Abstract
Purpose  The relation between dietary acrylamide intake and esophageal cancer (EC) risk, including esophageal adenocarcinoma (EAC) and esophageal squamous cell carcinoma (ESCC), has not been consistent. We evaluated the association between dietary acrylamide intake and EAC, ESCC, and overall EC in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort.
Methods  Multivariate Cox proportional hazards models were used to estimate the HR and 95 % confidence interval (95 % CI). Since nonlinear relations were observed, HRs were displayed for quartiles of acrylamide intake in μg per day.

Dietary intake of acrylamide and esophageal cancer risk in the European Prospective Investigation into Cancer and Nutrition cohort

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Results After a mean follow-up of 11 years, 341 EC were identified, 142 of which were EAC, 176 ESCC, and 23 other histological types or not specified. An increase in EC risk was observed in the second and third quartiles (HR\textsubscript{Q2 vs Q1} 1.75, 95 % CI 1.12–2.74; HR\textsubscript{Q3 vs Q1} 1.66, 95 % CI 1.05–2.61), but not in the fourth quartile, and there was no evidence for a linear dose–response trend. HRs were similarly elevated but not statistically significant when ESCC and EAC were analyzed separately, due to the small number of cases observed. No associations were observed when quartiles were based on energy-adjusted acrylamide intake.

Conclusions In the EPIC cohort, an association between estimated dietary acrylamide intake and an increased risk of developing EC was observed in the middle quartiles but not in the highest quartile; however, results from other larger cohorts or consortia, and results from biomarker studies, might add to the evidence provided by this analysis, suggesting that acrylamide is not an important risk factor for EC.

Keywords Esophageal cancer · Esophageal squamous cell carcinoma · Esophageal adenocarcinoma · Acrylamide intake · Cohort · Nutrition

Introduction In 1994, the International Agency for Research on Cancer (IARC) classified acrylamide as ‘probably carcinogenic’ to humans based on animal studies and evidence in humans [1]. In 2002, acrylamide was discovered at relatively high concentrations in some foods. Acrylamide in foods is formed through the Maillard reaction during high temperature (>120° C) cooking, primarily in foods of plant origin such as potatoes, breads, and cereals [2]. The main determinants of dietary intake of acrylamide in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort based on a 24-h dietary recall (24HDR) were bread, crispbread, rusks, coffee, potatoes, cakes, biscuits, and cookies [3].

The evidence for an association between estimated acrylamide intake based on dietary questionnaires (DQs) and cancer risk has been inconsistent in epidemiological studies [2]. Two case–control studies [4, 5] and one case–cohort study [6] have evaluated the association between estimated acrylamide intake and esophageal cancer (EC) including the histological subtypes esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC), but only the Swedish case–control study (n = 594 EC, including n = 189 EAC and n = 167 ESCC cases) [4] observed an increase in overall EC risk. This association was stronger among overweight or obese persons (n = 268 EC). The Netherlands Cohort Study on Diet and Cancer (NLCS) (n = 216 EC, including n = 115 EAC and n = 90 ESCC cases) observed an increase in risk per 10 μg increment of acrylamide intake per day in obese persons, but this observation was based on only 20 EC cases, including 14 EAC [6].

The aim of the present study was to assess whether pre-diagnostic dietary acrylamide intake levels based on DQs are associated with the risk of developing, ESCC, EAC, and overall EC in the EPIC cohort.
Materials and methods

EPIC is a multicenter cohort study which recruited participants from 23 centers located in ten European countries. At baseline, information was collected on lifestyle factors, sociodemographic characteristics, medical history, and the usual diet over the previous 12 months using validated country-specific DQs [7]. To estimate the average daily intake of acrylamide, we matched the DQ food intake data to a harmonized acrylamide database, which we compiled from the EU monitoring database of acrylamide levels in food maintained by the European Community Institute for Reference Materials and Measurements (IRMM) and other sources [3, 8]. Case definitions for EC, EAC, and ESCC have been previously published [9].

