Acrylamide intake and endometrial cancer risk: a meta-analysis

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Abstract: Background: Some observational studies have indicated that acrylamide intake is associated with endometrial cancer risk; however, the association was not supported by all published observational studies. This study aimed to assess the relationship between acrylamide intake and endometrial cancer risk. Materials and methods: We conducted a meta-analysis to estimate the association of acrylamide intake with endometrial cancer risk by searching potential studies from PubMed, Medline and Embase through February 2017. The pooled OR and 95% CI of endometrial cancer were computed for the highest versus lowest levels of acrylamide intake. Result: Five observational studies were included into the present meta-analysis. The pooled OR (95% CI) of endometrial cancer for the highest vs. the lowest levels of acrylamide intake was 1.07 (0.94, 1.23). The dose-response analysis showed that the risk of endometrial cancer did not change significantly for every 10 µg/d increment in acrylamide intake, the pooled OR (95% CI) was 1.01 (0.98, 1.05). In subgroup-analysis, this study found an increased endometrial cancer risk in never-smoking women who consumed high levels of acrylamide intake. However, in the ever smokers, premenopausal or postmenopausal women, and the prospective cohort studies, no significant positive association of acrylamide intake and endometrial cancer risk was found. Conclusion: The present meta-analysis did not support a significant association of acrylamide intake and endometrial cancer risk. however, never-smoking women who consumed high acrylamide had an increased risk of endometrial cancer.

Keywords: Acrylamide, endometrial cancer, meta-analysis

Introduction

Endometrial cancer is a common cancer among females and the most common gynecological cancer, and approximately more than 50000 endometrial cancer cases were diagnosed in 2015 in the Americans [1], moreover, the incidence rate of endometrial cancer has been rising rapidly over the past decades both locally and globally. Although with many promising advances over the past several years, the understandings of the initiation, maintenance, and metastasis of endometrial cancer remain far from thorough.

As known, acrylamide is a neurotoxin and carcinogen in humans [2, 3]. Study showed acrylamide was metabolized to a chemically reactive epoxide and mutagen in animals, which was called glycaldamide via the Cyp2e1, enzyme system [4]. In 1986, Johnson et al. observed some hormone-related cancers and other tumors occurred after acrylamide intake in rats [5], which suggested that acrylamide intake was linked to cancers.

Some epidemiologic studies showed a positive relationship between acrylamide intake and endometrial cancer risk among the never-smokers or all women [6, 7], however, no increased risk of endometrial cancer was observed among the females which consumed high acrylamide in the other epidemiologic studies [8-10]. The association of acrylamide intake and endometrial cancer risk was uncertain which may be partly due to the differences in population, study design, smoking status, and other varied characteristics of participants, furthermore, the sample size was relatively small in each single study, the evidence was limited. In order to increase statistical power and clarify these conflicting results, a meta-analysis was conducted to assess the association between acrylamide intake and endometrial cancer risk.
Materials and methods

We performed a study search with Medline, PubMed, and Embase databases to search the potential articles which showed the relationship between acrylamide intake and endometrial cancer risk up to February 2017, the following terms were used as the search strategy: “acrylamide intake”, “dietary acrylamide” and “acrylamide” combined “endometrial cancer”. If the study had an observational study (case-control or cohort), reported the relationship between acrylamide intake and endometrial cancer risk, reported the OR (95% CI) for the highest vs. the lowest levels of acrylamide intake, and published in the English, which should be included. However, if the article was a review, or previous meta-analysis, or animal experiment, or not published the English, or reported an exposure factor or endpoint that was not relevant to our study, which should be excluded.

The study quality assessment was conducted using the Newcastle-Ottawa quality assessment scale (NOS) [11]. The total score was 9 stars, and a study with seven or more stars was considered as high-quality.

The following information were extracted according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) [12]: the last name of the first author, publication year, area, study design, sample size, OR (95% CI) from the most fully adjusted model for the highest vs. the lowest levels of acrylamide intake, and the adjustment factors.

All above processes were conducted by 2 independent authors, and any disagreements were resolved by discussion.

In the present study, STATA version 12.0 was used to analyze data. The association between acrylamide intake and endometrial cancer risk was assessed with the pooled OR and the corresponding 95% CI by using a random-effects or fixed-effects model.

Homogeneity test was performed with the use of Q statistic at the P < 0.05 level of significance and I² statistic, which is a quantitative measure of inconsistency across studies. If the Q statistic at the P < 0.05 level of significance and I² > 50%, the random effects model was chose; however, If the Q statistic at the P > 0.05 level of significance and I² < 50%, the fixed effects model was selected. To examine a dose-response relationship and calculate a pooled OR for an increase of 10 lg/day of acrylamide intake, a generalized least-squares trend estimation analysis was conducted. Subgroup analysis was performed to clarify the influences of various factors on the pooled estimate. Additionally, sensitivity analysis was used to investigate the influence of a single study on the overall risk estimate by eliminating one study in turn. Publication bias was through funnel plot, and Begg’s and Egger’s test [13, 14]. A two-tailed P value of < 0.05 was considered statistically significant.

