



A Systematic Review on Association between Dietary Acrylamide and Cancer Risk

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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ABSTRACT

Acrylamide is a yellowish, odorless solid that is water-soluble and is used in a variety of organic solvents and organic chemical compounds. It is used as a precursor or substitute for water-soluble thickeners in a variety of applications. It is very toxic and hence carcinogenic, and it is administered as a watery solution. Aside from exposure to the industry and cigarettes, food appears to be the most common source of human exposure. Cancer has remained the second-leading cause of death, with a global increase in the number of cases. Increasing the cancer burden necessitates the use of cancer preventive methods. Because of the present results of several future investigations, specialists have conducted a new meta-analysis on the usage of acrylamide-related illness incidence in various areas. Authors discovered 32 publications on their own. The researchers conducted a meta-analysis utilizing corrected or spontaneous modeling, based on the heterogeneous method, to assess the overall chance for each cancer site for highest versus lowest consumption levels, including an increase in nutritional acrylamide by 10 mg/day. Acrylamide has been classified by the International Agency for Research on Cancer as a human category 2A carcinogen, based on evidence of acrylamide carcinogenicity in animals.

Keywords: *Asparagine; breast cancer; dietary Acrylamide; flocculation agents; maillard reaction.*

1. INTRODUCTION

Acrylamide is a crystalline industrial chemical that is pure, odorless, and non-toxic. It has been on the market since the mid-1950s and is primarily employed as a flocculating agent in the purification of drinking water and wastewater, however, it is also utilized as a settling agent in buildings and the manufacture of energy and polymers. Acrylamide was identified by the International Agency for Testing on Cancer (IARC) in 1994 as a probable human carcinogen (2A) based on animal research. Following the release of our first systematic review and meta-analysis on acrylamide and human cancer, epidemiological evidence on the link between dietary acrylamide and the prevalence of several malignancies has continued to gather over the last several years [1]. Many findings from large longitudinal studies have recently been published including, among others, the European Prospective Investigation on Cancer and Nutrition (EPIC) and the Nurses' Health Service (NHS). In particular, the EPIC study published findings for oesophageal, pancreatic, and endometrial cancer, which included over 500,000 participants [2–4].

Acrylamide was first reported in products by the Swedish National Food Administration in 2002. The acrylamide is the by-product of the roasting process that develops through the Chemical reaction towards the amino acid asparagine, this same response caused browning of the food during baking, frying, and roasting, by reducing sugar (glucose or fructose) [2]. The levels of acrylamide in cooked meals are therefore determined by parameters including cooking temperatures, heating duration, moisture content as well as the reduction of sugar as well as aspartic acid in the raw foods. Potatoes may have an impact on the diversity of cultivars, the use of fertilizers as well as storage conditions. The storage of potatoes at 2°C, for particular, leads to an increased concentration of free glucose which transforms potatoes held at the heater to greater levels of acrylamide comparison to 20°C. Acrylamide content variations in many meals and many of the same foods presented a problem in determining actual intake using widely-used methodologies, including the questionnaire survey (FFQ). These differences frequently present a great problem for those with little or substantial acrylamide consumption, in particular [5–7].

The hypothalamus of the hypothalamus-pituitary-thyroid axis is stimulated to release thyrotropin-

releasing hormone when exposed to AA (TRH). TRH causes the pituitary gland to produce thyroid-stimulating hormones (TSH) and stimulates the thyroid gland to commence cell proliferation or, ultimately, thyroid tumor growth, as shown in Fig. 1.

The finding that carboxylate is generated in human consumption at high temperatures when cooking and is found in typical, high temperature human cooked meals has sparked an interest in the potential carcinogenicity of acrylamide exposure in diet. Acrylamide is produced by the Maillard reaction during food heating between the amino acid asparagine as well as the extraction of sugars, also including sucrose [9]. Throughout recent times, new epidemiological studies were produced, the maximum contribution for food exposure to acrylamide was documented as well as labor investigations vulnerable with acrylamide have been amended, but no systematic reviews or meta-analyses were collected. The definitions of exposure were employed in studies linked to diet acrylamide:

- Food acrylamide intake as well as converting chart.
- Food consumption of slightly elevated boiled potatoes, in particular, acrylamide.
- Biomarkers include such protein adducts. Just like with other experimental carcinogens, the assessment of human risk is complicated by issues in the generalization of animal's present measurements to people as well as in the understanding of finds through epidemiologic studies.

