

## Debate

# Coffee, pancreatic cancer and the question of causation

The article by Miquel Porta and his colleagues<sup>1</sup> 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<sup>2</sup> are both important. The study by Porta *et al* epitomises 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.<sup>3</sup> 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,<sup>4</sup> 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.

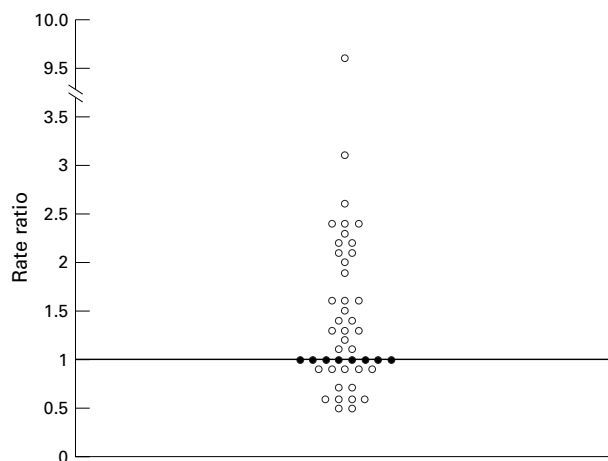


Figure 1 The distribution of rate ratios contrasting the highest with the lowest exposure of coffee drinkers among 46 groups.<sup>5-39</sup>

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.<sup>5-39</sup> 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<sup>40</sup> 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*<sup>41</sup> 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.

HANNAH E KUPER

LORELEI A MUCCI

DIMITRIOS TRICHOPOULOS

Department of Epidemiology, Harvard School of Public Health, 677  
Huntington Avenue, Boston, MA 02115, USA

Correspondence to: Dr Trichopoulos

- Porta M, Malats N, Guarner L, *et al*. Association between coffee drinking and K-ras mutations in exocrine pancreatic cancer. *J Epidemiol Community Health* 1999;53:702-9.
- Vineis P. K-ras mutations and a cup of coffee: cause, confounder, effect modifier, or what else? *J Epidemiol Community Health* 1999;53:685.
- Begg CB, Zhang ZF. Statistical analysis of molecular epidemiology studies employing case-series. *Cancer Epidemiol Biomarkers Prev* 1994;3:173-5.
- Rothman KJ. Causes. 1976 [classical article] *Am J Epidemiol* 1995;141:90-5.
- MacMahon B, Yen S, Trichopoulos D, *et al*. Coffee and cancer of the pancreas. *N Engl J Med* 1981;304:630-3.
- Jick H, Dinan BJ. Coffee and pancreatic cancer. *Lancet* 1981;iii:92.
- Goldstein HR. No association found between coffee and cancer of the pancreas. *N Engl J Med* 1982;306:997.
- Whittemore AS, Paffenberger RS, Anderson K, *et al*. Early precursors of pancreatic cancer in college men. *J Chron Dis* 1983;36:251-6.
- Wynder EL, Hall NE, Polansky M. Epidemiology of coffee and pancreatic cancer. *Cancer Res* 1983;43:3900-6.
- Kinlen LJ, McPherson K. Pancreas cancer and coffee and tea consumption: a case-control study. *Br J Cancer* 1984;49:93-6.
- Gold EB, Gordis L, Diener MD, *et al*. Diet and other risk factors for cancer of the pancreas. *Cancer* 1985;55:460-7.
- Nomura A, Heilbrun LK, Stemmermann GN. Prospective study of coffee consumption and the risk of cancer. *J Natl Cancer Inst* 1986;76:587-90.
- Mack TM, Yu MC, Hanisch R, *et al*. Pancreas cancer and smoking, beverage consumption, and past medical history. *J Natl Cancer Inst* 1986;76:49-60.
- Norell SE, Ahlbom A, Erwald R, *et al*. Diet and pancreatic cancer: a case-control study. *Am J Epidemiol* 1986;124:894-902.
- Wynder EL, Dieck GS, Hall NE. Case-control study of decaffeinated coffee consumption and pancreatic cancer. *Cancer Res* 1986;46:5360-3.

