnaire contained a question on hobbies for men only.

**Table 2 Association between dietary acrylamide intake and cutaneous malignant melanoma in men and women: the Netherlands cohort study on diet and cancer, 1986–2003**

|  | Overall   |                  |                          |                               | Never-cigarette-smokers and 10-year quitters of cigarette smoking |                  |                          |                          |
|--|-----------|------------------|--------------------------|-------------------------------|---|------------------|--------------------------|--------------------------|
|  | N (cases) | N (person years) | HR (95% CI) <sup>a</sup> | HR (95% CI) <sup>b</sup>      | N (cases)   | N (person years) | HR (95% CI) <sup>a</sup> | HR (95% CI) <sup>c</sup> |
| <b>Men</b>                             |           |                  |                          |                               |   |                  |                          |                          |
| Total cutaneous malignant melanoma     |           |                  |                          |                               |   |                  |                          |                          |
| AA (10 µg/day)                         | 224       | 28 124           | 1.10 (0.99–1.22)         | 1.13 (1.01–1.26)              | 136   | 13 340           | 1.04 (0.90–1.20)         | 1.07 (0.92–1.26)         |
| Q1                                     | 45        | 5625             | Reference                | Reference                     | 32  | 2870             | Reference                | Reference                |
| Q2                                     | 46        | 5435             | 1.08 (0.70–1.67)         | 1.14 (0.73–1.80)              | 28  | 2675             | 0.96 (0.55–1.67)         | 0.99 (0.55–1.77)         |
| Q3                                     | 35        | 5734             | 0.81 (0.51–1.30)         | 0.90 (0.55–1.45)              | 21  | 2383             | 0.82 (0.45–1.50)         | 0.85 (0.46–1.58)         |
| Q4                                     | 38        | 5609             | 0.91 (0.57–1.44)         | 1.03 (0.64–1.66)              | 22  | 2482             | 0.83 (0.46–1.49)         | 0.89 (0.48–1.64)         |
| Q5                                     | 60        | 5721             | 1.37 (0.90–2.07)         | 1.52 (0.98–2.33)              | 33  | 2930             | 1.03 (0.60–1.77)         | 1.13 (0.63–2.00)         |
| <i>P</i> <sub>trend</sub> <sup>d</sup> |           |                  | 0.29                     | 0.12                          |   |                  | 0.94                     | 0.81                     |
| Nodular melanoma                       |           |                  |                          |                               |   |                  |                          |                          |
| AA (10 µg/day)                         | 39        | 28 124           | 1.27 (1.07–1.51)         | 1.36 (1.11–1.67)              | 25  | 13 340           | 1.37 (1.11–1.69)         | 1.60 (1.19–2.15)         |
| Superficial spreading melanoma         |           |                  |                          |                               |   |                  |                          |                          |
| AA (10 µg/day)                         | 86        | 28 124           | 1.10 (0.94–1.28)         | 1.14 (0.97–1.34)              | 54  | 13 340           | 0.92 (0.74–1.13)         | 0.94 (0.75–1.18)         |
| Q1                                     | 14        | 5877             | Reference                | Reference                     | 20  | 4122             | –                        | –                        |
| Q2                                     | 23        | 6829             | 0.96 (0.51–1.81)         | 1.02 (0.53–1.95)              | 19  | 4457             | –                        | –                        |
| Q3                                     | 23        | 8228             | 1.10 (0.59–2.05)         | 1.26 (0.66–2.40)              | 15  | 4762             | –                        | –                        |
| Q4                                     | 26        | 7189             | 1.26 (0.69–2.31)         | 1.42 (0.77–2.64) <sup>f</sup> | –   | –                | –                        | –                        |