Several epidemiological studies research assessed their probable relationship with cancers in many organisms, including reproduction bodies, gastrointestinal system, kidney, lung as well as brain since before the identification of acrylate in daily foodstuffs. The consumption of acrylamide has been evaluated using FFQ in most epidemiological investigations whereas some have investigated biomarkers. The quantity of acrylamide in foods, the portion size ingested as well as the frequency of intake as well as the cooking or storage techniques, influence nutritional acrylamide exposures. Therefore, the variances in world dietary patterns make a major contribution to various food products to acrylamide's dietary consumption. Although the most prevalent suppliers in each country are coffee, fried/baked potatoes as well as bakery products. A thorough overview of the global

content in foodstuffs or the overall diet is available in the United States Food and Drug Administration (FDA) database. While in laboratory animals' acrylamide has been proven to be carcinogenic, neurotoxic, as well as unfavorable, inadequate as well as contradictory data is available for its impacts on human health [10,11].

Laboratory investigations have shown detrimental effects on both the peripherals as well as the central nervous system, mainly by inhalation of high acrylamide dosage ranging from around 80-1000 µg/day, corresponding to 1.4-18 µg/kg body weight/day during acute exposure. Acrylamide and glycidamide, their metabolite of epoxy, are genotoxic and might even act as just an endocrine disruptive agent, affecting the endogenous endocrine system at a smaller concentration compared to environmental research. For instance,

acrylamide consumption in pre-, as well as premenopausal women, is related to changing the level of the reproductive hormones, namely increasing estradiol as well as follicular stimulation [12]. Previous investigations have been conducted for hormone-dependent gynecological neoplasia. Many epidemiological findings on acrylamide well as breast as well as gynecological cancer have been published, however, there have been few systemic investigations on this issue. These findings suggest that the risk of endometrial and ovarian cancers, particularly in people who are not smoking, is minimal but that there is zero breast cancer hazard. No dose-response meta-analysis was performed before. The investigators carried out a meta-analysis of dose-response curve focusing on epidemiological studies on food consumption-related chances of breast, endometrial as well as ovaries cancer in people. acrylamide [13].

