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# Dietary Intake of Acrylamide and Risk of Breast, Endometrial, and Ovarian Cancers: A Systematic Review and Dose–Response Meta-analysis

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## ABSTRACT

Acrylamide is a probable human carcinogen. Aside from occupational exposures and smoking, diet is the main source of exposure in humans. We performed a systematic review of the association between estimated dietary intake of acrylamide and risk of female breast, endometrial, and ovarian cancers in nonexperimental studies published through February 25, 2020, and conducted a dose–response meta-analysis. We identified 18 papers covering 10 different study populations: 16 cohort and two case–control studies. Acrylamide intake was associated with a slightly increased risk of ovarian cancer, particularly among never smokers. For endometrial cancer, risk was highest at intermediate levels of exposure, whereas the association was more linear and positive among never smokers. For breast cancer, we found evidence of a null or inverse relation between exposure and risk, particularly among never smokers and postmenopausal women. In a subgroup analysis limited to premenopausal women, breast cancer risk increased linearly with acrylamide intake starting at 20 μg/day of intake. High acrylamide intake was associated with increased risks of ovarian and endometrial cancers in a relatively linear manner, especially among never smokers. Conversely, little association was observed between acrylamide intake and breast cancer risk, with the exception of premenopausal women.

## Introduction

Acrylamide is an organic industrial chemical that is white, odorless, and crystalline in structure. It has been available commercially since the mid-1950s, and is used primarily in paper and plastic production as a flocculating agent to purify drinking water and wastewater, and as a sealing agent in buildings (1). In 1994, International Agency for Research on Cancer classified acrylamide as a probable human carcinogen (2A) based on animal experiments, considering exposure mainly from occupational and tobacco sources (2, 3). Only in 2002, Tareke and colleagues demonstrated the presence of acrylamide in foods and the importance of cooking technique in the formation of acrylamide (4). The main chemical process involved in acrylamide production is known as the "Maillard reaction" (5). In particular, acrylamide occurs naturally in starchy foods during cooking processes at high temperatures such as frying, baking, and grilling, even during industrial transformation processes at over 120°C and at low humidity. Conversely, boiling and steaming do not typically form acrylamide. Acrylamide is formed from sugars and proteins with high content of asparagine, an amino acid that is naturally present in many foods, especially potatoes, grain products, and coffee (5, 6). In contrast, meat, dairy, and seafood products have lower acrylamide content (6). In adults, foods that contribute most to dietary intake of acrylamide include French fries, potato chips, biscuits, and coffee (7, 8). On the basis of their usual serving size (9, 10) and according to acrylamide survey data in food (11), a standard portion of French fries (70 g) accounts for 30 μg/day of acrylamide, potato chips (27 g) for around 11 μg/day, while coffee (355 g) and biscuits (57 g) for about 4 and 3 μg/day, respectively.

Although acrylamide has been shown to have carcinogenic, neurotoxic, and adverse reproductive effects in animal models (12, 13), evidence of its health effects in humans is scarce and inconsistent. Occupational studies have shown adverse effects on both the peripheral and central nervous system after acute exposure, mainly via inhalation of high doses of acrylamide ranging from approximately 80 up to 1,000 μg/day, corresponding to 1.4–18 μg/kg of body weight/day (5). Acrylamide and glycidamide, its epoxide metabolite, are genotoxic and may potentially act as endocrine-disrupting chemicals, thereby altering physiologic hormonal balance at lower doses compared with exposure levels in occupational studies (14–17). In particular, acrylamide intake is associated with alteration of sex hormone levels in both pre- and postmenopausal women (18, 19), mainly increasing estradiol and follicle-stimulating hormone levels (19). Its association with hormone-dependent gynecologic neoplasms has been investigated previously. Many epidemiologic studies on acrylamide exposure (assessed either through diet or hemoglobin adducts) and breast and gynecologic cancers have been published, but few systematic reviews have addressed this topic (20–22). These reviews tend to report small increases in risk of endometrial and ovarian cancers, especially in never-smoking populations, but null risk for breast cancer. No dose–response meta-analysis has been performed previously. We conducted a dose–response meta-analysis based on

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**Note:** Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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epidemiologic studies of acrylamide dietary intake and risks of female breast, endometrial, and ovarian cancer.

## Materials and Methods

### Literature search

We carried out a systematic literature PubMed/Medline database search through February 25, 2020 using the entry terms acrylamide and (cancer or neoplasm or tumor) and (dietary or diet or nutritional or food) and (ovarian or ovary or endometrial or breast or mammalian). After assessing the results, we limited our review to studies on dietary exposure to acrylamide, with case–control or cohort designs, and those studies that reported breast, endometrial, or ovarian cancer risk estimates along with their 95% confidence intervals (CI) according to acrylamide exposure (μg/day). We excluded nonepidemiologic studies, studies not reporting risk estimates, and studies assessing acrylamide exposure using hemoglobin adducts.

### Data extraction

For each study, we abstracted country, design, cohort name, and population characteristics including range of study years, follow-up duration, total number and mean age of participants, number of cases, and adjustment factors. We compiled data on acrylamide levels divided into available categories (e.g., quantiles) and risk estimates. When reported, we also abstracted data stratified for smoking status, menopausal status, body mass index (BMI) category, and hormone receptor status (breast cancers only).

### Data analysis

We first conducted a meta-analysis of the overall measure of association (risk ratio, RR; hazard ratio, HR; or odds ratio, OR; hereafter reported as RR) and corresponding 95% CIs of each cancer type by comparing the highest versus the lowest level of exposure in a random effect model. In this analysis, we assessed heterogeneity by reporting $I^2$ statistics, and by carrying out stratified analyses.

We also performed a dose–response meta-analysis, implementing the recently developed one-stage methodology (23, 24) that we have applied previously (25–27), which allows the estimation of RRs across a large range of acrylamide intake alongside with their approximate point wise 95% CIs. For the exposure categories reported in each study, we extracted the mean or median depending on which was available. If unavailable, we inputted in the model the midpoint of each category or, when the extreme boundaries for the highest and the lowest exposure category were not reported, we entered a value 20% higher or lower than the closest cutoff (28, 29). For this analysis, we used restricted cubic splines with three knots at fixed percentiles (10th, 50th, and 90th) of exposure distribution using generalized least-squares regression model (24). To do this we took into account the correlation within each set of published RRs, and the study-specific estimates were combined using multivariate random-effect meta-analysis through the restricted maximum likelihood method (23). For all studies, we also fitted a linear regression analysis model and reported its slope alongside with the shape of the nonlinear relation yielded by the spline analysis (23).

In sensitivity analyses, we provided a graphical overlay of study-specific predicted curves including fixed and random effects, displaying the influence of variation across studies (24). We also reran all analyses by removing one study at a time to evaluate the specific influence of the omitted study on the results, and to assess source and magnitude of any heterogeneity. We performed all statistical analyses using the "metan" and "drmeta" routines in the STATA Software (version 16.1; StataCorp).

## Results

In **Fig. 1**, we report overall results of our database search. We retrieved 343 unique publications from online databases, which were reduced to 22 based on title and abstract screening. We excluded four studies for being conference abstracts (two studies, all followed by eligible publications), a literature review, and a commentary, leaving 18 studies for the qualitative analysis. We report general characteristics of included studies in **Table 1**. The most common study designs were the cohort (11 studies; refs. 30–40) and case cohort (five studies; refs. 7, 41–44), followed by two case–control studies (28, 29). These studies were published between 2005 and 2019, and the vast majority were carried out in Europe ($n = 15$), followed by the United States ($n = 2$), and Japan ($n = 1$). Some studies assessed more than one cancer type. Overall, 10 studies assessed breast cancer (28, 30–35, 42, 44), seven endometrial cancer (7, 29, 35–37, 40, 43), and seven ovarian cancer (7, 28, 35, 36, 38, 39, 41), with a total of 18,100, 3,561, and 3,569 cases of breast, endometrial, and ovarian cancer, respectively. Acrylamide dietary intake ranged from 3.6 μg/day to 44 μg/day, with both mean and median values of 21 μg/day (range 6.3–29.8 μg/day). All but three studies reported risk estimates among never-smoking women (28, 33, 39), while six carried out stratified analysis according to menopausal status (29–31, 35–37) or recruited either pre- (34) or postmenopausal women only (7, 32, 40, 41, 43). Finally, five studies presented results stratified by BMI (i.e., <25 and ≥25 kg/m$^2$; refs. 29, 31, 35–37), and six studies on breast cancer stratified the results by hormone receptor status, that is, estrogen receptor (ER) status and/or progesterone receptor (PR) status (refs. 31, 32, 34, 35, 42, 44; Supplementary Table S1). Five reports were available on the same study population (7, 41–44), and in these cases we included only the most recent and complete papers in our analyses (41–43).

