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PANCREAS NEWS

Pancreatic Cancer and Cancer Screening Programs: From Nihilism to Hope

Raffaele Pezzilli, Roberto Corinaldesi, Antonio Maria Morselli-Labate

Pancreas Unit, Department of Digestive Diseases and Internal Medicine,
Sant'Orsola-Malpighi Hospital, Alma Mater Studiorum, University of Bologna. Bologna, Italy

The most common incipit of papers published regarding exocrine pancreatic neoplasms is that pancreatic cancer is one of the most lethal cancers, with a rate of incidence equal to that of mortality. Pancreatic cancer is a heterogeneous group of neoplasms in which pancreatic ductal adenocarcinoma is the most common. For the most part, the problems related to the early diagnosis of pancreatic adenocarcinoma are three: 1) to better understand the biology of this tumor; 2) to better investigate the precursors of this tumor; and 3) to plan projects for pancreatic cancer screening in high-risk individuals.

Recently, Yachida *et al*. [1] performed rapid autopsies on seven individuals with Stage IV pancreatic cancer and they found that the clonal populations which give rise to distant metastases are represented within the primary carcinoma, but these clones are genetically evolved from the original parental, non-metastatic clone. Thus, the genetic heterogeneity of the metastases reflects that of the primary carcinoma. Most important, when the authors performed a quantitative analysis of the timing of the genetic evolution of pancreatic cancer, they found that there was at least a decade between the occurrence of the initial mutation and the birth of the parental, non-metastatic founder cell. At least five more years are required for the acquisition of metastatic ability and patients die an average two years thereafter. As underscored by the authors, these data have an important implication in planning population screening for the purpose of preventing pancreatic cancer deaths: in fact, quantitative analysis indicated a large window, of at least a decade, in which the disease could be diagnosed while it is still in the curative stage. This model also predicts an average of 6.8 years between the birth of the cell giving rise to the parental clone and the seeding of the index metastasis.

Thus, we have to change our perspective regarding the early detection of pancreatic cancer because the diagnostic challenge is to detect these tumors early, possibly at a preneoplastic stage. Is this possible? The answer comes from a study of Haugk [2]. It has now been established that pancreatic adenocarcinoma develops through stepwise progression from precursor lesions. At present we are aware of three precursor lesions for pancreatic adenocarcinoma. As pointed out by Haugk, two of these precursors are mucinous cystic neoplasms and intraductal papillary mucinous neoplasms; they are rare, radiologically detectable and can be cured if treated at the preinvasive stage. The third, and most common precursor lesion, is pancreatic intraepithelial neoplasia (PanIN). Unfortunately, PanINs are microscopic lesions without clinical signs, and these lesions display a spectrum of cyto-architectural changes, called PanIN-1, PanIN-2 and PanIN-3, which are mirrored in an increasing accumulation of molecular genetic changes. PanIN-3 shares many of its alterations with pancreatic adenocarcinoma. The limits of early diagnosis of PanIN-3s are the limited access to the pancreas and the fact that molecular tests are not presently available. Similarly to what happens now for colon cancer, a physician can investigate only those people having positive DNA tests instead of screening the entire population [3].

What should the preventive strategy be while we are waiting for these molecular tests? In a previous issue of JOP. Journal of the Pancreas [4] commenting on some papers reporting the usefulness of clinical history for the early diagnosis of pancreatic cancer, we suggested that a prompt diagnosis of pancreatic adenocarcinoma comes from the identification of a larger risk population than that known at present, such as members of families with a history of pancreatic cancer

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Correspondence Raffaele Pezzilli
Unità Pancreas, 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: +39-051.636.4148
E-mail: raffaele.pezzilli@aosp.bo.it

URL http://www.serena.unina.it/index.php/jop/article/view/3422/3723

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. A recent paper of Verna *et al*. [5] confirms our belief. These authors studied 51 patients, coming from 43 families, at high risk for pancreatic cancer. Of these patients, endoscopic ultrasonography (EUS), magnetic resonance imaging (MRI) and endoscopic retrograde cholangiopancreatography (ERCP) were carried out in 31, 33, and 7 patients, respectively. They found six pancreatic neoplasms (11.8%): two pancreatic adenocarcinomas, three IPMNs, and one cyst with elevated fluid CEA. Of these six patients, five were operated on. A total of 24 (47.1%) had genetic testing and 7 (29.2%) were positive for BRCA1/2 mutations. In addition, four extrapancreatic neoplasms were also found (7.8%): two ovarian cancers on prophylactic total abdominal hysterectomy and bilateral salpingo-oophorectomy, one carcinoid and one papillary thyroid carcinoma. Overall, 6 (11.8%) of the 51 patients had neoplastic lesions in the pancreas and 10 (19.6%) had neoplasms in various locations and, most important, all patients have remained alive as a result of the screening program.

In conclusion, pancreatic cancer screening for high-risk patients with a comprehensive strategy of imaging and genetics may be effective in identifying those patients with neoplasms which can be resected.

Conflict of interest None

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