British Journal of Cancer (2003) 89, 774 – 776

www.bjcancer.com

Letters to the Editor

Inconclusive results from an epidemiological study on dietary acrylamide and cancer

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British Journal of Cancer (2003) **89,** 774–775. doi:10.1038/sj.bjc.6601016 www.bjcancer.com

Sir,

The association between dietary acrylamide and cancer of the large bowel, kidney and bladder was assessed in a Swedish case–control study, with a total of 987 cases and 538 healthy controls, that originally had been created for evaluating the carcinogenic effects of heterocyclic amines from diet (Mucci *et al*, 2003). Individual dietary acrylamide intakes were crudely estimated from food frequency questionnaires and reported levels of acrylamide in frequently consumed food products. No associations were observed between dietary acrylamide and any cancer risk. The authors state: 'The first study of dietary acrylamide in relation to three major human cancers is reassuring.' We think that this is too strong a conclusion.

A basal aspect to consider when interpreting the Swedish results is the size both of the expected cancer risk enhancement and of the cancer risk possible to detect. The authors correctly state, '…a true association may be concealed if the level of exposure in the studied population is low and/or if the range of variation is limited.' Unfortunately, the authors provide only limited information about the estimated daily intake of acrylamide among cases and controls, which makes it virtually impossible to get the full picture of absolute levels and interindividual variations in exposure. The interquartile comparisons given in cannot be interpreted in terms of absolute levels and variation of exposure. The only acrylamide dose figures given in the paper concern the estimated mean daily intakes (27.5 μg among the controls and 28.4 – 29.4 μg among the cases), and that less than 2% of the population was estimated to have a daily intake as high as 1 μg acrylamide per kilogram body weight per day. If we assume an average body weight of 70 kg in the population, those 2% of the population with a 'high' exposure had an estimated excess intake of about 42.5 μg acrylamide per day; this corresponds to an increase in lifetime cancer mortality of 2.7 per 1000, based on the risk assessment model of the United States Environmental Protection Agency (1990). An estimate based on a multiplicative model (Granath *et al*, 1999) would arrive at roughly nine extra cancer deaths per 1000 (Törnqvist *et al*, 1998). Assuming a cumulative total cancer mortality of about 18%, and also assuming that the carcinogenicity of acrylamide is not different with respect to fatal or nonfatal malignant neoplasms, relative risks for cancers of approximately 1.015 and 1.05, respectively, could be expected for those 2% of the Swedish study population with the highest daily intake of acrylamide as compared to the mean intake. It can be calculated that from a purely statistical point of view about 470000 (!) cases, with half as many controls, are needed in order to show a relative risk of 1.05 in a statistically significant way ($P<0.05$), and with 80% statistical power, among those 2% with 'high' exposure. It can also be calculated that, assuming an exposure prevalence of 2%, the lowest possible relative risk that would have 80% chance of being significantly detected in a study of 987 cases and 538 controls is as high as 2.4; this type of power calculation assumes that there is no residual confounding or misclassification bias. However, the Swedish study is likely to suffer from considerable nondifferential misclassification of exposure to acrylamide, taking into account both lack of precision in food frequency questionnaire data and the sparse data on acrylamide levels in food products that were available for the intake calculations. Thus, it is not realistic that not even a 'true' relative risk as high as 2.4 could have been detected in the Swedish study.

There is a need to validate the type of exposure assessments for acrylamide that were used in the Swedish study using biomarkers for acrylamide exposure, for example, haemoglobin adducts of acrylamide, which reflect the cumulative dose during the preceding months (Granath *et al*, 1992; Törnqvist *et al*, 2002). It needs to be assessed first, whether food frequency data can be used for quantifying dietary intake of acrylamide and second, the variation in acrylamide intake in the population. More specifically, we need to know whether there are sufficient subjects with high intake, as this is a prerequisite for the design of epidemiological studies with a prospect of evaluating the carcinogenicity to humans of dietary acrylamide.

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Reply: Dietary acrylamide and cancer risk: additional data on coffee

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British Journal of Cancer (2003) **89,** 775–776. doi:10.1038/sj.bjc.6601180 www.bjcancer.com

Sir,

We appreciate the comments of Drs Hagmar and Törnqvist (2003) on our article assessing dietary acrylamide and cancer risk (Mucci *et al*, 2003). We take this opportunity to clarify some issues and to present data from additional analyses.

We undertook the original investigation in light of claims by the Swedish National Food Administration that acrylamide in foods could have global impacts on cancer incidence rates. In spite of the potential limitations of the study design, our data are reassuring that acrylamide seems unlikely to be responsible for a major fraction of these cancers. As stated in our discussion, however, additional data are needed before a global assessment of any risks of dietary acrylamide can be undertaken in relation to other cancer sites and neurological diseases.

The reliance on toxicological risk assessment models employed by Hagmar and Törnqvist may be questionable. Estimates of human cancer risk were extrapolated from animal models, given doses of acrylamide several fold higher than those to which humans are exposed (International Agency for Research on Cancer (IARC), 1994). We think that animal data must be generalized to humans with caution. This sentiment is reflected by IARC (2002) who considers an agent as definitely carcinogenic to humans when there is sufficient evidence from studies in humans (i.e. epidemiological evidence) and only 'exceptionally' in other situations.

The authors present evidence from power analyses on the substantial sample size needed to detect an effect of acrylamide on human cancer risk. Notwithstanding the limitations of the risk assessment models, the authors determined an expected relative risk of 1.05 for the highest *vs* lowest dose. An effect estimate of this size is almost impossible to determine in any observational study. Indeed, not even a randomised clinical trial would have the power to detect this effect. The scientific methods to study such a small effect currently do not exist, and beg the question of how to best proceed to address the question of acrylamide and cancer. In addition, we must ask whether a relative risk of this size warranted the public health alarm that was generated when the findings of acrylamide in food were first announced.

Additional data

Since our study was published, new data have come available on acrylamide content in additional food items. In particular, acrylamide has been detected in coffee. Although the range of exposure ($\sim 8\,\mu g\,kg^{-1}$) is lower than other items, coffee may account for a substantial proportion of total dose because of the frequency of consumption. We present updated data from the original case–control study, using a similar methodology.

Coffee consumption was common in this Swedish population, with 23.5% of controls consuming four or more cups of coffee per day. The daily mean (standard error) dietary acrylamide dose (μg) increased with the addition of coffee data: 34.0 (0.6) for controls, 34.8 (0.6) for colorectal, 36.8 (1.0) for bladder, and 34.5 (1.4) for kidney cancers. Crisp breads (28%) and coffee intake (20%) contributed to the largest sources of acrylamide in the diet among controls (Figure 1). Quartiles of dietary acrylamide dose were calculated based on the distribution among the controls. Adjusting for potential confounders, the risk of colorectal (Figure 2A) and kidney cancers (Figure 2C) decreased with increasing acrylamide dose. The apparent protective effect of acrylamide parallels the lower risk associated in this study with crisp breads and for coffee, a finding consistently observed in the literature (Ekbom, 1999). The relative risk estimate of acrylamide and bladder cancer was essentially null (Figure 2B).

Expanding the range of exposure and achieving a more complete estimate of acrylamide intake, there remains no evidence of an excess risk of the three studied cancers in relation to acrylamide, and provides further reassurance that acrylamide in diet does not appear to be responsible for a major fraction of these three cancers.

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