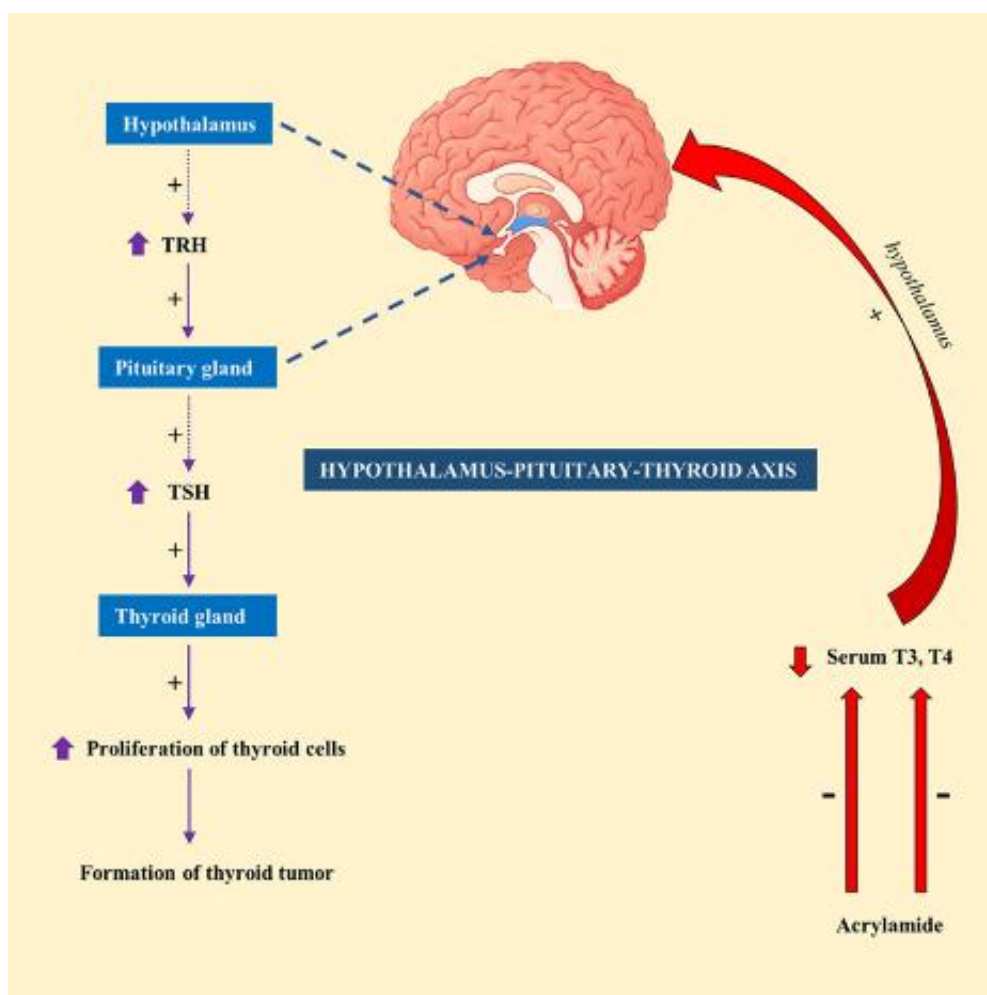


Fig. 1. The mode of action of acrylamide (AA) in thyroid tumors in rats is shown schematically [8]

In both female's and males' versions, butadiene is cytotoxic to various organs. Acrylamide Carcinogenicity in a range of neurological models, including rats as well as mice, has been very well established yet, based upon the weights to which human beings are exposed via food sources, the dosages within research are 1.000–100.000 times higher than normal levels[14]. Moreover, investigations however have replied that the decomposition of acrylamide differs as well as its metabolites glycidamide have such a four or more times lower inner exposure in people. study about one of the researchers has recently compared epidemiological and laboratory work, and another researcher has conducted 19 nutritional meta-analyses and 6 acrylamide and cancer occupational studies. Alleged infringer as well as three clinical case-control unique investigations, which have been published to present, evaluated the relationship of dietary acrylamide and various kinds of cancer, comprising 11 progressives, 10 cases-cohort, six inhabitants particular instance and 3 hospital-based interior dosages data. Major science publication warehouses, including PubMed, google as well as the Joint Institute for Food Protection as well as Applied Nutrition (JIFSAN), the World Health Organization (WHO and the FDA), were examined for epidemiology ethanolamine reporting. The literature search focused on documents produced from 2002 to March 2013. The following evaluation phrases have been integrated: dietary production of acrylamide, sources of carboxylate food, consumption of acrylamide, chemicals that are thermally generated, culinary temperatures, the metabolization of acrylamide as well as hemoglobin intermediates [8,15,16].

1.1 Acrylamide Exposures As Well As Internally Dosage

Vulnerability to carboxylate to an adult means cumulative ingestion of food, tobacco, second-hand smoke, drinkable water, employment sources, domestic toiletries, and goods. The absorption of Acrylamide through dermal penetration is significantly lower, as the skin has a barrier to the absorption of Acrylamide. However, oral usage is crucial in determining the circulation of acrylamide as well as its metabolites inside the body [17]. Acrylamide, which has reported half-lives of 3.1–3.5 hours, is absorbed as well as eliminated in the urine quickly following oral consumption in people. Glutathione conjugation pathways represent an essential role in protecting the body remove acrylamide as urinary metabolites (Fig. 1).