In the meta-analysis summarizing the RR in the highest category of exposure versus the lowest, we found little evidence of any change in cancer risk at higher levels of acrylamide exposure, with a summary RR (sRR) of 0.96 (95% CI, 0.91–1.02) for breast cancer, 1.03 (95% CI, 0.91–1.17) for endometrial cancer, and 1.01 (95% CI, 0.87–1.18) for ovarian cancer (**Table 2**; Supplementary Fig. S1). All summary estimates were statistically imprecise. Restricting the analysis to never smokers, we observed similar results for breast cancer, but stronger although statistically imprecise risks for endometrial and ovarian cancer (sRR, 1.14; 95% CI, 0.96–1.36 and sRR, 1.17; 95% CI, 0.79–1.72, respectively; **Table 2**; Supplementary Fig. S2). In analyses stratified by menopausal status (**Table 2**; Supplementary Fig. S3), we found no appreciable association between exposure and risk of breast cancer among premenopausal women, and an inverse association in postmenopausal participants. Regarding endometrial cancer, we found lower risk among premenopausal women and a slightly higher risk among postmenopausal with higher exposure, although associations were imprecise. Ovarian cancer showed a positive association with acrylamide exposure among premenopausal women, although these findings were based on only two studies reporting opposite results (35, 36), while there was little evidence of increased risk among postmenopausal women. Results among never-smoking premenopausal women were available only for one study, which reported a positive association between acrylamide exposure and breast cancer risk (30). Conversely, among postmenopausal women, we found no association for breast cancer, and positive associations between acrylamide exposure and both endometrial and ovarian cancers (**Table 2**; Supplementary Fig. S4).

After stratifying analyses by BMI, we observed statistically imprecise, slightly positive associations between acrylamide intake

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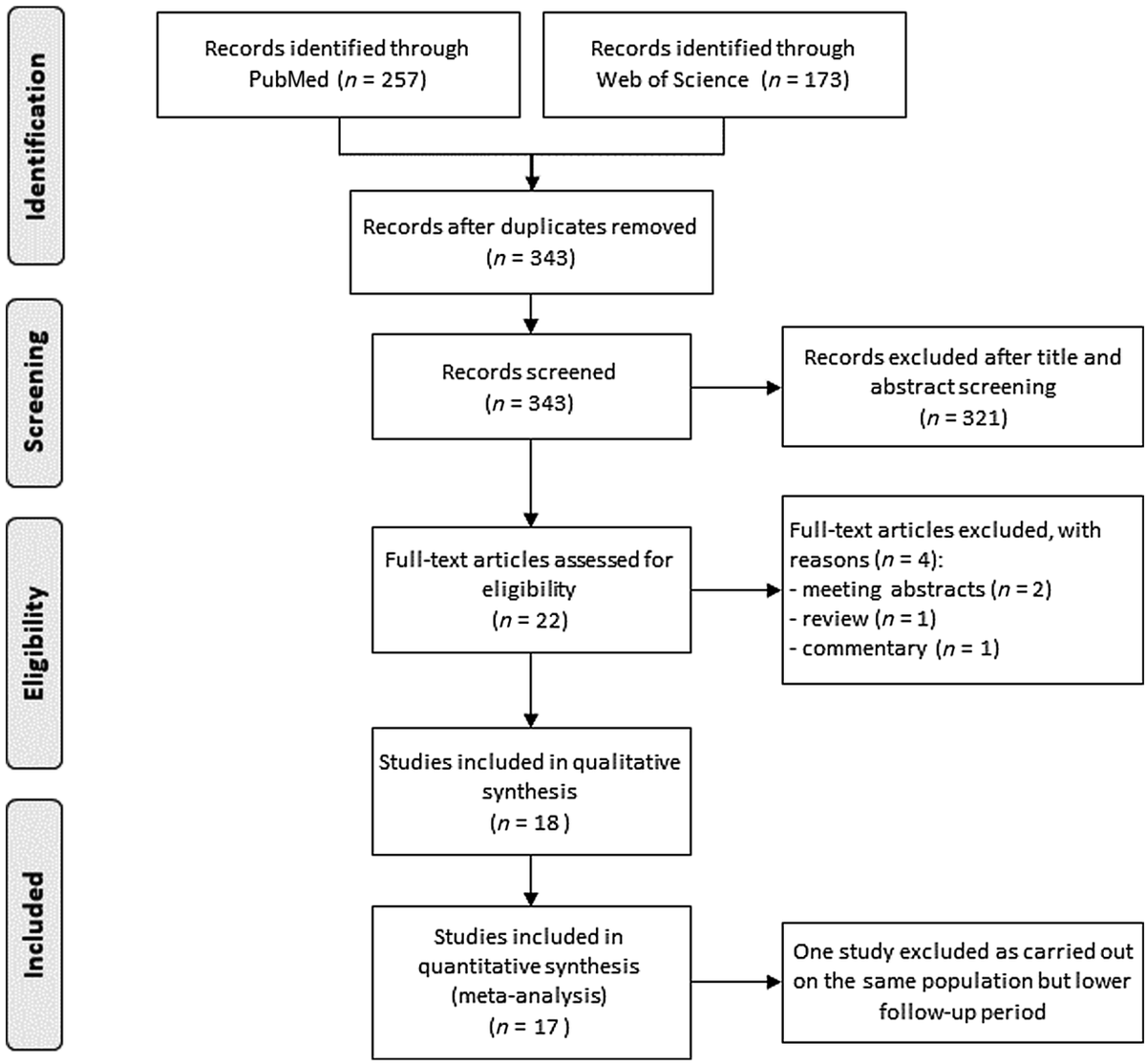


**Figure 1.**
Flowchart of literature search and identification through February 25, 2020.

and risk of endometrial and ovarian cancers only among women with BMI <25 kg/m$^2$ (**Table 2**; Supplementary Fig. S5). When stratifying for hormonal receptor status, we did not detect subgroup-specific changes in risk (**Table 2**).

In the dose–response meta-analysis, we found little association between dietary acrylamide intake and breast cancer risk, but rather some evidence of a slight inverse relation among never smokers (**Fig. 2**). For endometrial cancer, risk slightly increased for increasing exposure until the intermediate levels of exposure. At the highest levels of intake, risk tended to decrease among women overall, but remained constant in never smokers. Acrylamide intake was positively associated with risk of ovarian cancer, although at levels above 20 μg/day of acrylamide, the slope attenuated. Analyses restricted to never-smoking women showed the same pattern, but a higher risk at the corresponding levels of exposure (**Fig. 2**).

Dose–response analyses by menopausal status showed different patterns of association. Among premenopausal women, risk started to increase from approximately 20 μg/day of acrylamide intake for breast cancer in a linear manner, while the association was inverse and linear among postmenopausal women (Supplementary Figs. S6 and S7). The graph of the association between exposure and endometrial cancer did not suggest clear evidence of association and trends. The number of ovarian cancer studies was too few to carry out a dose–response analysis. Among postmenopausal women, increasing acrylamide intake was associated with greater breast cancer risk until 20 μg/day of exposure, after which the relation flattened (Supplementary Fig. S6). Because of the small number of studies, no dose–response meta-analysis by menopausal status among never-smokers could be performed.

In general, we found some heterogeneity in results between studies (**Table 2**). Conversely, when we reported study-specific dose–response

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**Table 1.** Characteristics of included studies, divided by cancer site.