| <i>P</i> <sub>trend</sub> <sup>d</sup> |           |                  | 0.40                     | 0.21                          |   |                  |                          |                          |
|  |           |                  |                          |                               |   |                  |                          |                          |
| Overall                                |           |                  |                          |                               |   |                  |                          |                          |
|  | n (cases) | n (person years) | HR (95% CI) <sup>a</sup> | HR (95% CI) <sup>b</sup>      | n (cases)   | n (person years) | HR (95% CI) <sup>a</sup> | HR (95% CI) <sup>e</sup> |
| <b>Women</b>                           |           |                  |                          |                               |   |                  |                          |                          |
| Total cutaneous malignant melanoma     |           |                  |                          |                               |   |                  |                          |                          |
| AA (10 µg/day)                         | 224       | 32 990           | 0.97 (0.87–1.09)         | 0.97 (0.86–1.08)              | 123   | 19 939           | 1.03 (0.88–1.20)         | 1.02 (0.88–1.20)         |
| Q1                                     | 43        | 6433             | Reference                | Reference                     | 21  | 4238             | Reference                | Reference                |
| Q2                                     | 47        | 6695             | 1.08 (0.70–1.67)         | 1.10 (0.71–1.72)              | 27  | 4060             | 1.37 (0.75–2.48)         | 1.39 (0.76–2.56)         |
| Q3                                     | 48        | 6354             | 1.19 (0.77–1.84)         | 1.25 (0.80–1.96)              | 28  | 3561             | 1.74 (0.96–3.15)         | 1.78 (0.96–3.30)         |
| Q4                                     | 47        | 6857             | 1.07 (0.69–1.66)         | 1.11 (0.71–1.73)              | 25  | 4107             | 1.30 (0.71–2.39)         | 1.31 (0.71–2.43)         |
| Q5                                     | 39        | 6650             | 0.91 (0.58–1.43)         | 0.91 (0.57–1.44)              | 22  | 3972             | 1.16 (0.62–2.15)         | 1.16 (0.62–2.19)         |
| <i>P</i> <sub>trend</sub> <sup>d</sup> |           |                  | 0.70                     | 0.71                          |   |                  | 0.72                     | 0.74                     |
| Nodular melanoma                       |           |                  |                          |                               |   |                  |                          |                          |
| AA (10 µg/day)                         | 29        | 32 990           | 0.94 (0.68–1.29)         | 0.92 (0.68–1.25)              | 14  | 19 939           | –                        | –                        |
| Superficial spreading melanoma         |           |                  |                          |                               |   |                  |                          |                          |
| AA (10 µg/day)                         | 94        | 32 990           | 0.92 (0.77–1.10)         | 0.91 (0.76–1.08)              | 52  | 19 939           | 0.95 (0.76–1.19)         | 0.94 (0.75–1.19)         |
| Q1                                     | 26        | 9424             | Reference                | Reference                     | 22  | 7828             | –                        | –                        |
| Q2                                     | 28        | 8405             | 1.25 (0.72–2.20)         | 1.30 (0.73–2.31)              | 18  | 5816             | –                        | –                        |
| Q3                                     | 23        | 7077             | 1.11 (0.62–1.99)         | 1.16 (0.64–2.09)              | 12  | 6295             | –                        | –                        |
| Q4                                     | 17        | 8084             | 0.73 (0.39–1.37)         | 0.71 (0.37–1.35)              | –   | –                | –                        | –                        |
| <i>P</i> <sub>trend</sub> <sup>d</sup> |           |                  | 0.27                     | 0.25                          |   |                  |                          |                          |

