CORRESPONDENCE

Re: Etiology of Pancreatic Cancer, With a Hypothesis Concerning the Role of N-Nitroso Compounds and Excess Gastric Acidity

We read with great interest the exhaustive review from Risch (1), which focused on the possible role of gastric acid hypersecretion in the etiology of pancreatic cancer. The author presented several strands of evidence connecting alterations of gastric physiology in the course of Helicobacter pylori infection with pancreatic cancer. It is hypothesized that the decrease in somatostatin release by gastric delta cells in H. pylori–infected patients may increase the secretion of secretin from S cells in the duodenum and jejunum that, in turn, may favor carcinogenesis through its trophic effect on pancreatic duct epithelium. This view is supported by the fact that gastric acid hypersecretion, like that observed in most duodenal ulcer patients, causes increased bicarbonate secretion from the pancreas by increased secretin release.

Although we agree with the rationale of the hypothesis, we think that some points remain at least controversial, and additional observations may help to clarify the previously reported (2) possible link between H. pylori infection and pancreatic cancer.

The first point of doubt about the relationship between increased gastric acid secretion and pancreatic cancer arises from the fact that most of the studies cited by Risch (1) that report an increased risk of pancreatic cancer involve patients who underwent gastric surgery for duodenal ulcers. These subjects will have decreased acid secretion after gastrectomy and, when pancreatic cancer has subsequently developed, it has typically been decades after gastrectomy. To further confound the hypothesis, although some have reported an epidemiologic association between duodenal ulcers and pancreatic cancer, others have suggested that pernicious anemia is a risk factor for the development of pancreatic cancer (3). Moreover, although decreased concentrations of somatostatin are observed in the gastric antral mucosa of patients with H. pylori infection (as pointed out by Risch), the density of delta cells is reduced more in patients with pernicious anemia than in patients with duodenal ulcers (4).

Pernicious anemia represents the clinical end stage of atrophic body gastritis which, in most cases, is linked to H. pylori infection and is characterized by hypochlorhydria or achlorhydria, being the exact opposite of duodenal ulcers in terms of pathophysiologic consequences of H. pylori infection. What eventually links duodenal ulcers and pernicious anemia, apart from H. pylori infection, is hypergastrinemia caused by the infection impairing the acid-mediated inhibitory control of gastrin release in the former and by negative feedback as a consequence of the reduction of gastric acid secretion by parietal cells in the latter.

It is therefore tempting to speculate that hypergastrinemia itself may be the link between gastric pathology and pancreatic cancer. Hypergastrinemia can indeed play a role in the development of various digestive malignancies (5). Gastrin has been shown to increase the growth of human pancreatic cancer cells in culture, and both gastrin and its receptor are expressed by pancreatic cancer cells, thus supporting recent use of anti-gastrin antibodies in pancreatic cancer patients (6).

Finally, another plausible link between gastritis and pancreatic cancer may be represented by the decreased plasma concentration of a spectrum of antioxidant compounds observed in patients with H. pylori gastritis (7), particularly ascorbic acid, which decreases the risk of developing various neoplasms including pancreatic cancer.

In conclusion, although we agree that altered gastric physiology may have an impact on cell proliferation and the subsequent risk of carcinogenesis in other organs, we believe that hypotheses other than those presented by Risch may be reasonably considered for the increased risk of pancreatic cancer in H. pylori–infected subjects.

Gabriele Capurso
Gianfranco Delle Fave
Nick Lemoine

REFERENCES


NOTES

Affiliations of authors: Cancer Research UK Molecular Oncology Unit, Imperial College London Faculty of Medicine at Hammersmith Campus, London, U.K. (GC, NL); Digestive and Liver Disease Unit, II Medical School, University “La Sapienza,” Rome, Italy (GC, GDF).

Correspondence to: Gabriele Capurso, MD, Cancer Research UK Molecular Oncology Unit, Imperial College London Faculty of Medicine at Hammersmith Campus, Du Cane Rd., W12 0NN London, U.K. (e-mail: gabriele.capurso@cancer.org.uk).