Proportional hazards modeling was used to estimate HRs and 95% confidence interval (95% CI) for estimated dietary acrylamide intake and EC, ESCC, and EAC risk. Age at recruitment was used as entry time and age at first EC for cases or age at censoring time for non-cases were used as exit time. EC, ESCC, and EAC multivariate models were stratified by country to control for country effects (recruitment strategies, questionnaire design, and follow-up procedures). Age at recruitment (1-year categories) was used as the primary time variable. All models were adjusted for total energy intake, sex, cigarette smoking status, number of cigarettes, time since quitting, intakes of total fruits and processed meat. ESCC and EAC multivariate models were also adjusted for body mass index (BMI), and EC and ESCC for alcohol intake [9]. Different risk factors in the multivariate models were used because of etiologic heterogeneity between ESCC and EAC [10]. Schoenfeld residuals were used to assess the proportional hazard assumption [11]. Restricted cubic splines (RCS) with 3–5 knots were used to explore dose–response linearity [12]. Akaike information criterion (AIC) was used to select the best representation of the relation between dietary acrylamide intake and EC, also comparing with the linear model. The minimum AIC was found with the RCS with four knots (5, 35, 65, and 95th percentiles of the distribution of dietary acrylamide intake). Since the relation was not linear, different transformations of the estimated acrylamide intake variable (such as natural logarithm and root square) were evaluated; however, the relation remained nonlinear (with higher estimated intakes showing weaker associations with EC risk) (data not shown). Thus, results for continuous variables of estimated acrylamide intake were not displayed. HRs are presented as the change in cancer risk for each quartile relative to the lowest quartile of estimated acrylamide intake (quartiles were calculated based on the full cohort). Estimations of acrylamide intake were corrected using the residual method to control for the effect of total energy intake and to reduce the impact of measurement error in DQs [13, 14]. Quartiles of acrylamide intake were also based on energy-adjusted intake in both men and women in the EPIC cohort.

Effect-measure modification by smoking status (smokers vs. never smokers + ≥20 years quitters), sex, BMI (normal vs. overweight or obese), and alcohol intake was evaluated using a likelihood ratio test (LRT). Since some risk factors differ for ESCC and EAC, effect-measure modification was evaluated separately for EC, ESCC, and

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EAC. A positive association between obesity and EAC has been demonstrated [9, 15], and EPIC [9] and other studies [16] have observed that obesity may be inversely related to ESCC. Since the direction of risk with obesity is different for EAC and ESCC, potential effect-measure modification between estimated acrylamide intake and body weight (BMI <25 vs. BMI ≥25) was evaluated for ESCC and EAC separately. Since alcohol drinking is a risk factor for ESCC, effect-measure modification by alcohol intake was only evaluated for ESCC, comparing low intakes (<12 g/day for men and <6 g/day for women) versus higher intakes. Finally, due to the low number of female EAC cases (n = 28), effect-measure modification by sex was evaluated only for EC and ESCC. Tertiles and quartiles of estimated acrylamide intake were used to evaluate effect-measure modification for ESCC, EAC, and EC.

Sensitivity analyses, excluding EC cases and censoring participants during the first 2 years of follow-up, were carried out to evaluate the possible influence of prior diseases on dietary habits. Further, because smoking is an important determinant of acrylamide exposure, analyses were performed in never smokers and those individuals who had quit at least 20 years before being enrolled in the EPIC cohort.

Results

After a mean follow-up of 11 years, 341 ECs cases were identified including 142 EACs, 176 ESCCs, and 23 that were other histological types or were not specified. At baseline, the mean of estimated dietary acrylamide intake based on DQs in EPIC was 26.22 μg/day. More details on the distribution of dietary acrylamide intake in the EPIC cohort centers have been previously published [8]. Individuals with the lowest estimated acrylamide intake values had the highest intakes of total fruits (Table 1), and participants with the highest quartile of acrylamide intake had the highest intakes of processed meat, alcohol, and total energy and were more likely to be current smokers at baseline (Table 1).

For overall EC, participants with estimated acrylamide intakes ranging from 15.7 to 23.3 μg/day (second quartile) had a 75 % increased risk of developing EC compared with participants in the lowest quartile of estimated intake (0–15.6 μg/day), while participants with a range of estimated intake from 23.4 to 30.7 μg/day (third quartile) had a 66 % higher risk of developing cancer (Table 2). Individuals in the highest quartile of estimated intake (34.2–261.4 μg/day) were not at statistically significantly increased risk of EC, and further, no linear dose–response trends were observed for overall EC. The analysis was repeated using the sex-specific quintile cut-points defined in the NLCS study, and the association between estimated acrylamide intake and EC was statistically significant in the third and fourth quintiles (HRQ3 vs Q1 1.87, 95 % CI 1.01–3.47; HRQ4 vs Q1 2.17, 95 % CI 1.20–3.92), but not in the second or fifth (HRQ2 vs Q1 1.70, 95 % CI 0.88–3.26; HRQ5 vs Q1 1.67, 95 % CI 0.91–3.12) (data not in tables).