| First author, year (reference) | Region | Cohort name | Study design, cohort years range/age | Follow-up (years) | *N* cases/ population | Acrylamide average intake (μg/day)[a] | Acrylamide intake by categories (μg/day)[a] | Cancer risk in all women RR (95% CI)[b] | Cancer risk among never smokers RR (95% CI)[b] | Adjustments factors |
|---|---|---|---|---|---|---|---|---|---|---|
| **Breast cancer** | | | | | | | | | | |
| Burley, 2010 (30) | United Kingdom | UK Women's Cohort | Cohort 1995–1998 age 35–69 | 11 | 1,084/35,372 | 15 | Q1: 6<br>Q2: 11<br>Q3: 15<br>Q4: 20<br>Q5: 32 | Ref 1.00<br>1.06 (0.83–1.35)<br>1.05 (0.82–1.34)<br>1.12 (0.87–1.45)<br>1.16 (0.88–1.52) | Ref 1.00<br>0.87 (0.63–1.20)<br>0.95 (0.69–1.30)<br>0.96 (0.69–1.34)<br>0.98 (0.69–1.40) | Premenopausal and postmenopausal women separately and combined, first as a simple model adjusting for age, smoking status and amount smoked, weight, height, physical activity, oral contraceptive use, hormone replacement therapy use, parity, age at menarche, alcohol intake, energy intake other than from alcohol, and level of education |
| Hogervorst, 2007 (7) | The Netherlands | Netherlands Cohort Study on diet and cancer | Case–cohort 1986–1997 age 55–69 | 11.3 | 1,835/62,573 (2,247 subcohort[c]) | 21 | Q1: 9.5<br>Q2: 14<br>Q3: 17.9<br>Q4: 24.3<br>Q5: 36.8 | Ref 1.00<br>0.80 (0.64–1.02)<br>0.92 (0.72–1.17)<br>0.86 (0.67–1.10)<br>0.93 (0.73–1.19) | Ref 1.00<br>0.97 (0.72–1.32)<br>1.17 (0.85–1.61)<br>1.00 (0.73–1.38)<br>1.10 (0.80–1.52) | Age, age at menarche, age at menopause, age at first childbirth, parity, duration of oral contraceptives use, duration of postmenopausal hormone use, BMI, height, current smoking, quantity of smoking, duration of smoking, nonoccupational physical activity, energy intake, trans-unsaturated fatty acid intake, carbohydrate intake, and alcohol consumption |
| Hogervorst, 2019 (44) | The Netherlands | Netherlands Cohort Study on diet and cancer | Case–cohort 1986–2006 age 55–69 | 20.3 | 1,238/62,573 (1,449 subcohort[c]) | 21 | Q1: 9.5<br>Q2: 14<br>Q3: 17.9<br>Q4: 24.3<br>Q5: 36.8 | Ref 1.00<br>0.88 (0.69–1.11)<br>1.01 (0.79–1.29)<br>0.93 (0.73–1.20)<br>0.85 (0.66–1.09) | Ref 1.00<br>1.08 (0.78–1.49)<br>1.44 (1.04–2.01)<br>1.34 (0.96–1.86)<br>1.18 (0.85–1.64) | Age, age at menarche, age at menopause, age at first childbirth, parity, ever use of oral contraceptives, ever use of postmenopausal hormone treatment, height, BMI, educational level, energy intake, history of benign breast disease, family history of breast cancer, smoking status, smoking quantity, and smoking duration |
| Kotemori, 2018a (31) | Japan | Japan Public Health Center-based Prospective Study | Cohort 1990–2013 age 45–74 | 15.4 | 792/48,910 | 7 | T1: 3.6<br>T2: 6.3<br>T3: 11.1 | Ref 1.00<br>1.00 (0.84–1.18)<br>0.95 (0.79–1.14) | Ref 1.00<br>0.97 (0.81–1.17)<br>0.93 (0.77–1.12) | Age, area, BMI, family history of breast cancer, age at menarche, age at first delivery, number of deliveries, menopausal status and age at menopause, use of exogenous female hormones, smoking status, and alcohol intake |
| Larsson, 2009a (32) | Sweden | Swedish Mammography Cohort | Cohort 1987–2007 age ≈54 | 17.4 | 2,952/61,433 | 24.6 | Q1: 16.9<br>Q2: 22.3<br>Q3: 26.4<br>Q4: 32.5 | Ref 1.00[d]<br>1.02 (0.92–1.14)<br>0.95 (0.85–1.06)<br>0.91 (0.80–1.02) | Ref 1.00[d]<br>1.18 (0.92–1.51)<br>1.03 (0.78–1.37)<br>0.91 (0.65–1.27) | Age, education, BMI, height, parity, age at first birth, age at menarche, age at menopause, use of oral contraceptives, use of postmenopausal hormones, family history of breast cancer, history of benign breast disease, alcohol intake, coffee intake, energy-adjusted cereal fiber intake, and total energy intake |
| Mucci, 2005 (33) | Sweden | Swedish Women's Lifestyle and Health Cohort | Cohort 1991–2002 age 39 ± 5 | 11 | 667/43,404 | 25.9 | Q1: 12<br>Q2: 20<br>Q3: 25<br>Q4: 31<br>Q5: 44 | Ref 1.00<br>0.9 (0.7–1.1)[e]<br>1.0 (0.8–1.3)[e]<br>1.0 (0.8–1.3)[e]<br>1.19 (0.91–1.55) | NA | Age, education, alcohol intake, smoking status, oral contraceptive use, parity, age at first birth, menopausal status, family history of breast cancer, fiber intake, saturated fat intake, and total energy intake |

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| First author, year (reference) | Region | Cohort name | Study design, cohort years range/age | Follow-up (years) | *N* cases/ population | Acrylamide average intake (μg/day)[a] | Acrylamide intake by categories (μg/day)[a] | Cancer risk in all women RR (95% CI)[b] | Cancer risk among never smokers RR (95% CI)[b] | Adjustments factors |
|---|---|---|---|---|---|---|---|---|---|---|
| Pedersen, 2010 (42) | The Netherlands | Netherlands Cohort Study on diet and cancer | Case–cohort 1986–1999 age 55–69 | 13.3 | 2,225/ 62,573 (2,247 subcohort[c]) | 21 | Q1: 9.5<br>Q2: 14<br>Q3: 17.9<br>Q4: 24.3<br>Q5: 36.8 | Ref 1.00<br>0.91 (0.73–1.23)<br>0.96 (0.76–1.19)<br>0.89 (0.72–1.12)<br>0.92 (0.73–1.15) | Ref 1.00<br>1.11 (0.84–1.48)<br>1.28 (0.95–1.72)<br>1.08 (0.80–1.45)<br>1.15 (0.86–1.53) | Age, age at menarche, age at menopause, age at first childbirth, parity, BMI, family history of breast cancer, history of benign breast disease, use of oral contraceptive, postmenopausal hormone use, energy intake, smoking status, duration of smoking, quantity of smoking |
| Pelucchi, 2006 (28) | Italy-Switzerland | Case–control study | Case–control 1991–2001 | – | 2,900/3,122 controls | 23.3–29.24 | *Q1: <10.57*<br>*Q2: 10.57–20.58*<br>*Q3: 20.58*<br>*Q4: 20.58–34.25*<br>*Q5: >34.25* | Ref 1.00<br>1.01 (0.85–1.20)<br>1.01 (0.85–1.20)<br>1.09 (0.92–1.31)<br>1.06 (0.88–1.28) | NA | Age, study center, education, BMI, energy intake, family history of breast and/or ovarian cancer, and parity |
| Wilson, 2009 (34) | United States | Nurses' Health Study II | Cohort 1989–2005 age 25–42 | 15 | 1,179/116,671 | 20.2 | Q1: 10.8<br>Q2: 16.6<br>Q3: 20.2<br>Q4: 24.6<br>Q5: 37.8 | Ref 1.00[d]<br>0.95 (0.79–1.14)<br>0.94 (0.78–1.13)<br>1.03 (0.87–1.24)<br>0.92 (0.76–1.11) | Ref 1.00[d]<br>0.91 (0.73–1.14)<br>0.94 (0.75–1.18)<br>1.08 (0.86–1.34)<br>0.82 (0.64–1.05) | Age in months and calendar year and adjusted for the following: BMI, height, oral contraceptive use, parity and age at first birth, age at menarche, family history of breast cancer, history of benign breast disease, smoking, physical activity, animal fat, glycemic load, alcohol intake, and total energy intake |
| Wilson, 2010 (35) | United States | Nurses' Health Study | Cohort 1980–2006 age 33–55 | 26 | 6,301/88,672 | 16 | Q1: 9<br>Q2: 13<br>Q3: 16<br>Q4: 19<br>Q5: 26 | Ref 1.00[d]<br>0.93 (0.86–1.01)<br>0.98 (0.91–1.06)<br>0.98 (0.90–1.06)<br>0.95 (0.87–1.03) | Ref 1.00[d]<br>0.91 (0.81–1.02)<br>0.93 (0.83–1.05)<br>0.94 (0.84–1.06)<br>0.89 (0.78–1.02) | Age, smoking, BMI, height, menopausal status/ age at menopause/postmenopausal hormone use, parity and age at first birth, family history of breast cancer, benign breast disease, age at menarche, physical activity, folate, glycemic index, animal fat intake, alcohol intake, and energy intake |
| **Endometrial cancer** | | | | | | | | | | |
| Hogervorst, 2007 (7) | The Netherlands | Netherlands Cohort Study on diet and cancer | Case–cohort 1986–1997 age 55–69 | 11.3 | 327/62,573 (1,911 subcohort[c]) | 21 | Q1: 9.5<br>Q2: 14<br>Q3: 17.9<br>Q4: 24.3<br>Q5: 36.8 | Ref 1.00<br>0.95 (0.59–1.54)<br>0.94 (0.56–1.56)<br>1.21 (0.74–1.98)<br>1.29 (0.81–2.07) | Ref 1.00<br>1.16 (0.63–2.15)<br>1.35 (0.73–2.51)<br>1.30 (0.69–2.46)<br>1.99 (1.12–3.52) | Age, age at menarche, age at menopause, age at first childbirth, parity, duration of oral contraceptives use, duration of postmenopausal hormone use, BMI, height, current smoking, quantity of smoking, duration of smoking, nonoccupational physical activity, energy intake, trans-unsaturated fatty acid intake, carbohydrate intake, and alcohol consumption |
| Hogervorst, 2016 (43) | The Netherlands | Netherlands Cohort Study on diet and cancer | Case–cohort 1986–2006 age 55–69 | 20.3 | 393/62,573 (1,474 subcohort[c]) | 21 | Q1: 9.5<br>Q2: 14<br>Q3: 17.9<br>Q4: 24.3<br>Q5: 36.8 | Ref 1.00<br>0.87 (0.60–1.27)<br>0.86 (0.58–1.28)<br>0.95 (0.64–1.41)<br>1.03 (0.71–1.51) | Ref 1.00<br>1.07 (0.67–1.70)<br>1.14 (0.70–1.86)<br>1.08 (0.66–1.77)<br>1.44 (0.90–2.28) | Age, age at menarche, age at menopause, parity, ever use of oral contraceptives, ever use of postmenopausal hormone use, BMI, and in the analyses for all women: current smoking, quantity of smoking, duration of smoking, family history of endometrial cancer, and energy intake |