Acrylamide is sometimes used to epoxidize this same genotoxic intermediate glycidamide via cytochrome P450 2E1 (CYP2E1). Variability in exposure to glycidamide can arise as polymorphisms in CYP2E1 that cause the enzyme to have variable catalytic levels [18]. Furthermore, substances including allyl as well as diallyl sulfides, that can inhibit activities of CYP2E1, can reduce glycidamide production in adults. Bipolar garlic disulfide inhibits CYP2A1 as well as eliminates acrylamide transformation to glycidamide in rats' livers [19]. is used. Moreover, the acrylamide bioconversion to glycidamide was down 95 percent relative to the wild, compared to CYP2E1 nodulous mouse [20].

In red blood cells, Acrylamide, Glycidamide, and now the resultant actin filaments are associated with hemoglobin and give an approximation of something like the internal dosage in which both absorb and contribute to their metabolism throughout red blood cells' lives (120 days). For instance, smokers have 3 to 5 times more hemoglobin adduced acrylamide as well as glycidamide. Second-hand smoke exposure also affects levels of HbAA and HbGA [21].

2. MATERIALS AND METHODS

They actively searched the PubMed/Medline databases systematically until February 25, 2020, using Acrylamide input terms. After evaluating the research results, the analyses were reduced to studies with case-control or cohort designs on exposure to acrylamide in diets and studies providing estimates of risk for breast, endometrial, or ovarian cancer, together with 95 % of confidence intervals (CI) ($\mu\text{g}/\text{day}$). They exclude non-epidemiological research, which does not reveal adjusted hazard calculations, and therefore have conducted acrylamide exposures experiments with hemoglobin intermediates.

2.1 Data Extraction

The data came from a collection of hospital-based case-control studies that all used the same format, questionnaire, or methodology. Between 1991 and 2002, data were gathered in many locations in northern Italy (greater Milan, the provinces of Udine, Padua, Pordenone and Gorizia, the city of Genoa, as well as the province of Forl'), center Italy (the provinces of Rome or Latina), and southern Italy (the provinces of Rome or Latina). Table 1 illustrates the gender distribution of cases or controls.

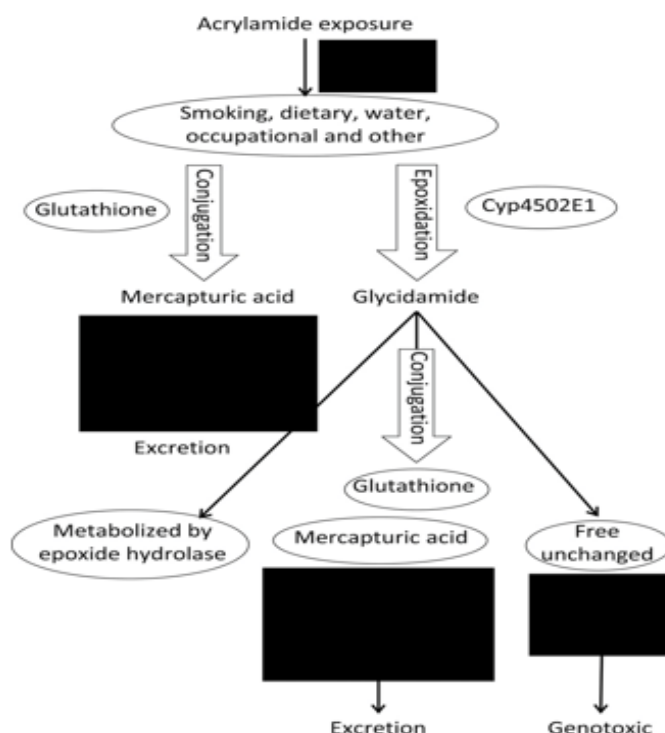


Fig. 2. The metabolism of Acrylamide

Table 1. Cases and controls were distributed by sex from 1991 to 2002

Cancer	Years	Male	Females
Pharynx /Oral cavity	1992-1997	764 to 1352	120 to 525
Large bowel	1992- 2001	1,418 to 2,403	972 to 2,362
Rectum	1993- 2002	787 to 2,404	607 to 2,364
Larynx	1992 - 2002	468 to 1,062	48 to 265
Breast	1991- 2001		2,900 to 3,222
Ovary	1992–1998		1,041 to 2,511