The median acrylamide intake of the male subcohort in the quintiles was 10.8, 15.6, 19.6, 25.4, and 37.6 µg/day. The median acrylamide intake of the female subcohort in the quintiles was 9.5, 14.0, 17.9, 24.3, and 36.8 µg/day.

–, Too few cases to carry out the analysis; 95% CI, 95% confidence interval; HR, hazard ratio.

<sup>a</sup>Adjusted for age.

<sup>b</sup>Adjusted for age, education level (primary school, lower vocational school, intermediate vocational/high school, higher vocational school/university), BMI (kg/m<sup>2</sup>), cigarette smoking status (never/former/current smokers), number of cigarettes smoked per day, number of years of smoking cigarettes.

<sup>c</sup>Adjusted for age, education level (primary school, lower vocational school, intermediate vocational/high school, higher vocational school/university), BMI (kg/m<sup>2</sup>), number of cigarettes smoked per day, number of years of smoking cigarettes.

<sup>d</sup>The *P*-value for trend was calculated by modeling the median acrylamide intake value in each quantile as a continuous variable.

<sup>e</sup>Adjusted for age, education level (primary school, lower vocational school, intermediate vocational/high school, higher vocational school/university), BMI (kg/m<sup>2</sup>).

<sup>f</sup>Proportional hazards assumption was violated.

educated than subcohort members, whereas smoking was more prevalent among subcohort members.

There was a statistically significant positive multivariable-adjusted association between acrylamide intake modeled per 10 µg/day increment and total CMM risk among men [HR 1.13 (95% CI: 1.01–1.26)] (Table 2). The quintile analysis, however, did not reflect a linear dose-response relationship (*P*<sub>trend</sub>: 0.12). The association was less strong in nonsmoking men, with an HR of 1.07 (95% CI: 0.92–1.26) per 10 µg acrylamide increment.

Subtype analyses showed a statistically significant positive association between dietary acrylamide and the risk for NM among men [HR 1.36 (95% CI: 1.11–1.67)] per 10 µg acrylamide increment (Table 2). A stronger association was seen among nonsmoking men [HR 1.60 (95% CI: 1.19–2.15)]. No statistically significant associations were observed between dietary acrylamide intake and the risk for SSM among men. The proportional hazards assumption was violated in the highest quartile of dietary acrylamide intake in the analysis of SMM but no statistically significant interaction with time was observed.

Among women, there was no association between acrylamide intake and melanoma risk (Table 2).

## Discussion

This study provides some indications that dietary acrylamide may increase the risk for overall CMM and NM among men. There was no positive association with total CMM risk in the group of nonsmoking men. For NM, however, the association between dietary acrylamide intake and NM risk was stronger in nonsmoking men. The latter finding may be spurious because of the small number of cases. No association was observed for SSM. No statistically significant associations were observed among women.

Differences in biological mechanisms in the etiology of different histological CMM subtypes are still unclear (Whiteman *et al.*, 2011) but it is possible that acrylamide has a differential effect on different subtypes. Acrylamide has been previously shown to cause genotoxicity and to influence sex hormone levels in rodents (Besaratinia and Pfeifer, 2007). Although melanoma is not clearly a sex hormone-dependent cancer, it is likely that sex hormones are of importance in melanomagenesis (de Giorgi *et al.*, 2011) and their role may differ in men and women. Smoking influences sex hormone levels, which may explain the differential associations between acrylamide intake and melanoma risk based on smoking status.

Our study has a few limitations. FFQs have limitations with regard to assessing dietary acrylamide exposure (Hogervorst *et al.*, 2007). Nondifferential measurement error of the acrylamide intake resulting from the use of an FFQ in a prospective cohort study will push the risk estimate toward null. In addition, subgroup analyses were carried out with relatively small numbers. Therefore, the results have to be interpreted with caution. Proxies of sun exposure to the trunk and lower limbs due to hobbies and sports or occupational UV exposure were no confounders of the association between dietary acrylamide and the risk for CMM. In addition, the observation of similar risk estimates for different anatomical locations of CMM (results not shown) also suggests that UV exposure is not a confounder because anatomical location is a surrogate for assessing sun exposure patterns. All in all, it is unlikely that UV exposure was a confounder in this analysis but residual confounding cannot be ruled out.

Important strengths of the study are its prospective nature, large study size, and virtually no loss to follow-up.

In conclusion, our study gives some indications for a positive association between dietary acrylamide and the risk for total CMM and NM among men and no association among women.

## Acknowledgements

The authors thank Nadine Offermans (formerly from the Department of Epidemiology, GROW – School for Oncology and Developmental Biology, Maastricht, the Netherlands) and Timo Kauppinen from the Department of Occupational Health, Finnish Institute of Occupational Health, Helsinki, Finland, for assistance using the Finnish job exposure matrix (FINJEM).

The NLCS was established with funding from the Dutch Cancer Society. Dietary acrylamide analyses were funded by the Dutch Food and Consumer Product Safety Authority (nVWA).

## Conflicts of interest

There are no conflicts of interest.

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