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| First author, year (reference) | Region | Cohort name | Study design, cohort years range/age | Follow-up (years) | *N* cases/ population | Acrylamide average intake (μg/day)[a] | Acrylamide intake by categories (μg/day)[a] | Cancer risk in all women RR (95% CI)[b] | Cancer risk among never smokers RR (95% CI)[b] | Adjustments factors |
|---|---|---|---|---|---|---|---|---|---|---|
| Kotemori, 2018b (36) | Japan | Japan Public Health Center-based Prospective Study | Cohort age 45–74 | 15.4 | 161/47,187 | 6.3 | Q1: 3.7<br>Q2: 6.4<br>Q3: 11.1 | Ref 1.00<br>0.83 (0.57–1.22)<br>0.85 (0.54–1.33) | Ref 1.00<br>0.85 (0.57–1.25)<br>0.82 (0.51–1.31) | Age, area, BMI, age at menarche, age at first delivery, number of deliveries, menopause status and age at menopause, use of exogenous female hormones, smoking status, and alcohol intake |
| Larsson, 2009b (40) | Sweden | Swedish Mammography Cohort | Cohort 1987–2007 age ≈54 | 17.7 | 687/61,226 | 24.6 | Q1: 16.9<br>Q2: 22.3<br>Q3: 26.4<br>Q4: 32.5 | Ref 1.00[d]<br>1.10 (0.89–1.36)<br>1.08 (0.88–1.34)<br>0.96 (0.76–1.21) | Ref 1.00[d]<br>1.31 (0.85–2.04)<br>1.30 (0.83–2.02)<br>1.20 (0.76–1.90) | Age, education, BMI, parity, age at first birth, age at menarche, age at menopause, use of oral contraceptives, use of postmenopausal hormones, energy-adjusted carbohydrate intake, and total energy intake |
| Obon-Santacana, 2014 (37) | Europe | EPIC cohort | Cohort 1992–1998 | 6 | 1,382/301,113 | 24 | Q1: 10.8<br>Q2: 17.2<br>Q3: 21.9<br>Q4: 27.7<br>Q5: 39.5 | Ref 1.00<br>1.05 (0.86–1.29)<br>1.11 (0.90–1.36)<br>0.88 (0.71–1.10)<br>0.98 (0.78–1.25) | Ref 1.00<br>1.03 (0.79–1.34)<br>1.04 (0.79–1.36)<br>0.82 (0.61–1.10)<br>1.01 (0.75–1.38) | BMI, smoking status, history of diabetes, oral contraceptive use, hormone replacement therapy use, baseline menopause status combined with age at menopause, parity, and age at menarche |
| Pelucchi, 2016 (29) | Italy | Case–control study | Case–control 1992–2006 | — | 454/908 controls | 29.8 | *Q1: <17.7*<br>*Q2: 17.7–24.0*<br>*Q3: 24.0–30.4*<br>*Q4: 30.4–39.2*<br>*Q5: >39.2* | Ref 1.00[f]<br>1.02 (0.67–1.54)<br>1.20 (0.80–1.80)<br>1.00 (0.65–1.54)<br>1.17 (0.73–1.85) | Ref 1.00[f]<br>1.21 (0.75–1.95)<br>1.24 (0.76–2.01)<br>1.02 (0.60–1.73)<br>1.28 (0.73–2.25) | Study center and age, and adjusted for period of interview, education, tobacco smoking, BMI, occupational physical activity, history of diabetes, age at menarche, menopausal status/age at menopause, parity, oral contraceptive use, hormone replacement therapy, and total energy intake |
| Wilson, 2010 (35) | U.S.A. | Nurses' Health Study | Cohort 1980–2006 age 33–55 | 26 | 484/69,019 | 16 | Q1: 9<br>Q2: 13<br>Q3: 16<br>Q4: 19<br>Q5: 26 | Ref 1.00<br>1.12 (0.83–1.50)<br>1.31 (0.97–1.77)<br>1.35 (0.99–1.84)<br>1.41 (1.01–1.97) | Ref 1.00<br>0.97 (0.64–1.46)<br>1.35 (0.90–2.02)<br>1.47 (0.97–2.24)<br>1.43 (0.90–2.28) | Smoking, BMI, age at menarche, menopausal status/age at menopause/postmenopausal hormone use, parity, oral contraceptive use, high blood pressure, diabetes, physical activity, caffeine intake, and energy intake |
| | | | | | **Ovarian cancer** | | | | | |
| Hogervorst, 2007 (7) | The Netherlands | Netherlands Cohort Study on diet and cancer | Case–cohort 1986–1997 age 55–69 | 11.3 | 300/62,573 (2,216 subcohort[c]) | 21 | Q1: 9.5<br>Q2: 14<br>Q3: 17.9<br>Q4: 24.3<br>Q5: 36.8 | Ref 1.00<br>1.22 (0.73–2.01)<br>1.12 (0.65–1.92)<br>1.28 (0.77–2.13)<br>1.78 (1.10–2.88) | Ref 1.00<br>1.60 (0.85–3.02)<br>1.64 (0.84–3.19)<br>1.86 (1.00–3.48)<br>2.22 (1.20–4.08) | Age, age at menarche, age at menopause, parity, duration of oral contraceptives use, duration of postmenopausal hormone use, BMI, height, current smoking, quantity of smoking, duration of smoking, saturated fat intake, and trans-unsaturated fatty acid intake |
| Hogervorst, 2017 (41) | The Netherlands | Netherlands Cohort Study on diet and cancer | Case–cohort 1986–2006 age 55–69 | 20.3 | 373/625,73 (1,474 subcohort[c]) | 21 | Q1: 9.5<br>Q2: 14<br>Q3: 17.9<br>Q4: 24.3<br>Q5: 36.8 | Ref 1.00<br>1.07 (0.73–1.54)<br>1.10 (0.75–1.61)<br>1.05 (0.71–1.53)<br>1.38 (0.95–1.99) | Ref 1.00<br>1.37 (0.85–2.21)<br>1.61 (0.98–2.65)<br>1.50 (0.92–2.44)<br>1.85 (1.15–2.95) | Age, age at menarche, age at menopause, parity, ever use of oral contraceptives, ever use of postmenopausal hormone treatment, height, BMI, energy intake, and in the analyses for all women: smoking status, smoking quantity, and smoking duration |