The oral cavity/pharynx, larynx, esophagus, colorectum, and breast were all studied by the Swiss canton of Vaud. The investigator has collected country, quantity, cohort name, and demographic data, including the number of treatment years, follow-up length, and the total, as well as necessary, suggest age of the respondents, for each research. Investigators obtained acrylamide rates in the categories of accessibility (e.g. quantiles) and effect size calculations. It also distinguished complicated data on prevalence rates, menopausal status, BMI, and hormone-receptor (breast cancer only) status since it was supplied whenever it was available.

2.2 Data Analysis

Right off the bat, researchers have meta-analyzed the total association measurement

(RR-RR, potential danger proportion HR, or odds-RR, as hereinafter described as RR) whilst also going to compare the largest increase to the least inhalation exposure in a multiple regression analysis, with commensurate 95 % of confidence interims (CIs) from each type of cancer. In this work, the scientists assessed the heterogeneity through statistics as well as stratification analysis. The investigators also did a contextual of something like the dose-response, using a current one-stage approach that we previously employed, which permits RRs to be estimated across a wide range of acrylamide intakes together with their 95% CI. Researchers extracted the mean or median for the exposure categories listed in each sample, depending on which one was available. If unavailable, a value of 20% in front or behind the nearest slashed being input by each classification throughout the simulation, or whether the extreme limits for the

highest as well as lower exposure category weren't recorded. The researcher conducted a generalized minus-square estimation technique in this investigation utilizing tiny cubic surfaces utilizing 3 knots at predetermined percentiles (10, 50, and 1990).

To this purpose, researchers take the relationship under accounting with each set of documented RRs as well as combine the structured questionnaire estimates utilizing the restricted maximum likelihood approach with multivariable random-effects meta-analysis. Including all studies, the researchers have generally adapted as well as recorded the pitch alongside the form of something like the nonlinear connection created by that of the spline analysis. The researchers showed a visual overlaying of something like the anticipated studies with fixed effect and random in susceptibility assessments. In subsequent studies, a visual overlay was given to demonstrate the influence of the variation across the experiments, including fixed and random effects. All analyses are also re-run by deleting one study at a time to measure the precise impact of the missing analysis on the tests and to assess the heterogeneity as well as source. All quantitative analyses were performed by using 'meta' as well as 'dementia' routines in the STATA program.

3. RESULTS

The total number of Google searches in the database has been confirmed. Researchers found 343 distinct title-based and abstract-based online papers in databases, which they narrowed down to 22. They took out four studies (all of which had qualitative publications), a literary survey, and a remark, leaving 18 qualitative scientific works. Cohorts (–11 research) and specific instances (five studies) were by far the most common outlines offered, followed by two methods. The studies were published between 2005 and 2019, with the vast majority (N=15) taking place in Europe, followed by the United States (N=2) and Japan (N=1). Certain studies have looked at more than one type of cancer. In total, 10 studies looked at breast cancer, 7 endometrial cancers, and 7 ovarian cancers, involving 1,041 to 2,511 and 2,900 to 3,222 breasts, endometrial cancers, and ovarian cancers, respectively. Five studies have finally published height and weight stratification results (i.e. <25 and <25 kg/m²) and six studies of metastatic breast cancer stratified hormone

levels, i.e., androgen receptor level ER and/or progesterin transmitter level PR results. Five papers were available on the same study population and that only the latest and full publications have been included in the analysis in all of these situations.