When we analyzed ESCC and EAC separately, the same pattern was observed, but none of the HR estimates were statistically significant (Table 2). When the analysis was restricted to never smokers and former smokers who had quit at least 20 years before baseline, similar results were observed (Table 2). Quartiles based on energy-adjusted acrylamide intake showed no association with EC, even when EC was evaluated by histological subtypes (Table 2). Further, there was no evidence for effect-measure modification of the relation between acrylamide intake and EC risk by smoking status, sex, BMI, or alcohol intake (all LRT p values >0.06) (data not shown).

Discussion

We did not observe convincing evidence that estimated acrylamide intake based on DQs is associated with esophageal cancer risk in the EPIC cohort. While we detected elevated and significant HRs for estimated acrylamide intake in the second and third quartiles, we did not observe a statistically significant increase risk in the fourth quartile, and there was no evidence for a linear dose–response trend. When the analysis was performed using quartiles based on energy-adjusted acrylamide intake, none of the results were statistically significant. Similar patterns were seen when results were analyzed by histological subtype (ESCC or EAC), but none of the HRs were statistically significant. Because smoking is an important determinant of acrylamide exposure, analyses were carried out in never smokers and former smokers who had quit at least 20 years before baseline, and similar patterns were observed.
The only other prospective study to analyze the association between estimated dietary acrylamide intake and EC was in the NLCS which detected no overall associations between acrylamide intake and EC, ESCC, or EAC risk; however, in a subsample of obese participants (20 EC and 14 EAC cases), some elevated risk estimates were observed. In EPIC, no statistically significant associations between estimated acrylamide intake and EAC or ESCC risk were observed in overweight or obese participants (ESCC: HR T2 vs T1 1.47, 95 % CI 0.74–2.94; HR T3 vs T1 1.08, 95 % CI 0.50–2.33, and EAC: HR T2 vs T1 1.33, 95 % CI 0.64–2.77; HR T3 vs T1 1.23, 95 % CI 0.56–2.67). When we re-analyzed the relation between estimated acrylamide intake and EC using the same sex-specific cut-points used in the NLCS study, we observed significant HRs in the third and fourth quintiles (which had similar estimated intake ranges to our second and third quartiles), but not in the fifth quintile. The Swedish case–control study reported a positive association with overall EC (ORQ4 vs Q1 1.23, 95 % CI 1.02–1.75), and in overweight or obese persons (ORQ4 vs Q1 1.88, 95 % CI 1.06–3.34). The Italian case–control study (n = 395 EC cases) reported no association between estimated dietary acrylamide intake and overall EC.

Results presented for overall EC should be interpreted with caution because while ESCC and EAC share some risk factors, they are also known to have distinct etiologies [10]. ESCC is usually located in the middle of the esophagus and the principal risk factors are tobacco smoking and high levels of alcohol consumption [10, 15]. Nearly, all EACs are located in the distal one-third of the esophagus, and Barrett’s esophagus [17], tobacco smoking, and obesity are major risk factors [15]. Both cancers share processed meat as a possible risk factor [18–20], and fruits and vegetables [15, 21, 22] have generally shown protective associations for both. Thus, as estimated dietary acrylamide associations in both subtypes gave similar HRs estimates, we posited that estimated acrylamide effects (if they exist) would be similar among histological subtypes; thus, overall results for combined histologies were also presented.

In light of the differences mentioned between the studies on acrylamide and EC, it is also worth noting that the three published studies and EPIC used different acrylamide