*(Continued on the following page)*

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**Table 1.** Characteristics of included studies, divided by cancer site. (Cont'd)

| First author, year (reference) | Region | Cohort name | Study design, cohort years range/age | Follow-up (years) | *N* cases/ population | Acrylamide average intake (μg/day)[a] | Acrylamide intake by categories (μg/day)[a] | Cancer risk in all women RR (95% CI)[b] | Cancer risk among never smokers RR (95% CI)[b] | Adjustments factors |
|---|---|---|---|---|---|---|---|---|---|---|
| Kotemori, 2018b (36) | Japan | Japan Public Health Center-based Prospective Study | Cohort Study age 45–74 | 15.4 | 122/47,187 | 6.3 | Q1: 3.7<br>Q2: 6.4<br>Q3: 11.1 | Ref 1.00<br>0.90 (0.59–1.38)<br>0.77 (0.49–1.23) | Ref 1.00<br>0.94 (0.60–1.48)<br>0.82 (0.50–1.33) | Age, area, BMI, age at menarche, age at first delivery, number of deliveries, menopause status and age at menopause, use of exogenous female hormones, smoking status, and alcohol intake |
| Larsson, 2009c (38) | Sweden | Swedish Mammography Cohort | Cohort 1987–2007 age ≈54 | 17.5 | 368/61,057 | 24 | Q1: 16.9<br>Q2: 22.3<br>Q3: 26.4<br>Q4: 32.5 | Ref 1.00[d]<br>0.91 (0.68–1.21)<br>0.97 (0.73–1.29)<br>0.86 (0.63–1.16) | Ref 1.00[d]<br>1.32 (0.71–2.45)<br>1.10 (0.57–2.09)<br>0.97 (0.49–1.93) | Age, education, BMI, parity, age at first childbirth, age at menarche, age at menopause, use of oral contraceptives, use of postmenopausal hormones, and total energy intake |
| Obon-Santacana, 2015 (39) | Europe | EPIC cohort study | Cohort 1992–1998 | 6 | 1,191/325,006 | 23.8 | Q1: 10.8<br>Q2: 17.2<br>Q3: 21.9<br>Q4: 27.7<br>Q5: 39.5 | Ref 1.00<br>0.89 (0.72–1.11)<br>0.87 (0.70–1.09)<br>1.08 (0.87–1.34)<br>0.97 (0.76–1.23) | NA | BMI, smoking, history of diabetes, oral contraceptive use, hormone replacement therapy use, baseline menopause status combined with age at menopause, parity, and age at menarche |
| Pelucchi, 2006 (28) | Italy-Switzerland | Case–control study | Case–control 1991–2001 | — | 1,031/2,411 controls | 23.3–29.24 | *Q1: <10.57*<br>*Q2: 10.57–20.58*<br>*Q3: 20.58*<br>*Q4: 20.58–34.25*<br>*Q5: >34.25* | Ref 1.00<br>1.03 (0.79–1.34)<br>1.09 (0.83–1.44)<br>1.01 (0.76–1.34)<br>0.97 (0.73–1.31) | NA | Age, study center, education, BMI, energy intake, family history of breast and/or ovarian cancer, and parity |
| Wilson, 2010 (35) | United States | Nurses' Health Study | Cohort 1980–2006 age 33–55 | 26 | 484/80,011 | 16 | Q1: 9<br>Q2: 13<br>Q3: 16<br>Q4: 19<br>Q5: 26 | Ref 1.00<br>0.93 (0.68–1.29)<br>1.29 (0.94–1.76)<br>1.17 (0.84–1.64)<br>1.25 (0.88–1.77) | Ref 1.00<br>1.17 (0.72–1.88)<br>1.04 (0.63–1.74)<br>1.11 (0.63–1.94)<br>1.19 (0.66–2.15) | Smoking, BMI, parity, oral contraceptive use menopausal status and post-menopausal hormone use, tubal ligation, physical activity, caffeine intake, and energy intake |

Abbreviations: BMI, body mass index; NA, not assessed; Ref, reference; RR, risk ratio.

[a]Median or mean value of each category reported whenever available, otherwise, cut-off points are reported in italics (28, 29).

[b]Where not differently reported, all values describe HR with 95% CI.

[c]We reported sample size of the total cohort and of the subcohort selected as control population, randomly drawn from total cohort according to the case–cohort design.

[d]Rate ratio (95% CI).

[e]Data retrieved from Hogervorst 2018 (22).

[f]OR (95% CI).

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**Table 2.** Summary risk ratios (RRs) for the association of breast, endometrial, and ovarian cancer risk with acrylamide intake comparing the highest versus the lowest exposure categories for overall study population and restricted to never-smoking women.

| | All women | | | Never-smoking women | | |
|---|---|---|---|---|---|---|
| | *n* | RR (95% CI) | $I^2$ (%) | *n* | RR (95% CI) | $I^2$ (%) |
| *Breast cancer* | | | | | | |
| All studies | 8 | 0.96 (0.91–1.02) | 0.0 | 6 | 0.92 (0.84–1.00) | 0.0 |
| Menopausal status | | | | | | |
| Premenopausal | 4 | 1.02 (0.85–1.21) | 38.5 | 1 | 1.17 (0.69–2.00) | — |
| Postmenopausal | 5 | 0.93 (0.87–1.00) | 0.0 | 3 | 1.02 (0.85–1.23) | 0.0 |
| BMI | | | | | | |
| <25 kg/m$^2$ | 2 | 0.93 (0.83–1.03) | 0.0 | | | |
| ≥25 kg/m$^2$ | 2 | 0.97 (0.87–1.08) | 0.0 | | | |
| Hormone receptor status | | | | | | |
| ER$^+$ | 3 | 0.90 (0.74–1.10) | 0.0 | 1 | 1.31 (0.87–1.97) | — |
| ER$^-$ | 2 | 0.87 (0.60–1.27) | 0.0 | 1 | 0.95 (0.52–1.72) | — |
| PR$^+$ | 2 | 1.02 (0.77–1.36) | 0.0 | 1 | 1.47 (0.86–2.51) | — |
| PR$^-$ | 2 | 0.84 (0.61–1.16) | 0.0 | 1 | 0.84 (0.63–1.56) | — |
| ER$^+$PR$^+$ | 5 | 0.98 (0.89–1.08) | 0.0 | 1 | 1.43 (0.83–2.46) | — |
| ER$^-$PR$^-$ | 5 | 0.89 (0.78–1.02) | 0.0 | | | |
| ER$^+$PR$^-$ | 2 | 1.09 (0.89–1.33) | 0.0 | | | |
| ER$^-$PR$^+$ | 1 | 1.09 (0.63–1.88) | — | | | |
| *Endometrial cancer* | | | | | | |
| All studies | 6 | 1.03 (0.91–1.17) | 0.0 | 6 | 1.14 (0.96–1.36) | 0.0 |
| Menopausal status | | | | | | |
| Premenopausal | 5 | 0.89 (0.62–1.29) | 43.4 | — | — | — |
| Postmenopausal | 5 | 1.05 (0.88–1.25) | 0.0 | 2 | 1.31 (0.95–1.82) | 0.0 |
| BMI | | | | | | |
| <25 kg/m$^2$ | 4 | 1.25 (0.73–2.13) | 73.4 | | | |
| ≥25 kg/m$^2$ | 4 | 0.98 (0.76–1.25) | 12.6 | | | |
| *Ovarian cancer* | | | | | | |
| All studies | 6 | 1.01 (0.87–1.18) | 25.9 | 4 | 1.17 (0.79–1.72) | 49.5 |
| Menopausal status | | | | | | |
| Premenopausal | 2 | 1.15 (0.51–2.60) | 41.2 | — | — | — |
| Postmenopausal | 4 | 1.05 (0.82–1.33) | 33.2 | 2 | 1.41 (0.75–2.63) | 56.8 |
| BMI | | | | | | |
| <25 kg/m$^2$ | 2 | 1.25 (0.57–2.73) | 78.0 | | | |
| ≥25 kg/m$^2$ | 2 | 0.78 (0.49–1.24) | 0.0 | | | |

Abbreviations: BMI, body mass index; ER, estrogen receptor; $I^2$ (%), heterogeneity; *n*, number of studies; PR, progesterone receptor.

trends (Supplementary Fig. S8), we found moderate variation in results for endometrial cancer only, while breast and ovarian cancers demonstrated more comparable study-specific dose–response trends. After systematically removing each study in turn from the analyses, we observed no appreciable change in summary estimates (Supplementary Figs. S9–S29). Among never smokers, results for breast and endometrial cancers were similar (Supplementary Figs. S12 and S13), while risk of ovarian cancer showed an inverse association after removing one study (ref. 41; Supplementary Fig. S14). Funnel plots showed substantial symmetric distributions for all cancer types (Supplementary Fig. S30), with little indication of any publication bias.

## Discussion

We observed that acrylamide intake was associated with small increased risks of endometrial and ovarian cancer, with stronger and almost linear associations among never smokers. However, no positive relation emerged for breast cancer, except among premenopausal women for exposure above 20 μg/day. Data were too limited to examine endometrial and ovarian cancers by menopausal status with reasonable precision. In the literature, studies of glycidamide hemoglobin adducts have been conflicting, with a positive association observed in a European population (45) and no association in a comparable U.S. study (46). Conversely, hemoglobin adducts of acrylamide and glycidamide showed little association with endometrial cancer risk in a recent cohort-nested case–control study (47).

