

LETTERS TO THE EDITOR

Cancer risk in patients treated surgically for duodenal ulcer

EDITOR,—Macintyre and O'Brien (*Gut* 1994; 35: 451–4), although discussing our paper¹ in some detail, seem to have misunderstood it.

They claim that Caygill *et al* reported an 'increased risk of cancers of the colon, rectum, biliary tract and female breast', in contrast with their own results in duodenal ulcer patients. In fact, firstly we did not separate colon and rectum but, like them we reported a decreased risk (relative risk 0.8) in duodenal ulcer patients of colorectal cancer (see our Table I).

We did report an excess risk of biliary tract cancer in duodenal ulcer patients but it was not significant. The excess risk of female breast cancer that we reported was seen only after a 20 year latency. Elsewhere in the paper they claim that we reported an excess risk of oesophageal cancer, again in contrast with their own results. But like them we found no significant excess of oesophageal cancer in duodenal ulcer patients (see our Table I).

We did report significant excess risks at these sites in gastric ulcer patients or in our whole cohort of peptic ulcer patients.

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1 Caygill CPJ, Hill MJ, Hall CN, Kirkham JS, Northfield TC. Increased risk of cancer at multiple sites after gastric surgery for peptic ulcer. *Gut* 1985; 28: 924–8.

Reply

EDITOR,—We are grateful to Drs Caygill and Hill for their response to our paper. Confusion over deaths from cancer of the colon and rectum has probably arisen because while they did not separate these in their Table I they did so in Table III. There has, however, been no misunderstanding on our part about their conclusions. They state in their summary '... from 20 years after operation there was a significant excess risk not only of cancer of the stomach but also of the large bowel, bronchus, pancreas, biliary tract, oesophagus, bladder, breast, and cancer of all sites. These findings are consistent with the production in the operated upon stomach of circulating carcinogens with a 20 year latency period'. The evidence from our study and from others does not support their suggestion of a circulating carcinogen being produced in the operated stomach. Furthermore we take issue with their statement that cancers in such patients 'are unrelated to a common predisposition such as smoking'. We believe that the evidence of our study, and the others that we quoted in our paper, suggests that cigarette smoking is indeed the most important risk factor in carcinogenesis in such patients.

While Drs Caygill and Hill did find differences in subsequent cancer mortality between patients operated on for duodenal ulcer and gastric ulcer, they did not draw attention to this in subsequent discussion or summary.

As the debate draws to a close with the disappearance of elective surgical treatment for peptic ulcer, it is appropriate that the conclusions from this area should be clarified. We believe that these are as follows: that patients operated on for gastric ulcer are at significantly higher risk of developing gastric cancer 20 years postoperatively: that there is a significant increase in smoking related cancers as a result of the excess of cigarette smokers in this group, and finally that there is no evidence to support production of circulating carcinogens by the operated stomach.

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Intestinal permeability in patients with Crohn's disease

EDITOR,—We read with great interest the article by Munkholm *et al* (*Gut* 1994; 35: 68–72). While this is very interesting work we feel that several important facts must be pointed out.

An important conclusion reached by the authors is that these data do not support the hypothesis that asymptomatic first degree relatives of patients with Crohn's disease have increased intestinal permeability. Furthermore, they state that as a large number of participants were included in their study, it had minimal risk of a type 2 error. We would like to point out that in another study, similar in design to this one, we have examined a comparably sized group and by combining data from two separate studies we have in fact studied almost twice as many relatives of patients with Crohn's disease as reported here.¹ Most importantly, our interpretation of the data differs dramatically from that presented in this paper. We described in our paper a fundamental flaw in the analysis of this type of data that has potentially contributed to much of the confusion in published works concerning these issues. We are disappointed to see the same flaw repeated in this work.

Not all relatives of patients with Crohn's disease ultimately develop the disease. In fact it has been estimated that only 10% of this group will develop disease during their lifetime.² Therefore, even if increased intestinal permeability is a prerequisite for disease and, furthermore, is manifested lifelong only 10% of the relative group would be expected to show increased intestinal permeability. In the study by Munkholm *et al* only 39 relatives of patients with Crohn's disease were studied, therefore, given these assumptions only four subjects should have increased permeability. It is almost inconceivable that such a small fraction would significantly change the mean of the entire group. We discuss this more fully in our paper. The point that must be made is that this type of data analysis cannot disprove the hypothesis that relatives of patients with Crohn's disease have increased intestinal permeability.

The most effective means to analyse the data obtained in this study is to construct a normal range of permeabilities and to ask whether a subgroup of relatives exists with increased permeability and disregard group statistics. These points were clearly made in

our paper and we are disappointed that they have been ignored. From our perspective, unless the study by Munkholm *et al* deals with these issues it is merely a repetition of numerous previous studies that have completely missed the point. With only 10% of relatives having abnormal permeability the approach used in this paper will be unlikely to even show a statistical difference between control and relative groups. Thus, we believe the conclusions reached by the authors are unwarranted as the statistical analysis fails to consider the question that the authors intended to ask.

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- 1 May GR, Sutherland LR, Meddings JB. Is small intestinal permeability really increased in relatives of patients with Crohn's disease? *Gastroenterology* 1993; 104: 1627–32.
- 2 Yang H, McElree C, Roth M-P, Shanahan F, Targan SF, Rotter JL. Familial empiric risks for inflammatory bowel disease: differences between Jews and non-Jews. *Gastroenterology* 1992; 102: A31.

Reply

EDITOR,—We only became aware of the publication of May *et al*¹ when our article was in press.

Although the analytical methods for determination of urine concentrations used by May *et al* seem to be identical to those of our study, the results obviously differ in that we did not find any difference in permeability among Crohn's disease patients, healthy or inflammatory bowel disease (IBD) diseased relatives, ulcerative colitis patients, and controls.

The proposed method for statistical evaluation is in our opinion not acceptable because non-parametric statistics should be applied in data not normally distributed. Furthermore the correct comparison between controls and patients data seem to be a direct test.

Defining absolute normal limits for permeability based on data from 31 controls does not seem reasonable, which is further illustrated by the 'borderline' values considered abnormal by May *et al*.

The calculations of the Canadian group on the probability of relatives of Crohn's disease patients developing the disease are based on all first degree relatives. In our study we examined only relatives from 18 families with known familial IBD occurrence where the expected inheritance will be higher.² Furthermore the individual values of diseased relatives were not different from controls.

We thus conclude that even with the most positive and optimistic view of our permeability data we cannot see anything that points to the very interesting hypothesis suggested by the study of Hollander *et al* in 1984.³

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- 1 May GR, Sutherland LR, Meddings JB. Is small intestinal permeability really increased in relatives of patients with Crohn's disease? *Gastroenterology* 1993; 104: 1627–32.
- 2 Orholm M, Munkholm P, Langholz E, Nielsen OH, Sørensen TIA, Binder V. Familial occurrence of inflammatory bowel disease. *N Engl J Med* 1991; 324: 84–8.