Results

In the beginning, we searched 56 relevant articles from PubMed, Medline and Embase according to the search strategy (Figure 1). Following the inclusion and exclusion criteria, however, most of them were excluded. At last, 5 articles (3228 endometrial cancer cases and 514492 participants or controls) were included [6-10].
# Table 1. The characteristics of included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Publication year</th>
<th>Area</th>
<th>Study design</th>
<th>Sample size</th>
<th>Adjusted OR (95% CI) (highest vs. lowest)</th>
<th>Quality score</th>
<th>Variables used in multivariate model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hogervorst et al.</td>
<td>2007</td>
<td>Netherlands</td>
<td>Cohort</td>
<td>221/62573</td>
<td>1.29 (0.81, 2.07)</td>
<td>9</td>
<td>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, non-occupational physical activity, energy intake, transunsaturated fatty acid intake, carbohydrate intake, alcohol consumption.</td>
</tr>
<tr>
<td>Larsson et al.</td>
<td>2009</td>
<td>Sweden</td>
<td>Cohort</td>
<td>687/61226</td>
<td>0.96 (0.76, 1.21)</td>
<td>8</td>
<td>Age, education, body mass index, 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.</td>
</tr>
<tr>
<td>Wilson et al.</td>
<td>2010</td>
<td>USA</td>
<td>Cohort</td>
<td>484/88672</td>
<td>1.41 (1.01, 1.97)</td>
<td>8</td>
<td>Smoking, BMI, age at menarche, menopausal status/age at menopause/PMH use, parity, oral contraceptive use, high blood pressure, diabetes, physical activity, caffeine intake, energy intake.</td>
</tr>
<tr>
<td>Obo’én-Santacana et al.</td>
<td>2014</td>
<td>European countries</td>
<td>Cohort</td>
<td>1382/301113</td>
<td>0.98 (0.78, 1.25)</td>
<td>8</td>
<td>Age at recruitment, centre, smoking status, OC use, HRT use, total energy intake, BMI, prevalent diabetes, menopause status combined with age at menopause, parity, and age at menarche.</td>
</tr>
<tr>
<td>Pelucchi et al.</td>
<td>2016</td>
<td>Italy</td>
<td>Case-control</td>
<td>454/908</td>
<td>1.17 (0.73, 1.85)</td>
<td>8</td>
<td>Study centre, age, adjusted for period of interview, education, tobacco smoking, body mass index, occupational physical activity, history of diabetes, age at menarche, menopausal status/age at menopause, parity, oral contraceptive use, hormone replacement therapy, total energy intake.</td>
</tr>
</tbody>
</table>
Acrylamide intake with endometrial cancer risk

Among the included studies, 4 prospective cohort studies [6-9] and 1 case-control study [10], 4 studies were conducted in European populations [6, 8-10], and 1 in American populations [7]. All OR and corresponding 95% CI of them were based on the highest vs. the lowest levels of acrylamide intake. All studies were adjusted for multiple factors. Table 1 presents the main characteristics of the included studies.

Among the five included studies, only one showed a significant positive relationship between acrylamide intake and endometrial cancer risk [7]. After analysis, there was no significant relationship between acrylamide intake and endometrial cancer risk among the overall women, the pooled OR (95% CI) of endometrial cancer for the highest vs. the lowest levels of acrylamide intake was 1.07 (0.94, 1.23), P > 0.05. The result was presented in Figure 2.

By removing one study at a time, the combined ORs for the remaining studies were similar to

![Figure 2. Meta-analysis of the relationship between acrylamide intake and endometrial cancer risk among the all populations.](image)

![Figure 3. Forest plot for sensitivity analysis.](image)
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Figure 4. Forest plot for publication bias.

others, and did not change the overall OR significantly. The result of sensitivity analysis is presented in Figure 3.

The funnel plot did not show any substantial asymmetry, and Egger’s regression test showed there was little evidence of publication bias in the present study (P = 0.150). Figure 4 presents the funnel plot of publication bias.

All included studies were eligible for the dose-response analysis. The dose-response analysis showed that the risk of endometrial cancer did not change significantly for every 10 µg/d increment in acrylamide intake, the pooled OR (95% CI) was 1.01 (0.98, 1.05), and little evidence of heterogeneity was found ($I^2 = 22.2\%$). The result was presented in Figure 5.