- 16 Hsieh CC, MacMahon B, Yen S, *et al.* Coffee and pancreatic cancer. *N Engl J Med* 1986;315:587-9.
- 17 La Vecchia C, Liati P, Decarli A, *et al.* Coffee consumption and risk of pancreatic cancer. *Int J Cancer* 1987;40:309-13.
- 18 Raymond L, Infante F, Tuyns AJ, *et al.* Diet and cancer of the pancreas. *Gastroenterol Clin Biol* 1987;11:488-92.
- 19 Hiatt RA, Klatsky AL, Armstrong MA. Pancreatic cancer, blood glucose and beverage consumption. *Int J Cancer* 1988;41:794-7.
- 20 Mills PK, Beeson WL, Abbey DE, *et al.* Dietary habits and past medical history as related to fatal pancreas cancer risk among Adventists. *Cancer* 1988; 61:2578-85.
- 21 Falk RT, Pickle LW, Fontham ET, *et al.* Life-style risk factors for pancreatic cancer in Louisiana: a case-control study. *Am J Epidemiol* 1988;128:324-36.
- 22 Gorham ED, Garland CF, Garland FC, *et al.* Coffee and pancreatic cancer in a rural California county. *West J Med* 1988;148:48-53.
- 23 Clavel F, Benhamou E, Auquier A, *et al.* Coffee, alcohol, smoking and cancer of the pancreas: a case-control study. *Int J Cancer* 1989;43:17-21.
- 24 Cuzick J, Babiker AG. Pancreatic cancer, alcohol, diabetes mellitus and gallbladder disease. *Int J Cancer* 1989;43:415-21.
- 25 Olsen GW, Mandel JS, Gibson RW, *et al.* A case-control study of pancreatic cancer and cigarettes, alcohol, coffee and diet. *Am J Public Health* 1989;79: 1016-19.
- 26 La Vecchia C, Ferraroni M, Negri E, *et al.* Coffee consumption and digestive tract cancers. *Cancer Res* 1989;49:1049-51.
- 27 Jain M, Howe GR, St Louis P, *et al.* Coffee and alcohol as determinants of risk of pancreas cancer: a case-control study from Toronto. *Int J Cancer* 1991;47:384-9.
- 28 Ghadirian P, Simard A, Baillargeon J. Tobacco, alcohol, and coffee and cancer of the pancreas. A population-based, case-control study in Quebec, Canada. *Cancer* 1991;67:2664-70.
- 29 Bueno de Mesquita HB, Maisonneuve P, Moerman CJ, *et al.* Lifetime consumption of alcoholic beverages, tea and coffee and exocrine carcinoma of the pancreas: a population-based case-control study in The Netherlands. *Int J Cancer* 1992;50:514-22.
- 30 Lyon JL, Mahoney AW, French TK, *et al.* Coffee consumption and the risk of cancer of the exocrine pancreas: a case-control study in a low-risk population. *Epidemiology* 1992;3:164-70.
- 31 Zatonski WA, Boyle P, Przewozniak K, *et al.* Cigarette smoking, alcohol, tea and coffee consumption and pancreas cancer risk: a case-control study from Opole, Poland. *Int J Cancer* 1993;53:601-7.
- 32 Kalapothaki V, Tzonou A, Hsieh CC, *et al.* Tobacco, ethanol, coffee, pancreatitis, diabetes mellitus, and cholelithiasis as risk factors for pancreatic carcinoma. *Cancer Causes Control* 1993;4:375-82.
- 33 Stensvold I, Jacobsen BK. Coffee and cancer: a prospective study of 43,000 Norwegian men and women. *Cancer Causes Control* 1994;5:401-8.
- 34 Partanen T, Hemminki K, Vainio H, *et al.* Coffee consumption not associated with risk of pancreas cancer in Finland. *Prev Med* 1995;24:213-16.
- 35 Gullo L, Pezzilli R, Morselli-Labate AM. Coffee and cancer of the pancreas: an Italian multicenter study. The Italian Pancreatic Cancer Study Group. *Pancreas* 1995;11:223-9.
- 36 Kokic NZ, Adanja JB, Vlajinac DH, *et al.* Case-control study of pancreatic cancer in Serbia, Yugoslavia. *Neoplasma* 1996;43:353-6.
- 37 Nishi M, Ohba S, Hirata K, *et al.* Dose-response relationship between coffee and the risk of pancreas cancer. *Jpn J Clin Oncol* 1996;26:42-8.
- 38 Harnack LJ, Anderson KE, Zheng W, *et al.* Smoking, alcohol, coffee, and tea intake and incidence of cancer of the exocrine pancreas: the Iowa Women's Health Study. *Cancer Epidemiol Biomarkers Prev* 1997;6:1081-6.
- 39 Soler M, Chatenoud L, La Vecchia C, *et al.* Diet, alcohol, coffee and pancreatic cancer: final results from an Italian study. *Eur J Cancer Prev* 1998;7:455-60.
- 40 IARC. Coffee, tea, mate, methylxanthines and methylglyoxal. In: *IARC monographs on the evaluation of carcinogenic risks to humans*. Vol 51. Lyon: IARC, 1991.
- 41 Viscoli CM, Lachs MS, Horwitz RI. Bladder cancer and coffee drinking: a summary of case-control research. *Lancet* 1993;341:1432-7.