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EDITORIAL

Duodenal Acidity May Increase the Risk of Pancreatic Cancer in the Course of Chronic Pancreatitis: An Etiopathogenetic Hypothesis

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Summary

Chronic pancreatitis patients have an increased risk of developing pancreatic cancer. The cause of this increase has yet to be fully explained but smoking and inflammation may play an important role. To these, we must now add a new potential risk factor, namely duodenal acidity. Patients with chronic pancreatitis very often present pancreatic exocrine insufficiency combined with a persistently low duodenal pH in the postprandial period. The duodenal mucosa in chronic pancreas patients with pancreatic insufficiency has a normal concentration of s-cells and, therefore, the production of secretin is preserved. Pancreatic ductal cells are largely responsible for the amount of bicarbonate and water secretion in response to secretin stimulation. When gastric acid in the duodenum is not well-balanced by alkaline pancreatic secretions, it may induce a prolonged secretin stimulus which interacts with the pancreatic ductal cells resulting in an increased rate of ductular cell activity and turnover. *N*-Nitroso compounds from tobacco, identified in human pancreatic juice and known to be important carcinogens, may then act on these active cells, thereby increasing the risk of cancer. Duodenal acidity is probably of particular concern in patients who have undergone a duodenum-preserving pancreatic head resection, since, in this anatomic situation, pancreatic juice transits directly via the jejunal loop, bypassing the duodenum. Patients undergoing a Whipple procedure or side-to-side pancreaticojejunostomy are probably less critically affected because secretions transit, at least in part, via the papilla.
If the duodenal acidity hypothesis proves correct, then, in addition to stopping smoking, reduction of duodenal acid load in patients with pancreatic insufficiency may help decrease the risk of pancreatic cancer.

Chronic pancreatitis (CP) patients have an increased risk of developing pancreatic cancer [1, 2]. The cause of this increase has yet to be fully explained and various hypotheses are being explored [3, 4, 5, 6, 7]. Nevertheless, smoking unquestionably plays an important role [4, 8, 9] because the great majority of CP patients have smoked a large number of cigarettes for a long period of time [10]. Excluding patients with a diagnosis of pancreatic cancer formulated within only a few years of the onset of symptoms (probably cases of misdiagnosis of chronic pancreatitis) [11], we have documented that at least one-third of pancreatic cancer risk in CP is due to smoking while the remaining two-thirds may be due to the interaction of smoking with inflammation and/or other factors [10]. We have tried to identify these other risk factors. In the general population, in very large series, cholecystectomy, gastrectomy and diabetes mellitus have been identified as weak risk factors for pancreatic cancer [12]; however, in

our patients with CP, these factors would appear not to be associated with any increased risk of pancreatic cancer [13].
Inflammation probably has a significant impact [14, 15]; illnesses such as a Barrett esophagus, atrophic gastritis, celiac disease, Crohn's or ulcerative colitis, and cirrhosis increase the risk of cancer in the respective organs. Mechanisms involving DNA modifications take many years and are not clearly understood [14, 15, 16]. The interaction between smoking and inflammation may also be very important in CP and may modify the host response to smoking in a chronic condition having a higher risk of cancer [7, 9, 17, 18, 19].

Duodenal Acidity

When seeking to understand pancreatic carcinogenesis in CP, it may now be necessary to consider a new potential source of risk in addition to the above-mentioned factors, namely duodenal acidity [20].
In CP patients, who very often present pancreatic exocrine insufficiency [21], duodenal pH may be persistently low. In fasting conditions gastric and duodenal pH are normal, whereas, in the postprandial period there is increased, prolonged acidity in both the stomach and the duodenum [22]. The increased acidification of the duodenum releases secretin from duodenal s-cells to the blood, probably in normal (or higher) concentrations for a prolonged period of time. Thus, the area under secretin curve after a meal should be increased. The duodenal mucosa in chronic pancreas patients with pancreatic insufficiency has a normal concentration of s-cells and, therefore, the production of secretin is preserved [23].
Of the total pancreatic mass, the acini account for about 85% whereas the ductal and centroacinar cells (also called principal cells) make up only about 5% of the glandular cell mass [24]. Even without conclusive evidence regarding the type of cell of origin, we know that phenotypic ductal pancreatic adenocarcinomas constitute about 80% of pancreatic cancers.
The centroacinar and ductal cells are largely responsible for a considerable amount of HCO_3^- and water secretion in response to secretin stimulation [24]. The maximum concentration of HCO_3^- is 150 mMol/L. These cells present high levels of activity of carbonic anhydrase. Secretin receptors increase the concentration of cyclic adenosine monophosphate (c-AMP) which activates Cl^- channels resulting in an exchange of CL^- for HCO_3^- at the luminal membrane with a subsequent cascade of events.
Duodenal pH is the most important regulator of secretin release and pancreatic bicarbonate secretion; the threshold value is 4.5 pH in the duodenum. Below this value, the secretin-releasing peptide in the intestinal mucosa (probably a phospholipase A_2 [25]) releases secretin into the plasma [24].
The secretin-stimulated pancreatic exocrine secretion is profoundly inhibited by atropine, suggesting a mediated muscarinic cholinergic pathway involving the vagus nerve [26]. Moreover, smoking reduces the pancreatic fluid and bicarbonate secretion in men for 60-90 min [27].
When gastric acid in the duodenum is not adequately buffered by alkaline pancreatic secretions, it may induce a prolonged secretin stimulus which interacts with pancreatic ductal cells with a subsequent increased rate of ductular cell activity and turnover.