In order to identify the influence of some factors on the overall risk estimate, stratified analyses were conducted. An increased endometrial cancer risk was found among never-smoking women who consumed high levels of acrylamide intake. However, among the ever smokers, no significant positive association of acrylamide intake and endometrial cancer risk was found, the pooled OR and 95% CI were 1.23 (1.01, 1.50) and 0.93 (0.69, 1.24) with no evidence of heterogeneity. Next, we did not find a significant relationship between acrylamide intake and endometrial cancer risk neither in premenopausal or postmenopausal women, the overall OR (95% CI) were 1.19 (0.37, 3.87) and 1.13 (0.91, 1.41). At last, we also did not find a significant relationship between acrylamide intake and endometrial cancer risk in the prospective cohort studies, the overall OR (95% CI) was 1.06 (0.92, 1.23), little evidence of heterogeneity was found ($I^2 = 34.7\%$). The results of subgroup analyses were presented in Figures 6-8.

Discussion

The present meta-analysis supports no significant association between acrylamide intake and endometrial cancer risk in all women, moreover, the dose-response analysis showed that the risk of endometrial cancer did not change significantly for every 10 µg/d increment in acrylamide intake, however, an increased risk of endometrial cancer was detected among the never-smoking women who had higher levels of acrylamide intake.

In subgroup-analysis, we also did not find a significant relationship between acrylamide intake and endometrial cancer risk neither in premenopausal or postmenopausal women, this result was similar with a previous study. Up to date, all published epidemiological studies do not report an association of acrylamide intake and major female hormone-related cancers. Hence, the result of this study was not beyond expectation.

Many studies agree undesignedly suggest cigarette smoke is an independent risk factor of various of cancers, however, cigarette smoke has been identified to be associated with a lower endometrial cancer risk [15], and thus cigarette smoke may decrease the risk of endometrial cancer. When excluding the possible influence of smoking on endometrial cancer risk, it was not difficult to deduce that there was a significantly increased risk in never-smoking women who consumed high acrylamide.
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Figure 5. The dose-response analysis of the relationship between acrylamide intake and endometrial cancer risk among the all populations.

Figure 6. The subgroup analysis of the relationship between acrylamide intake and endometrial cancer risk according to smoking status.
Although the mechanisms are unclear, this result may be explained by the following reasons: Firstly, cigarette smoke may induce the alterations of steroid metabolism [16], in con-
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Contrast to the 4-oestrogen metabolite, the 2-oestrogen metabolite is considered to be anti-carcinogenic, smoking induces the estrogen metabolism to toward the 2-hydroxylation pathway [17]. Secondly, acrylamide is metabolized to glycidamide, a chemically reactive epoxide and mutagen, lots of studies showed the carcinogenicity of acrylamide in experimental animals [18, 19]. Thirdly, exposure to excessive estrogens may lead to continued stimulation of the endometrium [20]. Consuming high acrylamide may activate enzymes involved in the metabolism of estrogens and thus lead to the development of endometrial cancer by hormonal pathways.

The present meta-analysis had some important significance. Although a previous study had reported the relationship between acrylamide intake and endometrial cancer risk through a meta-analysis [21], that study only observed influence of never-smoking on the relationship between acrylamide intake and endometrial cancer risk, other potential factors were not discussed. Moreover, a new study was published in 2016, this study should be included [10]. Individual studies had smaller sample size, and thus had insufficient statistical power, the present study included all published studies which reported the relationship between acrylamide intake and endometrial cancer risk, and involving a large number of cases and participants, which significant enhanced the statistical power. Most of the included studies were a prospective cohort study design [6-9], which greatly reduced recall and selection biases.

There were some potential limitations in our meta-analysis. Firstly, although more studies and larger sample size were included in the present meta-analysis, the number was still smaller, and only one study found a significant positive relationship which was not similar with others, more studies reported the relationship between acrylamide intake and endometrial cancer risk should be conducted in the future. Secondly, we conducted several subgroup analyses, however, many subgroups only included few studies, and the statistical power was insufficient. Thirdly, although all the included studies adjusted multivariate factors, residual confounders which influence the risk of endometrial cancer. Fourthly, most of the included studies assessed the acrylamide intake levels through questionnaires, which may provide some inaccurate reports. Fifthly, the results of the present meta-analysis were absolutely based on Western populations; more studies based on other populations are warranted to generalize the findings in the future.

In conclusion, the present meta-analysis did not support a significant association of acrylamide intake and endometrial cancer risk; however, never-smoking women who consumed high acrylamide had an increased risk of endometrial cancer. More prospective cohort studies based on other populations are warranted.

Disclosure of conflict of interest

None.

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