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PANCREAS NEWS

Familial Pancreatic Cancer: What's New

Raffaele Pezzilli

Department of Digestive Diseases and Internal Medicine,
Sant'Orsola-Malpighi Hospital. Bologna, Italy

About 90% of all pancreatic cancers are ductal adenocarcinomas with an overall 5-year survival rate of less than 5%. The explanation as to why most pancreatic cancers arise from ductal cells has only come to light in the past few years. Most knowledge has been found at the molecular level which shows an increasing number of genetic and epigenetic alterations, in particular on growth factors and related pathways. Furthermore, basic researchers have identified molecular alterations which render cancer cells capable of invading the perineurium and the retroperitoneal space, thus, explaining the high rate of local recurrence and severe pain syndrome [1].

A prompt diagnosis of pancreatic cancer depends on appropriate tests and the hope is that, in the near future, we will be able to identify a larger number of individuals at risk, such as those with a familial history of pancreatic cancer [2, 3]. Three articles have recently been published on this topic [4, 5 ,6] and they deserve to be mentioned.

The first paper that we present is a multicenter study aiming to collect data on the families of patients with pancreatic ductal adenocarcinoma [4]. The data for 570 families were collected, including 9,204 relatives. Probands were found 3- to 5-fold more often in heavy smokers than in the general population, and 9.3% of them reported a positive family history of pancreatic cancer. In first-degree relatives, only mortality from pancreatic cancer was significantly increased (relative risk at age 85 years equal to 2.7). The lifetime risk of dying from pancreas cancer was 4.1% for the relatives of all probands and 7.2% for the relatives of probands who developed disease before 60 years of age. Even if the data suggest that genetic susceptibility to pancreatic cancer may be attributable to moderate- to low-penetrance gene(s), in addition to BRCA2, we think that the main merit of this study is the confirmation that first-degree relatives of patients with pancreatic ductal adeno-carcinoma have an increased risk of developing pancreatic cancer, and specific follow-up programs should be created for this particular case.

The same conclusions are drawn by Gullo *et al*. [5] who studied a specific population of patients, i.e. those subjects with benign pancreatic hyperenzymemia. The authors studied 68 subjects with benign pancreatic hyperenzymemia, and the subjects who had relatives with pancreatic cancer and their immediate family members were included in the study. Six subjects had relatives who had died of pancreatic cancer and they underwent MRI (normal in all six) and endoscopic ultrasonography which was normal in five while, in the remaining subject, parenchymal abnormalities were present in the head of the pancreas. Two of the 10 relatives of these six subjects had pancreatic hyperenzymemia and, in both these subjects, MRI and endoscopic ultrasonography results were normal. Among the six study subjects, there were nine relatives who had died of pancreatic ductal cancer. Four of the six had only one relative,

one had two family members with pancreatic cancer and another had three relatives with pancreatic cancer. The diagnosis of pancreatic cancer was based on histology in seven of the nine subjects, and on clinical and imaging findings in the other two. These findings show that there may be a familial association between benign pancreatic hyperenzymemia and pancreatic cancer.

The crucial question posed by Gullo's study is which strategy should be used for the follow-up program of the relatives of patients with pancreatic cancer. A possible answer comes from the study of Rubenstein *et al*. [6]. The authors gathered information regarding the natural history of these patients to compare four management strategies. They performed a systematic review and created a Markov model for 45-year-old male 1st-degree relatives with findings of chronic pancreatitis on screening EUS. They compared four strategies: doing nothing, prophylactic total pancreatectomy, annual surveillance by EUS and annual surveillance with EUS and fine needle aspiration (EUS/FNA). The outcomes included mortality, quality of life, procedural complications and costs. In the "Do Nothing" strategy, the lifetime risk of cancer was 20%. Doing nothing provided the greatest remaining years of life, the lowest cost and the greatest remaining quality-adjusted life years (QALYs). Prophylactic total pancreatectomy provided the fewest remaining years of life, and the fewest remaining QALYs. Screening with EUS provided nearly identical results to prophylactic total pancreatectomy, and screening with EUS/FNA provided intermediate results between prophylactic total pancreatectomy and doing nothing. Prophylactic total pancreatectomy provided the longest life expectancy if the lifetime risk of pancreatic cancer was at least 46%, and provided the most QALYs if the risk was at least 68%. The authors concluded that 1st-degree relatives of familial pancreatic cancer patients who have EUS findings of chronic pancreatitis have an increased risk for cancer, but their precise risk is unknown. Without the ability of further quantifying that risk, the most effective strategy is to do nothing.

We believe that further prospective large studies are needed to change this nihilistic approach.

Keywords Carcinoma, Pancreatic Ductal; Decision Support Techniques; Endosonography; Family; Genetic susceptibility; Pancreatectomy

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Correspondence
Raffaele Pezzilli
Department of Digestive Diseases and Internal Medicine
Sant'Orsola-Malpighi Hospital
Via Massarenti, 9
40138 Bologna
Italy
Phone: +39-051.636.4148
Fax: +39-051.636.4148
E-mail: raffaele.pezzilli@aosp.bo.it

References

1. Pezzilli R. Pancreatic ductal carcinoma: from the bench to the bedside. JOP. J Pancreas (Online) 2006; 7:508-10. [PMID 16998251]

2. Pezzilli R. Screening tests for pancreatic cancer: searching for the early symptoms or the population at risk. JOP. J Pancreas (Online) 2004; 5:240-2. [PMID 15254357]

3. Pezzilli R, Fantini L. Familial pancreatic cancer: hope can become truth. JOP. J Pancreas (Online) 2007; 8:64-6. [PMID 17228136]

4. Del Chiaro M, Zerbi A, Falconi M, Bertacca L, Polese M, Sartori N, et al. Cancer risk among the relatives of patients with pancreatic ductal adenocarcinoma. Pancreatology 2007; 7:459-69. [PMID 17912010]

5. Gullo L, Migliori M, Fusaroli P, Caletti G. Familial association of benign pancreatic hyperenzymaemia and pancreatic cancer. Gut 2007; 56:1323-4. [PMID 17698873]

6. Rubenstein JH, Scheiman JM, Anderson MA. A Clinical and economic evaluation of endoscopic ultrasound for patients at risk for familial pancreatic adenocarcinoma. Pancreatology 2007; 7:514-25. [PMID 17912015]