Debate

Coffee, pancreatic cancer and the question of causation

The article by Miquel Porta and his colleagues indicating that pancreatic cancer cases without activating mutations in the K-ras gene drank significantly less coffee than cases with a mutation and the accompanying editorial by Paolo Vineis are both important. The study by Porta et al epito-nises the way epidemiology is likely to be practised in the future, and the editorial by Vineis highlights the issues that will confront investigators when molecular epidemiology becomes more mainstream. The two papers also bring forward a crucial question: “How do we assess causality in epidemiology?”.

The study by Porta and his colleagues has a considerable advantage over conventional case-control studies—it is less likely to have suffered from substantial selection or information bias. Unless chance has operated in a sinister way, you have to accept that there is indeed a positive association between coffee intake and K-ras mutations among patients with pancreatic cancer. You can never exclude residual confounding, but tobacco smoking has been adjusted for, and, in any case, beyond age no factor has been found to be related to pancreatic cancer with five-fold odds ratio.

Neither the authors of the paper, nor Dr Vineis in his editorial, consider causality as plausible. They argue instead for an interaction between coffee and an unknown factor (smoking?) in the development of pancreatic cancer. They indicate that coffee could work in two different ways; either by modifying metabolic pathways that are involved in the activation or inactivation of carcinogenic compounds, or by inhibiting relevant DNA repair mechanisms. Nevertheless, as Rothman has pointed out in his classic paper on the nature of causation, not only does interaction imply causation, but, in fact, it is an essential part of most causal processes. Both the authors of the research paper and the editorialist are, clearly, aware of this, but they are trying to emphasise that coffee is not a dominant or important causal exposure for pancreatic cancer. Yet if the findings by Porta et al are replicable and valid, drinking should still be considered a component cause, however minor.

Where does this leave us? There are only two options: either the study by Porta et al has fallen victim to an unusual chance phenomenon, or coffee increases, albeit slightly, the risk of pancreatic cancer. Indeed, the mechanisms postulated by Porta et al and Vineis would be compatible with a very minor increase in risk of pancreatic cancer.

It is clear that there is no strong association between coffee intake and risk for pancreatic cancer, but a weak positive association cannot be excluded. Although a formal meta-analysis has not been undertaken, figure 1 shows the distribution of the rate ratios contrasting the highest with the lowest exposure of coffee drinkers among 46 groups that have been investigated.

No account was taken of the size or the quality of the corresponding study, nor of covariates or exposure-response trends. The pattern evident in the figure, however, is not inconsistent with a minor increase in risk of pancreatic cancer among drinkers of large amounts of coffee.

The International Agency for Research on Cancer has indicated that there is limited evidence that coffee drinking may increase the risk of cancer of the urinary bladder. In a formal meta-analysis Viscoli et al found that there was a minimal yet statistically significant excess risk of bladder cancer among coffee drinkers. Viscoli and her colleagues dismissed the trivial increase as having little clinical importance, and the situation with respect to pancreatic cancer may be the same, or, indeed, may reflect the same underlying mechanism. We would agree that such associations have limited practical implications. Nevertheless, the findings by Porta and his colleagues are of considerable theoretical interest by allowing an insight into the complexity of the carcinogenic process.

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Figure 1 The distribution of rate ratios contrasting the highest with the lowest exposure of coffee drinkers among 46 groups.

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