DOI: 10.1093/jnci/djh018

RESPONSE

I thank Dr. Capurso and colleagues for their observations concerning the etiologic hypotheses I presented in my review of gastric pathophysiology, Helicobacter pylori, nitrite exposures, and pancreatic cancer. Studies in the literature provide a lot of suggestive evidence but are certainly not definitive for the hypotheses, and interpretations other than the ones I proposed are possible. Capurso et al. mention two areas of potential controversy. The first concerns the relation between chronically increased gastric acid secretion and risk of pancreatic cancer. In support of this association, I cited studies of in-
individuals with a history of duodenal ulcers, as well as studies of persons who had undergone gastrectomy for duodenal ulcer treatment. Capurso et al. are correct that gastrectomy usually decreases gastric acid output. Furthermore, duodenal ulcer patients treated with vagotomy and gastrojejunostomy or pyloroplasty can have elevated gastric nitrites and \( N \)-nitroso compounds that could be the reason for their increased risk of pancreatic cancer. However, as I noted in the review, a number of case–control studies examining only a history of duodenal ulcers, without considering gastrectomy, have shown an increased risk of pancreatic cancer.

Second, Capurso et al. state that pernicious anemia is associated with risk of pancreatic cancer. Although there have been two reports linking pernicious anemia and risk \((1,2)\), most studies of this relation, in fact, have not shown appreciable association, unlike the known association with gastric cancer [reviewed in \((2)\)]. Pernicious anemia is frequently the end result of \( H. pylori \)-induced corpus atrophic gastritis in hosts carrying inflammatory cytokine genetic variants that are associated with the suppression of gastric acid production. This syndrome favors the risk of gastric cancer rather than pancreatic cancer, and it must be distinguished from other causes of pernicious anemia to determine whether a relationship between those forms of pernicious anemia and pancreatic cancer exists.

Capurso et al. speculate that hypergastrinemia rather than excess gastric acidity might explain the various features of gastric pathology and the risk of pancreatic cancer. This hypothesis was originally proposed by Borch et al. \((2)\). To start with, it seems unlikely that gastrin, which has sequence homology within the gastrin–cholecystokinin (CCK) family, would have relevant hormonal effects on pancreatic ductal epithelial cells. Gastrin receptors are apparently not present on normal ductal epithelium \((3)\). Although not without some criticism, a case–control study did not find that serum levels of gastrin and CCK were associated with risk of pancreatic cancer \((4)\). Associations with hypergastrinemia can be distinguished from those with hyperchlorhydria when parietal cell gastric acid production itself is suppressed, allowing negative feedback hypergastrinemia. This effect occurs in \( H. pylori \)-related and other types of corpus atrophic gastritis and with use of histamine-receptor antagonists and proton-pump inhibitors \((5)\). At least in the rat azaserine acinar cell cancer model, proton-pump inhibitors have not been associated with increased tumor development \((5)\). Further work in ductal carcinoma models is needed.

One last piece of evidence bearing upon the issue of hypergastrinemia versus hyperchlorhydria involves chronic aspirin use. Acute intravenous aspirin administration suppresses secretin-induced pancreatic bicarbonate and fluid output. However, long-term use or high levels of aspirin intake cause gastric inflammation, which disinhibits acid production while not increasing gastrin secretion \((6)\). A recent report \((7)\) from the Nurses’ Health Study found that extended periods of regular aspirin use were statistically significantly associated with dose–response increases in risk of pancreatic cancer. Thus, excess gastric acidity, rather than elevated gastrin secretion, appears to be responsible for increased risk of pancreatic cancer.

Harvey A. Risch

REFERENCES


NOTES

Harvey A. Risch, MD, PhD, Department of Epidemiology and Public Health, Yale University School of Medicine, 60 College St., POB 208034, New Haven, CT 06520–8034 (e-mail: harvey.risch@yale.edu).

DOI: 10.1093/jnci/djh019