In the meta-analysis, researchers found no evidence of effectiveness across cancer risks at higher levels of acrylamide exposure, with RRs of 1.03 for breast cancer, 1.01 for endometrial cancer, and insignificant concentrations of acrylamide exposed in the highest incidence group when compared to the lowest. Both summary estimates were scientifically inaccurate. The researchers concluded that similar results for breast cancer, while conceptually unclear, confined the study to no smokers but raised the risk of endometrial and ovarian cancer. The researchers found no significant correlation between determinants of exposure to anything or breast cancer in premenopausal women, but a reverse link in postmenopausal women, in an analysis stratified by menopause. Premenopausal women had a lower risk of endometrial cancer than postmenopausal individuals, and the risk of longer accessibility was less accurate among postmenopausal women. Thyroid cancer has been linked to acrylamide exposure in premenopausal women, however, these findings were based entirely on two studies that found the contrary, whereas postmenopausal women's chances have increased. Only non-smoking premenopausal women had access to the data of one study that found a link between acrylamide exposure and the risk of breast cancer. In contrast, there has been no link found between acrylamide intake, endometrial and ovarian cancers in postmenopausal women, or positive associations with breast cancer.

4. DISCUSSION

This comprehensive systematic review of the evidence on food acrylamide and cancer incidence confirms earlier findings that more and more cancer sites are not linked, as well as possible small increases in kidney cancer risk, as well as an endometrial and ovarian cancer risk in women who have never smoked with such a high level of acrylamide. When just cohort investigations were conducted, the findings of various studies were generally not diverse, and the test results were validated. By integrating the most recent data, largely from large prospective cohort studies published in the last five years, the

number of cancer cases included in this revised meta-analysis has nearly doubled. As a result, the researchers were able to look at a larger number of cancer sites and improve their statistical skills with figures. This notwithstanding, the number of studies is still small for certain cancer sites.

With relation to kidney cancer, the researchers discovered a 20 percent increase in the risk in individuals with low consumption compared to the low acrylamide in diet using data from three studies as well as longitudinal direction investigations. Approximately 50 percent of the gains were slightly greater given simply the latter research size. On either side, there was no meaningful association because when the analysis was conducted with continuous exposure measurements (+2% at risk with such an increase in dietary acrylamide of 10 µg/day). The aforementioned results were nonetheless impacted, in Swedish case-check investigations, by the corresponding variability across sample estimates, ranging from 0.91 to 1.10 throughout the NCS. Different analyses of design results could at least partly justify this and prospective design likewise reveal considerably greater risk levels. Smoking is also a potential cause as well as a significant source of exposure to acrylamide for kidney cancer. Consequently, the connection between dietary acrylamide as well as bladder cancer may be unclear or changing. There has also been specific evidence indicating the function that acrylamide exposures to renal cancer could play in two occupational cohort studies. Consequently, the subject is still up to the dispute, despite the little but borderline relationship and the already little epidemiology information of bladder cancer.

5. CONCLUSION

The nutritional acrylamide hazard identification was unsatisfactory in the reviewed observational studies that contributed to the possible misunderstanding. Case-control studies found almost the same level of exposure to dietary acrylamide in both case and control groups. Vulnerability evaluation methodologies found in a variety of exposures are particularly suggested for sickness targets such as malignancies. However, the bulk of the epidemiological studies reviewed has estimated one-time baseline FFQ doses based on the strong assumption that dietary acrylamide and individual exposures were stable throughout time. This is especially significant because it seems like a new dish is

introduced every year. Seasonality, costs, marketing, and social variables such as holidays, among others, may modify calorie intake patterns, resulting in probable dietary changes to acrylamides. The breast or large bowel cancer studies had 80 percent power to predict unadjusted risk increases of more than 20 percent and 19 percent, respectively, for the highest quintiles of consumption. Other studies found that ovarian cancer was 29 percent, prostate cancer was 30 percent, and upper aerodigestive tract malignancies were 40–50 percent. As a result, our findings argue against significant increases in the risk of breast and other cancers as a result of acrylamide consumption in the diet. Other epidemiologic research on acrylamide or cancer risk has shown similar results. In total, ten studies looked at breast cancer, seven endometrial cancers, and seven ovarian cancers, including 1,041 to 2,511 breast cancers, endometrial cancers, or ovarian carcinoma, respectively. Five studies have ultimately published their height/weight stratification findings (i.e. 25 or 25 kg/m²), while six breast carcinoma studies have stratified hormone levels, i.e. androgen receptor level ER and/or progesterin transmitter level PR results.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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