To the best of our knowledge, this is the first systematic review examining the shape of the dose–response relation of dietary acrylamide with breast and gynecologic cancers. In addition, we updated the previous meta-analysis of cancer risk associated with acrylamide exposure (one including all cancers overall and one endometrial cancer only; refs. 20, 21) by adding six newly published studies, two studies each for breast (31, 44), endometrial (36, 43), and ovarian cancer (36, 41). Previous meta-analyses reported a slight increase in risk of endometrial and ovarian cancer at high levels of acrylamide intake, primarily among never smokers, and no association for breast cancer. In a nested case–control study evaluating acrylamide exposure through hemoglobin adduct concentration, higher exposure levels were positively associated with breast cancer risk, particularly among ER$^+$ women (48), although these results were opposite to those generated by a recent case–cohort study (44). In addition, in a cohort study evaluating exposure to air pollutants and breast cancer risk, ER$^+$/PR$^+$ cancers were associated with higher ambient concentrations of acrylamide (49), a finding consistent with observations from a

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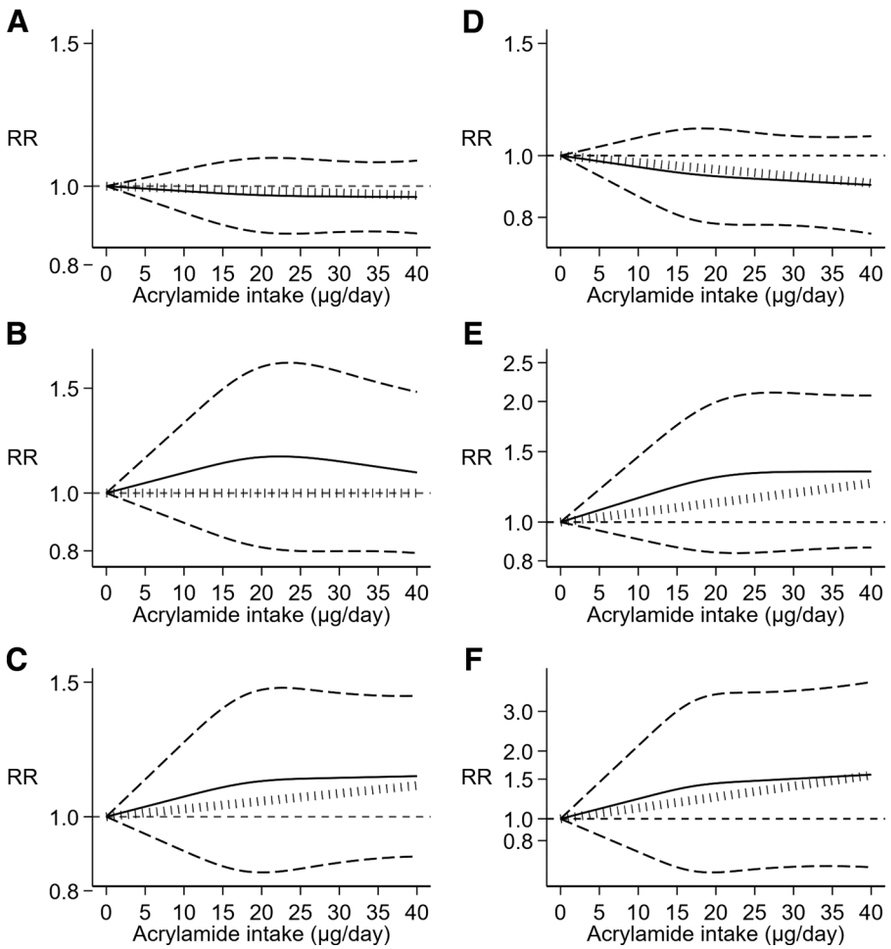


**Figure 2.**

Dose–response meta-analysis between acrylamide intake and risk of breast (**A**; refs. 28, 30–35, 42), endometrial (**B**; refs. 29, 35–37, 40, 43), and ovarian cancer (**C**; refs. 28, 36, 38, 39, 41) in all women, and with breast (**D**; refs. 30–32, 34, 35, 42), endometrial (**E**; refs. 29, 35–37, 40, 43), and ovarian cancer (**F**; refs. 36, 38, 39, 41) in never smokers. Spline curve (solid line) with 95% confidence limits (long-dashed lines), null association (short-dashed line), and linear trend (vertical bar line). RR, risk ratio.

case–cohort study by Hogervorst and colleagues based on dietary intake assessment (44). There is also evidence that acrylamide intake might alter levels of estrogens in premenopausal women, although two studies on this topic found opposite relations between dietary acrylamide intake and free estradiol levels (18, 19).

There is some biological plausibility for an association between acrylamide exposure and both breast and gynecologic cancers. Female rats exposed to high amounts of acrylamide had an increased incidence of breast adenocarcinomas and fibroadenomas (50–52), similarly to B6C3F1 mice and F344/N rats exposed to glycidamide through drinking water (53, 54). A study conducted on MCF10A human mammary cells confirmed their susceptibility to the toxicity of the acrylamide epoxide metabolite, glycidamide (55). Concerning endometrial cancer, glycidamide exposure induced uterine adenocarcinoma of the uterus and endometrial hyperplasia in female rats, and ovary cancer in mice (52, 54). In addition, acrylamide may induce genotoxic and cytotoxic effects through induction of oxidative imbalance (13) leading to cell death or neoplastic transformation (56), and can alter protein functions by binding to cysteine residues in proteins (22). Acrylamide might also have endocrine disrupting properties (5). Finally, glycidamide may alkylate DNA leading to point mutations and potential activation of oncogenes or tumor suppressor genes (57–59). Despite these findings in experimental animals, it is uncertain whether usual exposure to glycidamide in the general population may affect risk of gynecologic cancers, because its carcinogenicity may occur only at high doses (58). Specifically, in animal studies, the acrylamide dose may be as high as 9.5 mg/kg of body weight/day, a much higher exposure amount compared with that characterizing the human studies we considered, in which median level was 21 μg/day (corresponding to 0.3 μg/kg of body weight/day, range 0.05–0.63; refs. 51, 53). Similarly, for acute occupational exposure, acrylamide doses up to 18 μg/kg of body weight/day have been reported (5). We found different results between all women and never-smoking women, with stronger positive association for endometrial and ovarian cancers (but not for breast cancer) in the latter, which might be linked to some interactions between acrylamide exposure and smoking. In fact, smoking has antiestrogenic properties (60–62), and may alter acrylamide and glycidamide metabolism, thus modifying the association between acrylamide exposure and cancer risk (63).

A major strength of our review is the implementation of a newly developed biostatistical method to perform dose–response meta-analysis, allowing us to assess the shape of the relation between acrylamide intake with cancer risk over a wide range of exposure. In addition, we accounted for major established or putative risk factors such as body weight, smoking habits, hormone replacement therapy/oral contraceptive use, lack of physical activity, and alcohol intake (64–67) by using the most adjusted estimates from included studies. However, we acknowledge that unmeasured confounding may still have influenced these findings, with reference to environmental risk factors such

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as cadmium (68–70), pesticides (71–73), or air pollution (74–77). Moreover, food frequency questionnaires used for acrylamide intake estimation in the included studies did not generally collect information about cooking methods, potentially affecting the reliability of exposure assessment (78) and contributing to heterogeneity in results.

In conclusion, although some results were based on a small number of studies, our findings appear to support the currently ongoing efforts to monitor and minimize acrylamide intake (79–82) given some evidence of a small positive association with risks of endometrial and ovarian cancer, particularly among never smokers. Conversely, there was limited evidence for an association between acrylamide intake and breast cancer risk, with the exception of increased risks at ≥20 μg/day of acrylamide among premenopausal women.

## Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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## References

1. American Cancer Society. Acrylamide and cancer risk; 2019. Available from: https://www.cancer.org/cancer/cancer-causes/acrylamide.html.
2. International Agency for Research on Cancer. IARC monographs on the evaluation of carcinogenic risks to humans. Lyon, France: IARC; 1994. p 389–433.
3. Mojska H, Gielecinska I, Cendrowski A. Acrylamide content in cigarette mainstream smoke and estimation of exposure to acrylamide from tobacco smoke in Poland. Ann Agric Environ Med 2016;23:456–61.
4. Tareke E, Rydberg P, Karlsson P, Eriksson S, Tornqvist M. Analysis of acrylamide, a carcinogen formed in heated foodstuffs. J Agric Food Chem 2002;50:4998–5006.
5. EFSA CONTAM Panel. Scientific opinion on acrylamide in food. EFSA Journal 2015;13:4104.
6. U.S. Food and Drug Administration. Acrylamide and diet, food storage, and food preparation; 2017. Available from: https://www.fda.gov/food/chemicals/acrylamide-and-diet-food-storage-and-food-preparation.
7. 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;16:2304–13.
8. Dybing E, Farmer PB, Andersen M, Fennell TR, Lalljie SP, Muller DJ, et al. Human exposure and internal dose assessments of acrylamide in food. Food Chem Toxicol 2005;43:365–410.
9. Smiciklas-Wright H, Mitchell DC, Mickle SJ, Goldman JD, Cook A, editors. Foods commonly eaten in the United States: quantities consumed per eating occasion and in a day, 1994–96. 5th ed. Washington (DC): Agricultural Research Service, U.S. Department of Agriculture; 2005. p. 247.
10. Smiciklas-Wright H, Mitchell DC, Mickle SJ, Goldman JD, Cook A. Foods commonly eaten in the United States, 1989–1991 and 1994–1996: are portion sizes changing? J Am Diet Assoc 2003;103:41–7.
11. U.S. Food and Drug Administration. Survey data on acrylamide in food; 2018. Available from: https://www.fda.gov/food/chemicals/survey-data-acrylamide-food.
12. Kumar J, Das S, Teoh SL. Dietary acrylamide and the risks of developing cancer: facts to ponder. Front Nutr 2018;5:14.
13. Semla M, Goc Z, Martiniakova M, Omelka R, Formicki G. Acrylamide: a common food toxin related to physiological functions and health. Physiol Res 2017;66:205–17.
14. Matoso V, Bargi-Souza P, Ivanski F, Romano MA, Romano RM. Acrylamide: a review about its toxic effects in the light of developmental origin of health and disease (DOHaD) concept. Food Chem 2019;283:422–30.
15. Tyla RW, Friedman MA, Losco PE, Fisher LC, Johnson KA, Strother DE, et al. Rat two-generation reproduction and dominant lethal study of acrylamide in drinking water. Reprod Toxicol 2000;14:385–401.
16. Kassotis CD, Klemp KC, Vu DC, Lin CH, Meng CX, Besch-Williford CL, et al. Endocrine-disrupting activity of hydraulic fracturing chemicals and adverse health outcomes after prenatal exposure in male mice. Endocrinology 2015;156:4458–73.
17. Hass U, Christiansen S, Andersen MD, Abildgaard Rosenberg S, Egebjerg MK, Brandt S, et al. List of endocrine disrupting chemicals. Technical University of Denmark and University of Southern Denmark; 2017. Available from: https://backend.orbit.dtu.dk/ws/portalfiles/portal/162337566/DK_ED_list_final_2018.pdf.
18. Hogervorst JG, Fortner RT, Mucci LA, Tworoger SS, Eliassen AH, Hankinson SE, et al. Associations between dietary acrylamide intake and plasma sex hormone levels. Cancer Epidemiol Biomarkers Prev 2013;22:2024–36.
19. Nagata C, Konishi K, Tamura T, Wada K, Tsuji M, Hayashi M, et al. Associations of acrylamide intake with circulating levels of sex hormones and prolactin in premenopausal Japanese women. Cancer Epidemiol Biomarkers Prev 2015;24:249–54.
20. Pelucchi C, Bosetti C, Galeone C, La Vecchia C. Dietary acrylamide and cancer risk: an updated meta-analysis. Int J Cancer 2015;136:2912–22.
21. Je Y. Dietary acrylamide intake and risk of endometrial cancer in prospective cohort studies. Arch Gynecol Obstet 2015;291:1395–401.
22. Hogervorst J. Dietary acrylamide: an update on the chronic risks. In: Melton L, Shahidi F, Varelis P, editors. Encyclopedia of food chemistry. Oxford: Academic Press; 2019. p. 500–24.
23. Orsini N, Li R, Wolk A, Khudyakov P, Spiegelman D. Meta-analysis for linear and nonlinear dose-response relations: examples, an evaluation of approximations, and software. Am J Epidemiol 2012;175:66–73.
24. Crippa A, Discacciati A, Bottai M, Spiegelman D, Orsini N. One-stage dose-response meta-analysis for aggregated data. Stat Methods Med Res 2019;28:1579–96.
25. Vinceti M, Filippini T, Crippa A, de Sesmaisons A, Wise LA, Orsini N. Meta-analysis of potassium intake and the risk of stroke. J Am Heart Assoc 2016;5:e004210.
26. Filippini T, Hatch EE, Rothman KJ, Heck JE, Park AS, Crippa A, et al. Association between outdoor air pollution and childhood leukemia: a systematic review and dose-response meta-analysis. Environ Health Perspect 2019;127:46002.
27. Vinceti M, Filippini T, Rothman KJ. Selenium exposure and the risk of type 2 diabetes: a systematic review and meta-analysis. Eur J Epidemiol 2018;33:789–810.
28. Pelucchi C, Galeone C, Levi F, Negri E, Franceschi S, Talamini R, et al. Dietary acrylamide and human cancer. Int J Cancer 2006;118:467–71.
29. Pelucchi C, Galeone C, Negri E, Bosetti C, Serraino D, Montella M, et al. Dietary acrylamide and the risk of endometrial cancer: an Italian case-control. Nutr Cancer 2016;68:187–92.
30. Burley VJ, Greenwood DC, Hepworth SJ, Fraser LK, de Kok TM, van Breda SG, et al. Dietary acrylamide intake and risk of breast cancer in the UK Women's Cohort. Br J Cancer 2010;103:1749–54.
31. Kotemori A, Ishihara J, Zha L, Liu R, Sawada N, Iwasaki M, et al. Dietary acrylamide intake and risk of breast cancer: the Japan Public Health Center-based Prospective Study. Cancer Sci 2018;109:843–53.
32. Larsson SC, Akesson A, Wolk A. Long-term dietary acrylamide intake and breast cancer risk in a prospective cohort of Swedish women. Am J Epidemiol 2009;169:376–81.
33. Mucci LA, Sandin S, Balter K, Adami HO, Magnusson C, Weiderpass E. Acrylamide intake and breast cancer risk in Swedish women. JAMA 2005;293:1326–7.
34. Wilson KM, Mucci LA, Cho E, Hunter DJ, Chen WY, Willett WC. Dietary acrylamide intake and risk of premenopausal breast cancer. Am J Epidemiol 2009;169:954–61.

