Re: Maternal Inheritance Pattern of Hereditary Pancreatitis in Patients With Pancreatic Carcinoma

Since our original report (1), we now have 412 patients in the International Hereditary Pancreatitis Registry. Sixteen patients have developed biopsy-proven pancreatic cancer, with a parent of origin known for 11 patients—all paternal. Adding the two patients in the recent correspondence by Lerch et al. (2) makes 13 patients with a known parent of origin, of which 11 parents are paternal and two parents are maternal. Against an expected male-to-female parental distribution of 50:50, this is still statistically significant (P = .02). However, in our expanded database, we note that before 1960, when most of the pancreatic cancer patients were born, the male-to-female parent of origin ratio is 60:40, rather than 50:50. This slight difference may possibly be related to reduced fertility in females with hereditary pancreatitis married to normal males, compared with normal females married to males with hereditary pancreatitis. Similar fertility differences have been noted in females with much milder disorders (3). The probability of 11 paternal parents of origin against two maternal, if a 60:40 split is assumed, is about 0.06. We agree with Lerch et al. that hereditary pancreatitis patients with either a male or a female inheritance pattern are at risk for pancreatic cancer, but the risk appears to be higher in patients with a paternal inheritance pattern.

ALBERT B. LOWENFELS
PATRICK MAISONNEUVE
FOR THE INTERNATIONAL HEREDITY PANCREATITIS STUDY GROUP

REFERENCES


NOTES

Affiliations of authors: A. B. Lowenfels, Department of Surgery, New York Medical College, Valhalla; P. Maisonneuve, Division of Epidemiology and Biostatistics, European Institute of Oncology, Milan, Italy.

Correspondence to: Albert Lowenfels, M.D., Department of Surgery, New York Medical College, Munger Pavilion, Valhalla, NY 10595.

RESPONSE

We thank Dr. Lowenfels and Dr. Maisonneuve for their comments and the update on patients with pancreatic cancer from families with hereditary pancreatitis. Although the results of their original study could have suggested that patients who have inherited the defective gene from their mother are reasonably “safe” as far as the risk of developing pancreatic cancer is concerned, the most important conclusion from our report was that they are not. Dr. Lowenfels and Dr. Maisonneuve seem to agree with this conclusion. Unfortunately, our knowledge regarding the pathobiology of hereditary pancreatitis and its association with pancreatic cancer remains sketchy for several reasons, as follows: 1) The previously identified mutations of the trypsinogen gene (R117H and N21I) are found in only part—in Japan in the minority (1)—of families with hereditary pancreatitis. This fact suggests that other, as yet unknown mutations that may not even affect the trypsinogen gene could account for the onset of pancreatitis and for the development of pancreatic cancer in a substantial subgroup of affected families. 2) Among patients with sporadic chronic pancreatitis of unknown etiology, the number of patients who carry trypsinogen mutations is much higher than previously expected (2). Conclusive studies will now have to exclude a similar association in patients with seemingly sporadic pancreatic cancer. 3) An additional trypsinogen mutation (A16V), with surprisingly low penetrance, has only recently been identified in patients with hereditary and idiopathic pancreatitis. The location of this mutation is of particular interest because it affects the cleavage site for the trypsinogen signal peptide (3). For various reasons, it was assumed in the past that trypsinogen mutations lead to a gain of trypsin function (4). The location of the A16V mutation, however, suggests that a loss rather than a gain of trypsin function could represent the basis of hereditary pancreatitis, a heretical hypothesis because it implies a protective role of trypsin against the action of other pancreatic proteases.

For now, the only way to answer the question of how the risk of developing pancreatic cancer is determined by the parent of origin with hereditary pancreatitis is to collect more clinical data from affected families and make the data available for epidemiologic analysis. One of the institutions where such data have been collected for many years is the International Hereditary Pancreatitis Registry maintained by Dr. Lowenfels. We now continuously make patient information available to this registry and to the European Registry of Hereditary Pancreatitis and Familial Pancreatic Cancer in Liverpool, U.K., and encourage others to do the same. Only a concerted effort by those who look after patients with hereditary pancreatitis will result in a rapid gain of conclusive information on this rare, debilitating, and clearly premalignant disorder.

MARKUS M. LERCH
JOHN P. NEOPTOLEMOS

REFERENCES


NOTES

Affiliations of authors: M. M. Lerch, Department of Medicine B, Westfälische Wilhelms-Universität, Münster, Germany; J. P. Neoptolemos, European Registry of Hereditary Pancreatitis and Familial Pancreatic Cancer, University of Liverpool, U.K.

Correspondence to: Markus M. Lerch, M.D., Department of Medicine B, Westfälische Wilhelms-Universität, Albert-Schweitzer-Str. 33, D-48129 Münster, Germany (e-mail: markus.lerch@uni-muenster.de).