Tobacco Smoking

N-Nitroso compounds from tobacco, which are known to be important carcinogens [28] and have been identified in human pancreatic juice and rat acinar cells [29], may also act on the active ductal cells [30].
A cigarette contains up to 30 mg of nicotine, a volatile alkaloid rapidly absorbed by membranes, with a half life of 30-60 minutes. Peak arterial and venous nicotine levels after smoking reach 80 ng/mL and 5-15 ng/mL, repectively [31, 32]. In the saliva of smokers, bearing in mind that the salivary gland presents characteristics similar to the pancreas, nicotine levels are much higher than in the blood, i.e. 1,300 ng/mL [33]. Nicotine,

one of the main components of smoking, is a relatively inert chemical in carcinogenesis. It is metabolized to cotinine (mutagenic). Cigarette smoke, moreover, contains a large number of other more potent carcinogens (e.g. 4-(N-methylnitrosamino)-1-(3-pyridyl)-butanone (NNK) and N-nitrosonornicotine (NNN) [28, 30]).

Benzopyrene induces a specific type of G:C->T:A mutation found in K-*ras* and *p53* genes in lung tumors [34, 35], and loss of heterozygosity of the FHIT locus (located on chromosome 3p14.2) occurs in lung cancer and in 60% of pancreatic cancers [36]. In the pancreatic juice of CP patients, K-*p53* and *p53* mutation have been found with a high prevalence [37, 38].

Smoking may modify vascular reactivity [39], and interaction with alcohol may increase pancreatic damage [40].

Harvey A Risch [20] claims that, in normal subjects, the low duodenal pH due to *Helicobacter pylori* (HP) infection may account for the persistent stimulation of pancreatic ductal cells by secretin. A number of epidemiological studies support this hypothesis [41, 42]. Chronic pancreatitis patients, and even those with a prevalence of about 20% of duodenal ulcers [43, 44] would not seem to be at high risk of HP infection [45].

Unfortunately, in our series, we have few data concerning HP and we do not know whether patients with CP and pancreatic cancer are HP positive; consequently, we cannot evaluate the hypothetical increased risk of pancreatic cancer. We have also been unable to find any literature on this subject.

Alcohol, Pancreatic Insufficiency and Duodenal Acidity

Disregarding the HP component, the low duodenal pH hypothesis in CP patients may partly account for the increased risk of pancreatic cancer. In addition to pancreatic insufficiency, the ingestion of alcohol releases secretin in man by increasing the acid load of the duodenum [46, 47]. Our CP patients are very often wine drinkers even between meals, and so duodenal acidity during the day may prove persistently low.

When patients have been diagnosed as having pancreatic insufficiency, many doctors advise them to reduce their alcohol intake and increase the number of meals in order to obtain better digestion. The increase in the number of postprandial periods may induce a more prolonged acidic pH in the duodenum.

A few years after the onset of symptoms, pancreatic insufficiency usually increases [21] and thus the production of bicarbonate in the postprandial period proves increasingly insufficient to neutralize the duodenal acidity. We can postulate more frequent or prolonged s-secretin cell production from the duodenum, and more intense stimulation of the ductal cells.

Effect of Surgery on Anatomy and Physiology

The low duodenal pH hypothesis is probably of particular concern in CP with a duodenum-preserving pancreatic head resection (e.g. Beger's operation, consisting in a partial resection of the head with a Roux-en-Y pancreaticojejunostomy), since, in this anatomic situation, the pancreatic juice transits directly via the jejunal loop, bypassing the duodenum. From this point of view, patients undergoing pancreaticoduodenectomy (e.g. the Whipple procedure) or anastomotic surgery (e.g. side-to-side pancreaticojejunostomy) should probably be less critically affected. In the latter case, the low duodenal pH may be partly neutralized by HCO_3^- secreted via the papilla of Vater.

PPI Treatment

Very often, replacement therapy with pancreatic enzymes is associated with a proton pump inhibitor (PPI) to prevent their degradation and this means that, in many patients with chronic pancreatitis and advanced pancreatic insufficiency, the

duodenum happens to be protected against low pH, and the pancreas against chronic stimulation by secretin.
Administering omeprazole (and certainly other PPIs as well) to CP patients is a good strategy in that it reduces duodenal acidity and the consequent release of secretin [48].

Conclusions

It is reasonable to suppose that, in addition to stopping smoking, reduction of duodenal acid load in patients with pancreatic insufficiency may help decrease the risk of pancreatic cancer if the duodenal acidity hypothesis is confirmed.
In any event, the hypothesis that low duodenal pH may increase the risk of pancreatic cancer in CP warrants further study.

Keywords Carcinoma, Pancreatic Ductal; Epidemiology; Ethanol; Omeprazole; Pancreatic Neoplasms; Risk Factors; Secretin; Smoking
Abbreviations CP: chronic pancreatitis; HP: *Helicobacter pylori*; NNK: 4-(N-methylnitrosamino)-1-(3-pyridyl)-butanone; NNN: N-nitrosonornicotine; PPI proton pump inhibitor
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