35. Wilson KM, Mucci LA, Rosner BA, Willett WC. A prospective study on dietary acrylamide intake and the risk for breast, endometrial, and ovarian cancers. Cancer Epidemiol Biomarkers Prev 2010;19:2503–15.
36. Kotemori A, Ishihara J, Zha L, Liu R, Sawada N, Iwasaki M, et al. Dietary acrylamide intake and the risk of endometrial or ovarian cancers in Japanese women. Cancer Sci 2018;109:3316–25.
37. Obon-Santacana M, Kaaks R, Slimani N, Lujan-Barroso L, Freisling H, Ferrari P, et al. Dietary intake of acrylamide and endometrial cancer risk in the European prospective investigation into cancer and nutrition cohort. Br J Cancer 2014;111: 987–97.
38. Larsson SC, Akesson A, Wolk A. Long-term dietary acrylamide intake and risk of epithelial ovarian cancer in a prospective cohort of Swedish women. Cancer Epidemiol Biomarkers Prev 2009;18:994–7.
39. Obon-Santacana M, Peeters PH, Freisling H, Dossus L, Clavel-Chapelon F, Baglietto L, et al. Dietary intake of acrylamide and epithelial ovarian cancer risk in the European prospective investigation into cancer and nutrition (EPIC) cohort. Cancer Epidemiol Biomarkers Prev 2015;24:291–7.
40. Larsson SC, Hakansson N, Akesson A, Wolk A. Long-term dietary acrylamide intake and risk of endometrial cancer in a prospective cohort of Swedish women. Int J Cancer 2009;124:1196–9.
41. Hogervorst JGF, van den Brandt PA, Godschalk RWL, van Schooten FJ, Schouten LJ. Interactions between dietary acrylamide intake and genes for ovarian cancer risk. Eur J Epidemiol 2017;32:431–41.
42. Pedersen GS, Hogervorst JG, Schouten LJ, Konings EJ, Goldbohm RA, van den Brandt PA. Dietary acrylamide intake and estrogen and progesterone receptor-defined postmenopausal breast cancer risk. Breast Cancer Res Treat 2010;122: 199–210.
43. Hogervorst JG, van den Brandt PA, Godschalk RW, van Schooten FJ, Schouten LJ. The influence of single nucleotide polymorphisms on the association between dietary acrylamide intake and endometrial cancer risk. Sci Rep 2016;6:34902.
44. Hogervorst JGF, van den Brandt PA, Godschalk RWL, van Schooten FJ, Schouten LJ. Interaction between dietary acrylamide intake and genetic variants for estrogen receptor-positive breast cancer risk. Eur J Nutr 2019; 58:1033–45.
45. Obon-Santacana M, Lujan-Barroso L, Travis RC, Freisling H, Ferrari P, Severi G, et al. Acrylamide and glycidamide hemoglobin adducts and epithelial ovarian cancer: a nested case-control study in nonsmoking postmenopausal women from the EPIC cohort. Cancer Epidemiol Biomarkers Prev 2016;25:127–34.
46. Xie J, Terry KL, Poole EM, Wilson KM, Rosner BA, Willett WC, et al. Acrylamide hemoglobin adduct levels and ovarian cancer risk: a nested case-control study. Cancer Epidemiol Biomarkers Prev 2013;22:653–60.
47. Obon-Santacana M, Freisling H, Peeters PH, Lujan-Barroso L, Ferrari P, Boutron-Ruault MC, et al. Acrylamide and glycidamide hemoglobin adduct levels and endometrial cancer risk: a nested case-control study in nonsmoking postmenopausal women from the EPIC cohort. Int J Cancer 2016;138: 1129–38.
48. 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: 2094–100.
49. Garcia E, Hurley S, Nelson DO, Hertz A, Reynolds P. Hazardous air pollutants and breast cancer risk in California teachers: a cohort study. Environ Health 2015;14:14.
50. Friedman MA, Dulak LH, Stedham MA. A lifetime oncogenicity study in rats with acrylamide. Fundam Appl Toxicol 1995;27:95–105.
51. Maronpot RR, Thoolen RJ, Hansen B. Two-year carcinogenicity study of acrylamide in Wistar Han rats with in utero exposure. Exp Toxicol Pathol 2015;67:189–95.
52. Johnson KA, Gorzinski SJ, Bodner KM, Campbell RA, Wolf CH, Friedman MA, et al. Chronic toxicity and oncogenicity study on acrylamide incorporated in the drinking water of Fischer 344 rats. Toxicol Appl Pharmacol 1986; 85:154–68.
53. Beland FA, Mellick PW, Olson GR, Mendoza MC, Marques MM, Doerge DR. Carcinogenicity of acrylamide in B6C3F(1) mice and F344/N rats from a 2-year drinking water exposure. Food Chem Toxicol 2013;51:149–59.
54. Beland FA, Olson GR, Mendoza MC, Marques MM, Doerge DR. Carcinogenicity of glycidamide in B6C3F1 mice and F344/N rats from a two-year drinking water exposure. Food Chem Toxicol 2015;86:104–15.
55. Bandarra S, Fernandes AS, Magro I, Guerreiro PS, Pingarilho M, Churchwell MI, et al. Mechanistic insights into the cytotoxicity and genotoxicity induced by glycidamide in human mammary cells. Mutagenesis 2013;28:721–9.
56. Valko M, Izakovic M, Mazur M, Rhodes CJ, Telser J. Role of oxygen radicals in DNA damage and cancer incidence. Mol Cell Biochem 2004;266:37–56.
57. Hansen SH, Olsen AK, Soderlund EJ, Brunborg G. In vitro investigations of glycidamide-induced DNA lesions in mouse male germ cells and in mouse and human lymphocytes. Mutat Res 2010;696:55–61.
58. Ehlers A, Lenze D, Broll H, Zagon J, Hummel M, Lampen A. Dose dependent molecular effects of acrylamide and glycidamide in human cancer cell lines and human primary hepatocytes. Toxicol Lett 2013;217:111–20.
59. Puppel N, Tjaden Z, Fueller F, Marko D. DNA strand breaking capacity of acrylamide and glycidamide in mammalian cells. Mutat Res 2005;580: 71–80.
60. Band PR, Le ND, Fang R, Deschamps M. Carcinogenic and endocrine disrupting effects of cigarette smoke and risk of breast cancer. Lancet 2002;360:1044–9.
61. Tanko LB, Christiansen C. An update on the antiestrogenic effect of smoking: a literature review with implications for researchers and practitioners. Menopause 2004;11:104–9.
62. Felix AS, Yang HP, Gierach GL, Park Y, Brinton LA. Cigarette smoking and endometrial carcinoma risk: the role of effect modification and tumor heterogeneity. Cancer Causes Control 2014;25:479–89.
63. 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; 207:531–9.
64. Bjorge T, Haggstrom C, Ghaderi S, Nagel G, Manjer J, Tretli S, et al. BMI and weight changes and risk of obesity-related cancers: a pooled European cohort study. Int J Epidemiol 2019;48:1872–85.
65. Laaksonen MA, Arriaga ME, Canfell K, MacInnis RJ, Byles JE, Banks E, et al. The preventable burden of endometrial and ovarian cancers in Australia: a pooled cohort study. Gynecol Oncol 2019;153:580–8.
66. La Vecchia C. Ovarian cancer: epidemiology and risk factors. Eur J Cancer Prev 2017;26:55–62.
67. Raglan O, Kalliala I, Markozannes G, Cividini S, Gunter MJ, Nautiyal J, et al. Risk factors for endometrial cancer: an umbrella review of the literature. Int J Cancer 2019;145:1719–30.
68. Grioni S, Agnoli C, Krogh V, Pala V, Rinaldi S, Vinceti M, et al. Dietary cadmium and risk of breast cancer subtypes defined by hormone receptor status: a prospective cohort study. Int J Cancer 2019;144:2153–60.
69. Eriksen KT, Halkjaer J, Sorensen M, Meliker JR, McElroy JA, Tjonneland A, et al. Dietary cadmium intake and risk of breast, endometrial and ovarian cancer in Danish postmenopausal women: a prospective cohort study. PLoS One 2014;9: e100815.
70. McElroy JA, Kruse RL, Guthrie J, Gangnon RE, Robertson JD. Cadmium exposure and endometrial cancer risk: a large midwestern U.S. population-based case-control study. PLoS One 2017;12:e0179360.
71. Samtani R, Sharma N, Garg D. Effects of endocrine-disrupting chemicals and epigenetic modifications in ovarian cancer: a review. Reprod Sci 2018;25:7–18.
72. Engel LS, Werder E, Satagopan J, Blair A, Hoppin JA, Koutros S, et al. Insecticide use and breast cancer risk among farmers' wives in the agricultural health study. Environ Health Perspect 2017;125:097002.
73. Niehoff NM, Nichols HB, White AJ, Parks CG, D'Aloisio AA, Sandler DP. Childhood and adolescent pesticide exposure and breast cancer risk. Epidemiology 2016;27:326–33.
74. Datzmann T, Markevych I, Trautmann F, Heinrich J, Schmitt J, Tesch F. Outdoor air pollution, green space, and cancer incidence in Saxony: a semi-individual cohort study. BMC Public Health 2018;18:715.
75. White AJ, Bradshaw PT, Hamra GB. Air pollution and breast cancer: a review. Curr Epidemiol Rep 2018;5:92–100.
76. Andersen ZJ, Stafoggia M, Weinmayr G, Pedersen M, Galassi C, Jorgensen JT, et al. Long-term exposure to ambient air pollution and incidence of postmenopausal breast cancer in 15 European cohorts within the ESCAPE project. Environ Health Perspect 2017;125:107005.
77. Hung LJ, Chan TF, Wu CH, Chiu HF, Yang CY. Traffic air pollution and risk of death from ovarian cancer in Taiwan: fine particulate matter (PM2.5) as a proxy marker. J Toxicol Environ Health A 2012;75:174–82.
78. Ferrari P, Freisling H, Duell EJ, Kaaks R, Lujan-Barroso L, Clavel-Chapelon F, et al. Challenges in estimating the validity of dietary acrylamide measurements. Eur J Nutr 2013;52:1503–12.

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79. FoodDrink Europe. Acrylamide toolbox; 2019. Available from: https://www.fooddrinkeurope.eu/uploads/publications_documents/FoodDrinkEurope_Acrylamide_Toolbox_2019.pdf.
80. European Commission. Commission Regulation (EU) 2017/2158 of 20 November 2017 establishing mitigation measures and benchmark levels for the reduction of the presence of acrylamide in food. Official Journal of the European Union 2017;L304:24–44.
81. U.S. Food and Drug Administration. You can help cut acrylamide in your diet; 2016. Available from: https://www.fda.gov/consumers/consumer-updates/you-can-help-cut-acrylamide-your-diet.
82. U.S. Food and Drug Administration. Guidance for industry: acrylamide in foods; 2016. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-industry-acrylamide-foods.

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