| Table 1 Baseline characteristics by quartiles of estimated dietary acrylamide intake based on dietary questionnaires |
|---------------------------------------------------------------|---------------------------------------------------------------|
| Cohort Total estimated acrylamide intake (µg/day) | Q1: 0–15.6 | Q2: 15.7–23.3 | Q3: 23.4–34.1 | Q4: 34.2–261.4 |
| Estimated acrylamide median, µg/day | 23.3 (15.7–34.0) | 11.3 (8.3–13.6) | 19.4 (17.55–21.28) | 27.9 (25.5–30.7) | 37.9 (51.4–43.2) |
| Age at recruitment | 51.5 (45.1–58.2) | 51.5 (45.6–58.2) | 50.7 (44.9–57.9) | 51.4 (44.6–58.4) | 52.2 (45.0–58.3) |
| Sex (%) | | | | | |
| Male | 29.8 | 19.4 | 23.0 | 31.2 | 47.7 |
| Female | 70.2 | 80.6 | 79.0 | 68.8 | 52.3 |
| Cigarette smoking status (%) | | | | | |
| Never | 48.9 | 23.2 | 23.0 | 48.6 | 41.8 |
| Former | 26.6 | 26.3 | 25.2 | 27.4 | 29.8 |
| Current | 22.4 | 25.2 | 20.4 | 22.1 | 27.1 |
| Unknown | 2.0 | 2.3 | 2.6 | 1.9 | 1.3 |
| Number of cigarettes (c/day) | 14.0 (10.0–20.0) | 11.0 (6.0–20.0) | 10.0 (10.0–20.0) | 15.0 (10.0–20.0) | 15.0 (10.0–20.0) |
| Time since quitting smoking, y | 14.0 (6.5–22.0) | 13.0 (6.5–20.5) | 14.5 (6.5–22.0) | 14.5 (6.5–23.0) | 14.5 (6.5–23.0) |
| BMI, kg/m² | 24.8 (22.4–27.8) | 24.9 (22.4–28.0) | 24.5 (22.1–27.5) | 24.8 (22.3–27.7) | 25.1 (22.7–27.9) |
| Alcohol at recruitment, g/day | 5.3 (0.9–14.9) | 3.0 (0.3–12.3) | 3.9 (0.8–12.0) | 6.2 (1.3–15.6) | 8.4 (2.0–19.5) |
| Total fruits, g/day | 200.3 | 245.3 | 201.0 | 189.2 | 173.1 (98.1–282.2) |
| Processed meat, g/day | 24.3 (10.5–43.9) | 18.7 (7.9–34.3) | 25.2 (11.0–43.9) | 26.4 (11.6–47.2) | 28.4 (12.7–50.4) |
| Total energy intake, Kcal | 1,996 | 1,700 | 1,856 | 2,069 | 2,381 |
| a Median (25–75th percentile) | | | | | |
| b Only for current smokers | | | | | |
| c Only for former smokers | | | | | |
| d Total fruits: fruits, nuts, and seeds | | | | | |
| Quartiles (µg/day) | Estimated acrylamide intake (µg/day) | Cases PY | HR (95 % CI) | Cases PY | HR (95 % CI) | Cases PY | HR (95 % CI) |
|-------------------|--------------------------------------|----------|-------------|----------|-------------|----------|-------------|
| **Full cohort**   |                                      |          |             |          |             |          |             |
| **Quartiles**     |                                      |          |             |          |             |          |             |
| Q1 (0–15.6)       | 32 1,299,314 reference               | 23       | 1,299,314   | 8        | 1,299,314   |
| Q2 (15.7–23.3)    | 76 1,298,899 1.75 (1.12–2.74)       | 44       | 1,298,899   | 26       | 1,298,899   |
| Q3 (23.4–30.7)    | 104 1,323,954 1.66 (1.05–2.61)      | 53       | 1,323,954   | 44       | 1,323,954   |
| Q4 (34.2–261.4)   | 129 1,340,783 1.41 (0.86–2.71)      | 56       | 1,340,783   | 64       | 1,340,783   |
| **Energy-adjusted** |                                       |          |             |          |             |          |             |
| Q1 (0–17.7)       | 51 1,306,465 reference               | 34       | 1,306,465   | 13       | 1,306,465   |
| Q2 (17.8–24.4)    | 67 1,289,531 1.12 (0.75–1.68)       | 41       | 1,289,531   | 23       | 1,289,531   |
| Q3 (24.5–33.2)    | 96 1,327,405 1.11 (0.75–1.66)       | 43       | 1,327,405   | 48       | 1,327,405   |
| Q4 (33.2–244.6)   | 127 1,339,549 1.04 (0.69–1.56)      | 58       | 1,339,549   | 58       | 1,339,549   |
| **Never smokers + ≥ 20 years quitters** |         |          |             |          |             |          |             |
| **Quartiles**     |                                      |          |             |          |             |          |             |
| Q1 (0–15.6)       | 8 781,180 reference                  | 7        | 1,045,423   | 6        | 1,045,423   |
| Q2 (15.7–23.3)    | 24 784,146 1.97 (0.85–4.55)         | 22       | 1,034,795   | 25       | 1,034,795   |
| Q3 (23.4–30.7)    | 50 766,646 2.77 (1.21–6.33)         | 20       | 94,676      | 33       | 94,676      |
| Q4 (34.2–261.4)   | 37 695,007 1.66 (0.66–4.15)         | –        | –           | –        | –           |
| **Energy-adjusted** |                                       |          |             |          |             |          |             |
| Q1 (0–17.7)       | 13 763,926 reference                | 9        | 1,034,292   | 7        | 1,034,292   |
| Q2 (17.8–24.4)    | 24 799,093 1.13 (0.55–2.31)         | 20       | 1,040,872   | 23       | 1,040,872   |
| Q3 (24.5–33.2)    | 43 761,407 1.38 (0.68–2.78)         | 20       | 954,814     | 37       | 954,814     |
| Q4 (33.2–244.6)   | 39 705,551 0.98 (0.47–2.0)          | –        | –           | –        | –           |
| **Sensitivity analysis** |                                 |          |             |          |             |          |             |
| **Excluding first 2 years of follow-up** |                     |          |             |          |             |          |             |
| **Quartiles**     |                                      |          |             |          |             |          |             |
| Q1 (0–15.6)       | 27 1,297,226 reference               | 19       | 1,297,226   | 7        | 1,297,226   |
| Q2 (15.7–23.3)    | 65 1,296,721 1.69 (1.05–2.73)       | 36       | 1,296,721   | 24       | 1,296,721   |
| Q3 (23.4–30.7)    | 84 1,321,604 1.46 (0.89–2.39)       | 39       | 1,321,604   | 38       | 1,321,604   |
| Q4 (34.2–261.4)   | 111 1,338,682 1.30 (0.76–2.21)      | 48       | 1,338,682   | 54       | 1,338,682   |
| **Energy-adjusted** |                                       |          |             |          |             |          |             |
| Q1 (0–17.7)       | 40 1,304,405 reference               | 25       | 1,304,405   | 12       | 1,304,405   |
| Q2 (17.8–24.4)    | 61 1,287,225 1.31 (0.85–2.04)       | 38       | 1,287,225   | 20       | 1,287,225   |
| Q3 (24.5–33.2)    | 78 1,325,145 1.13 (0.73–1.77)       | 31       | 1,325,145   | 42       | 1,325,145   |
| Q4 (33.2–244.6)   | 108 1,337,459 1.10 (0.70–1.72)      | 48       | 1,337,459   | 49       | 1,337,459   |

