

Familial Pancreatic Cancer: Hope Can Become Truth

Raffaele Pezzilli, Lorenzo Fantini

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

The incidence of pancreatic cancer has increased steadily in most of the world and now this type of tumor ranks as the fifth or sixth most frequent cause of death due to cancer in many western countries [1]. In 2000, worldwide figures for pancreatic cancer were projected at 216,400 new cases and 213,500 deaths [2]; the data coming from the United States in 2004, estimated that 31,860 patients would be diagnosed with pancreatic cancer and 31,270 would die of the disease [3]. The 5-year survival rate estimated by the Surveillance Epidemiology and End Results Program is 4% and this figure is the lowest of all types of cancer [4]. Late diagnosis and the subsequently low resection rate is the reason for poor survival of these patients.

Despite technological advances, the diagnosis of pancreatic cancer continues to be made very late and the prognosis remains extremely poor.

We have recently suggested that a prompt diagnosis of pancreatic cancer depends on appropriate tests and our 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, as well as those of families with distinct hereditary cancer syndromes such as Peutz-Jeghers syndrome, hereditary pancreatitis, familial atypical multiple mole melanoma syndrome, hereditary breast and ovarian cancer syndrome and hereditary non-polyposis colorectal cancer [5].

For this reason, the paper of Pogue-Geile *et al.* is welcome [6]. These authors previously reported a family in which pancreatic

adenocarcinoma is inherited as an autosomal dominant with high penetrance [7]. The authors also developed an endoscopic surveillance program which assists in the detection of pancreatic precancerous dysplasia [8, 9] by the identification of pancreatic intraepithelial neoplasia (PanIN) which is a precancerous lesion of both sporadic and familial pancreatic cancers. PanIN lesions graded from 1 to 3 with increasing neoplastic progression (hyperplasia named PanIN 1, low-grade dysplasia named PanIN 2, and carcinoma in situ named PanIN 3) are prominent throughout the pancreatic tissue of affected family members prior to cancer formation [10]. Through this pancreatic cancer surveillance program the authors were able to identify the members of the family who were at risk of cancer. This program was able to identify the patients at a curable stage of their disease and to genotype them. By means of genotyping of family members, a pancreatic adenocarcinoma susceptibility locus was mapped at chromosomal location 4q32-34 [11]. The work of identifying the mutant gene has been difficult considering the size (16 megabase pairs) and the number of genes (approximately 250) located in this region [12]. In the last paper [6] the authors reported the identification of this familial pancreatic cancer gene and the assessment of the gene involvement in familial and sporadic pancreatic cancer.

A customized microarray of the candidate chromosomal region affecting pancreatic cancer susceptibility revealed that the greatest

expression change was found to be in palladin, a gene that encodes a component of the cytoskeleton that controls cell shape and motility. A mutation causing a proline (hydrophobic) to serine (hydrophilic) amino acid change (P239S) in a highly conserved region was found in all affected family members and was absent in the non-affected members. The mutational change is not a known single nucleotide polymorphism. Palladin RNA, measured by quantitative RT-PCR, was overexpressed in the tissues from precancerous dysplasia and pancreatic adenocarcinoma in both the familial and the sporadic disease. Transfection of wild-type and P239S mutant palladin gene constructs into HeLa cells revealed a clear phenotypic effect: cells expressing P239S palladin exhibited cytoskeletal changes, abnormal actin bundle assembly, and an increased ability to migrate.

These observations suggest the presence of an abnormal palladin gene in familial pancreatic cancer; the study also suggest a new hypothesis regarding the mechanism of pancreatic cancer development: the overexpression of palladin protein in sporadic pancreatic cancer causes cytoskeletal changes in pancreatic cancer and may contribute to the invasive and migratory abilities of the neoplasm.

The identification of germline mutations in genes predisposing to pancreatic cancer, together with the analysis of exogenous risk factors demonstrate that we are now able to have a more precise risk assessment for the development of this neoplasm. This may allow the application of screening methods for the identification of early pancreatic cancer providing the possibility of a timely curative pancreatectomy.

Keywords Diagnostic Tests, Routine; Genetic Screening; Pancreatic Neoplasms; Pathology, Clinical

Correspondence

Raffaele Pezzilli
Dipartimento di Malattie Apparato Digerente

e Medicina Interna
Ospedale Sant'Orsola-Malpighi
Via G. Massarenti, 9
40138 Bologna
Italy
Phone: +39-051.636.4148
Fax: +39-051.549.653
E-mail: pezzilli@aosp.bo.it

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