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Dietary acrylamide and human cancer; even after 20 years of research an open question

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This year marks the 20th anniversary of the discovery of acrylamide in food. In 2002, acrylamide was discovered in common foods, such as coffee, potato crisps and chips, cookies, and several other cereal and potato-based foods prepared at high temperatures (>120°C) under low-moisture conditions. In 1994, acrylamide was classified as a probable human carcinogen (group 2A) by the International Agency for Research on Cancer (IARC) (1), and it was also known to cause genotoxicity, neurotoxicity, and reproductive and developmental toxicity in animal experiments.

In this issue of the *American Journal of Clinical Nutrition*, Bellicha et al. (2) investigated whether dietary acrylamide is associated with an increased breast cancer risk, according to menopausal status and hormone receptor status. They used data from the NutriNet-Santé study, a French, web-based, prospective cohort. Acrylamide exposure was measured by collecting multiple 24-hour dietary records during the first 2 years of the study (on average, 5.5 per participant), and outcomes were ascertained by self-report and validated with linkage to the national health insurance database. Strengths of this study include the measurement of portion sizes, the use of national measurements to estimate acrylamide exposure, the inclusion of a large number of premenopausal cases, and study heterogeneity of associations according to hormone receptor status. A weakness is that hormone receptor status was not uniformly determined.

Bellicha et al. (2) observed a borderline significant increased risk of breast cancer in women with a high dietary acrylamide intake (HR: 1.21; 95% CI: 1.00, 1.47). The association was stronger in premenopausal women (HR: 1.40; 95% CI: 1.04, 1.88), especially in premenopausal women with hormone receptor–positive breast cancer (estrogen and/or progesterone receptors). These findings are an important contribution to the knowledge regarding the possible carcinogenicity of dietary acrylamide.

In 2005, the first formal risk assessment of dietary acrylamide exposure was conducted by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) (3). The committee concluded that dietary acrylamide exposure may entail a human health concern with regard to cancer, and recommended reduced exposure of the general population. In 2015, the European Food Safety Authority (EFSA) confirmed JECFA's conclusion, and also noted that acrylamide levels in foods were not consistently lower in the years leading up to its risk assessment (4).

Based on the EFSA's assessment and the conclusion that more should be done to reduce the public's exposure to dietary acrylamide, the European Union developed the Commission Regulation 2017/2158, which established mitigation measures for food producers and benchmark levels for the reduction of acrylamide in foods. Exceeding a benchmark level does not mean that a food product cannot be placed on the market. A benchmark level indicates a level at which, if exceeded, food manufacturers need to review their mitigation measures and work towards lower levels. However, maximum levels that do mean that a food product cannot be marketed are currently under consideration and may come into force in 2023. In the United States, the FDA issued guidance for industry in 2016, with instructions to lower acrylamide contents of foods (5).

The legal measures to reduce the public's exposure to acrylamide that followed from these risk assessments were based on animal studies, particularly on 2-year rodent carcinogen assays. However, this assay is known to have low specificity and sensitivity for predicting whether a compound is carcinogenic to humans (6), which is probably due not only to the massive differences between the doses that animals in carcinogenicity assays receive and the dietary doses to which humans are exposed through diets, but also to fundamental biological differences between animals and humans. Thus, epidemiological studies on the association between dietary acrylamide exposure and cancer risk are of the utmost importance.

So, what do the available epidemiological studies on dietary acrylamide and cancer risk tell us in 2022? Unfortunately, the body of evidence is still cloudy, even after 20 years of research.

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Abbreviations used: EFSA, European Food Safety Authority; IARC, International Agency for Research on Cancer; JECFA, Joint FAO/WHO Expert Committee on Food Additives.

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Several meta-analyses have been performed recently. A meta-analysis from 2020 concluded that dietary acrylamide exposure is positively associated with the risk of endometrial and ovarian cancers, particularly among never-smoking women, and with the risk of premenopausal breast cancer (7). In comparison, a meta-analysis from 2021 did not observe higher risks of endometrial, ovarian, and premenopausal breast cancers with acrylamide exposure (8). The reason for this discrepancy may be that the meta-analysis from 2020 included a study that the 2021 analysis did not and, to arrive at its conclusion, the 2020 analysis focused more on the dose-response meta-analysis than on the *P* value for the highest exposure quantile. Another meta-analysis from 2021 investigated nongynecological cancers and found no association with dietary acrylamide intake (9).

The general picture that has arisen up to now indicates that dietary acrylamide exposure could be associated with higher risks of sex hormone–driven cancers in women, if associated with anything. The results of Bellicha et al. (2) add more weight to this theory, considering that they observed stronger associations between acrylamide exposure and premenopausal breast cancer risks for tumors with a positive hormone receptor status.

It is important to consider that some individual studies included in the meta-analyses might have been more suitable for studying the associations between dietary acrylamide exposure and cancer risks than others. Studies that use detailed food questionnaires or repeated dietary records, asked about the specific foods that have high acrylamide levels, and included country-specific databases for acrylamide levels in foods and a large range in the acrylamide exposures of their study population are ideal. In addition, some foods show lower variations in acrylamide levels than others and, depending on which foods are the predominant sources of acrylamide in the study population, some studies may assess acrylamide exposure more reliably than others, which increases the chance that a study is able to pick up an association. Furthermore, the question arises of whether biomarkers or dietary assessment methods are more suited to study the association between acrylamide intake and cancer risks, with the former having more precision in the short term but the latter possibly being better for longer-term exposures.

The IARC has announced that acrylamide is high on its list of chemicals to be reevaluated in terms of the classification of carcinogenicity in humans (10). As opposed to the limited data from 1994, there is now a fair amount of epidemiological data for the agency to consider. In addition to the outcomes of the meta-analyses, the above-mentioned circumstances that determine whether an individual study is better or worse for picking up associations between dietary acrylamide exposure and cancer risks will likely be at the heart of the IARC's reevaluation. Whether the IARC deems the epidemiological evidence sufficient to change acrylamide's classification to a "human carcinogen" (group 1) remains to be seen.

In the meantime, it does seem fair to say that the available epidemiological evidence points in the direction of an increased risk for certain gynecological cancers. Combined with indications for adverse effects of acrylamide exposure on fetal growth (11), it seems prudent to reduce the public's exposure to acrylamide as much as possible; legally enforcing maximum levels of acrylamide in foods is a way to do that.

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