

Coffee, K-ras mutations and pancreatic cancer: A heterogeneous aetiology or an artefact?

Is coffee drinking a risk factor for pancreatic cancer, after all? Kuper and colleagues¹ argue on the basis of data presented by Porta and colleagues² that this may be distinct possibility.

Relations between coffee drinking and the risk of pancreatic cancer have been examined in numerous epidemiological studies, with the overall conclusion that there is essentially no association.³ This is also in accordance with two Norwegian prospective studies.⁴⁻⁶

Porta and colleagues found K-ras mutations in 78 per cent of the cases of pancreatic cancer in their dataset.² The mutation prevalence was directly related to coffee consumption.² How can it be explained, then, that coffee consumption is not related to the risk of pancreatic cancer? Porta and colleagues,² and Dr Vineis in the accompanying editorial,⁷ argue against a causal relation and suggest that substances in coffee may have an impact on the metabolic processes affecting carcinogens and on the DNA repair mechanisms. But, it may be argued, as Kuper and colleagues do: if the result of these processes, alone or in an interaction with, for example, smoking or dietary factors, is pancreatic cancer, then coffee is one of several causes of the cancer.¹

The interpretation of results from molecular epidemiology is fraught with difficulties,⁸ however, and Porta and colleagues considered several theories to explain their findings.² We would like to highlight two possible explanations for the apparent paradox. Firstly, coffee may have a different impact on the aetiology of distinct types of clinically similar pancreatic cancer. Secondly, the distribution of mutations found in the tumour at diagnosis may not be representative of the mutations that are causally related to the cancer.

Thus, if coffee drinking increases the risk of pancreatic cancer with K-ras mutations, but reduces the risk of cancer without these mutations (the "wild type"), no overall relation may appear between coffee and pancreatic cancer. To show this mathematically, consider a population with the proportion of coffee drinkers equal to *c*. Let the absolute risk of the cancer with K-ras mutations in persons who do not drink coffee be P_{K-ras} . The corresponding absolute risk of the cancer with a wild type gene is P_{wild} . Let r_{K-ras} be the relative risk for the cancer with the K-ras mutations for a coffee drinker compared with a person who does not drink coffee. The analogous relative risk for the wild type cancer is r_{wild} . Then the two types of cancer will be represented by the following population fractions:

	K-ras cancer	Wild type cancer
No regular coffee	(1-c) P_{K-ras}	(1-c) P_{wild}
Regular coffee drinkers	c $P_{K-ras} r_{K-ras}$	c $P_{wild} r_{wild}$

The odds ratio for a cancer with K-ras mutations, considering cancer cases only, is simply:

$$OR = \frac{r_{K-ras}}{r_{wild}}$$

as previously shown in a more general context.⁹

The overall relative risk (RR) of pancreatic cancer with regard to coffee drinking in the whole population, disregarding type of cancer is:

$$RR = \frac{P_{K-ras} r_{K-ras} + P_{wild} r_{wild}}{P_{K-ras} + P_{wild}}$$

or

$$RR = \frac{(P_{K-ras}/P_{wild})r_{K-ras} + r_{wild}}{(P_{K-ras}/P_{wild}) + 1}$$

From the data presented by Porta and colleagues, we can estimate P_{K-ras}/P_{wild} as 10/8=1.25. If we assume that the odds ratio r_{K-ras}/r_{wild} among cases is 3.7 (in accordance with the data presented by Porta and colleagues),² several combinations of r_{K-ras} and r_{wild} are compatible with an overall relative risk around 1.0 (table 1). If we imagine that coffee drinking is rather weakly positively associated with cancer with K-ras mutations ($r_{K-ras}=1.5$) and more strongly inversely associated with cancer with the wild type ($r_{wild}=0.41$), the overall relative risk can be practically 1.0. Thus, the results presented by Porta and colleagues² are consistent with an overall lack of association between coffee drinking and the risk of pancreatic cancer.

On the other hand, if K-ras mutations constitute an important step in the early stage carcinogenesis,³ examining the tumour at the clinical stage may be too late for evaluating the role of mutations in the aetiology. Many changes, not related to the aetiology, may already have taken place in the tumour cell.⁸ Coffee may even facilitate the persistence of the K-ras mutations at a later stage, without influencing the risk of initiation or the complete cancer development.

It is therefore of interest to examine the prevalence of K-ras mutations in normal pancreatic tissue according to coffee consumption. Berger and colleagues recently did an analysis of this kind for cigarette smoking, and found K-ras mutations in non-neoplastic pancreas only in heavy cigarette smokers.¹⁰ This is apparently inconsistent with the Spanish cancer data indicating a lower prevalence of K-ras mutations in cigarette smokers.² As cigarette smoking is an established risk factor for pancreatic cancer,³ Berger and colleagues were of the opinion that their results reflected a causal link.

K-ras mutations are also found in several non-malignant pancreatic conditions and may thus be a general indicator of a pathological process in the pancreas.¹⁰ If no association is found between coffee consumption and K-ras mutations among people affected with other diseases, the hypothesis that there is a complex causal relation with pancreatic cancer becomes more plausible. Thus, studies of relations between coffee consumption and mutation prevalence are called for in, for example, chronic pancreatitis.

In the years to come, we shall see many studies in molecular epidemiology following the general approach of Porta and colleagues. At present, it may not be easy to generate data that can throw sufficient light on the theories put

Table 1 Hypothetical combinations of relative risks r_{K-ras} , r_{wild} and overall relative risk for cancer given that the odds ratio r_{K-ras}/r_{wild} among cases is 3.7 and $P_{K-ras}/P_{wild} = 1.25$

r_{K-ras}	r_{wild}	Overall relative risk
1.0	0.27	0.68
1.25	0.34	0.84
1.50	0.41	1.01
1.75	0.47	1.18
2.0	0.54	1.35

The estimates of the odds ratio (3.7) and P_{K-ras}/P_{wild} (1.25) are as found by Porta and colleagues.²

forward. In our opinion, however, traditional epidemiological principles will still play an essential part in the interpretation of complex results from such studies.

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