**Note:**

- PY = person-years
- Adjusted for sex, total energy (kcal/d), total fruits (g/d), cigarette smoking status, number of cigarettes (c/d), time since quitting smoking (y), processed meat (g/d) and alcohol (g/d) and stratified by age and country. BMI was not included because it is a risk factor for EAC and a possible protective factor for ESCC
- Adjusted for sex, total energy (kcal/d), total fruits (g/d), cigarette smoking status, number of cigarettes (c/d), time since quitting smoking (y), processed meat (g/d), BMI (kg/m2) and alcohol (g/d) and stratified by age and country
- Adjusted for sex, total energy (kcal/d), total fruits (g/d), cigarette smoking status, number of cigarettes (c/d), time since quitting smoking (y), processed meat (g/d) and BMI (kg/m2) and stratified by age and country. Alcohol was not included because it is not considered a risk factor for EAC
- For ESCC and EAC, tertiles of acrylamide were analyzed (T1: 0–18.1, T2: 18.2–29.75, T3: 29.76–261.4)
- For ESCC and EAC, tertiles of energy-adjusted acrylamide were analyzed (T1: 0–20.03, T2: 20.04–29.63, T3: 29.64–244.6)
composition tables and used different cut-points for acrylamide intake in the analyses (although results in EPIC were unchanged when NLCS cut-points were used). The NLCS, the Italian, and the Swedish case–control studies estimated acrylamide intakes from country-specific acrylamide databases [4–6], while the EPIC study was based on the IRMM [3, 8]; thus, direct comparison of the results of these studies with EPIC should be made with caution.

Acrylamide was discovered in food in 2002 [2], and it has been shown that levels can vary in a single item by a factor of 100 or more depending on factors such as the cooking method and brand [2, 3]. We acknowledge some uncertainty in how well dietary acrylamide intake is captured by EPIC DQs (for example, information on extent of cooking which could influence acrylamide levels in foods was not accounted for). A recent publication from our group showed a low correlation between DQs and a single 24HDR (0.17) [13], but a single 24HDR may not be adequate to estimate daily acrylamide intake levels. The major strength of our study is that it is the largest prospective study of dietary acrylamide intake and EC to date.

In conclusion, results from the EPIC cohort suggest that estimated acrylamide intake is not linearly associated with an increased risk of developing EC. Although statistically significant elevated risks were observed in the middle quartiles for total EC, no statistically significant elevated risks were observed for the fourth quartile, neither for EAC or ESCC when analyzed separately nor when the estimation of dietary acrylamide intake was corrected using the residual method. Results from other large cohorts and consortia, and results from biomarker studies, might add to the evidence provided by this analysis, suggesting that acrylamide is not an important risk factor for EC.

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Conflict of interest The authors declare that they have no conflict of interest.

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