Pancreatic ductal adenocarcinoma screening: New perspectives

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Abstract

Pancreatic ductal adenocarcinoma accounts for more than 90% of all pancreatic cancers and its incidence has increased significantly worldwide. Patients with pancreatic ductal adenocarcinoma have a poor outcome and more than 95% of the people affected die from the disease within 12 mo after diagnosis. Surgery is the first-line treatment in the case of resectable neoplasm, but only 20% of patients are candidates for this approach. One of the reasons there are few candidates for surgery is that, during the early phases of the disease, the symptoms are poor or non-specific. Early diagnosis is of crucial importance to improve patient outcome; therefore, we are looking for a good screening test. The screening test must identify the disease in an early stage in order to be effective; having said this, a need exists to introduce the concept of "early" ductal adenocarcinoma. It has been reported that at least five additional years after the occurrence of the initiating mutation are required for the acquisition of metastatic ability of pancreatic adenocarcinoma and patients die an average of two years thereafter. We have reviewed the most recent literature in order to evaluate the present and future perspectives of screening programs of this deadly disease.

INTRODUCTION

Pancreatic ductal adenocarcinoma accounts for more than 90% of all pancreatic cancers. Over the last thirty years, its incidence in Europe and the United States has increased significantly; it ranks tenth among the most common solid tumours and it is the fourth leading cause of cancer death^[1]. In addition, patients with pancreatic ductal adenocarcinoma have a poor outcome; more than 95% of the people affected die from the disease within 12 mo after diagnosis^[2]. There is also a lack of really effective therapy; surgery is the first-line treatment in case of resectable neoplasm, but only 20% of patients are candidates for this approach^[3].

One of the reasons there are few candidates for surgery is that, during the early phases of the disease when there is greater possibility of radical surgical treatment, the symptoms are poor or non-specific. On the other hand, when the symptoms become clear, the prognosis is poor. Specifically, the majority of patients have some

disturbances only shortly before diagnosis or problems 6 mo or less before diagnosis (pain or jaundice), and only a small portion have problems more than 6 mo before diagnosis. Among the latter, some patients have anorexia and/or early satiety and/or asthenia (7-20 mo before pain or jaundice), others have a distaste for coffee and/or smoking and/or wine (7-20 mo before) and still others have diabetes (7-24 mo before) or acute pancreatitis (8-26 mo before)^[4]. Thus, the United States Preventive Services Task Force has a grade D recommendation against routine screening for pancreatic cancer for asymptomatic adults using abdominal palpation, ultrasonography or serologic markers for various clinical motives: (1) there is a poor prognosis for those diagnosed with pancreatic cancer; (2) it is thought that the evidence for diet-based prevention of pancreatic cancer is limited and conflicting; and (3) only some experts recommend lifestyle changes which may help to prevent pancreatic cancer, such as stopping the use of tobacco products, moderating alcohol intake and eating a balanced diet with sufficient fruit and vegetables^[5].

On the other hand, we encourage the search to continue; the do-nothing attitude must be abandoned. Early diagnosis would be of crucial importance in improving the course of the disease; therefore, we are looking for a good screening test. The screening test must identify the disease in an early stage in order to be effective; having said this, a need exists to introduce the concept of “early” ductal adenocarcinoma. Yachida *et al.*^[6] report the data generated by sequencing the genomes of seven pancreatic cancer metastases to evaluate the clonal relationships among primary and metastatic cancers. The authors found that 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. A quantitative analysis of the timing of the genetic evolution of pancreatic cancer indicates that there is at least a decade between the occurrence of the initiating mutation and the birth of the parental, non-metastatic founder cell. Thus, at least five additional years are required for the acquisition of metastatic ability and patients die on an average of two years thereafter. This conclusion indicates that the concept of early diagnosis of ductal adenocarcinoma should be moved back several years as compared to current practice, and this renders the screening increasingly more complicated.

PAST KNOWLEDGE

Traditionally, serum markers have been used for the early diagnosis and screening of ductal pancreatic adenocarcinoma, similar to what happens in other cancers. The most widely used serum markers for pancreatic cancer are the carcinoembryonic antigen and carbohydrate antigen 19-9 (CA 19-9); although their use has been extensively evaluated in clinical practice, several studies have shown that both have a low specificity as well as a low

sensitivity^[7]. We found that no significant differences in serum CA 19-9 levels were observed between patients with jaundice and those without as well as between those who underwent pancreatic resection and those who were medically treated because of advanced disease^[7]. In addition, we found that in the 50 patients with histological/cytological examination, the sensitivity of this marker was 57.4%, the specificity was 0%, the positive predictive value was 90.0% and the negative predictive value was 0%^[7]. Finally, elevated serum CA 19-9 values were present in similar proportions in patients with (61.9%) and without jaundice (64.7%, $P = 1.000$) as well as in 58.1% of resected patients and in 68.3% of those medically treated because of advanced disease ($P = 0.459$)^[7]. These data further support the conclusions of the two American Society of Clinical Oncology recommendations for the use of tumor markers in pancreatic cancer, suggesting that CA 19-9 determination is not recommended for use as a screening test for pancreatic cancer and the use of CA 19-9 testing alone is not recommended for use in determining operability or the results of surgery in pancreatic cancer^[8]. The reason for which biochemical screening fails to detect pancreatic cancer is that the production of CA 19-9 becomes readily detectable only in the advanced stages of pancreatic ductal adenocarcinoma after the onset of clinical symptoms, and it would not provide opportunities for early detection and cure (for example, in detecting precancerous lesions such as pancreatic intraepithelial neoplasia or intraductal pancreatic mucinous neoplasia at the initial stages)^[9]. In conclusion, it is now time to abandon the routine use of CA 19-9 determination when pancreatic cancer is suspected.

PRESENT KNOWLEDGE

Currently, screening strategy is based on the identification of genetic alterations and populations at risk in order to identify algorithms for prevention and treatment^[10].

There are many syndromes associated with pancreatic cancer, such as familial pancreatitis (associated with mutations in the *PRSS1* and *SPINK1* genes)^[11], Peutz-Jeghers syndrome and familial atypical multiple mole melanoma syndrome^[12]. In these cases, the suggested screening techniques are endoscopic ultrasound (EUS) or abdominal magnetic resonance imaging (MRI)^[13]. Another risk factor is the presence of chronic pancreatitis; in fact, approximately 5% of patients with chronic pancreatitis will develop pancreatic cancer over a 20-year period. In these cases, until the development of more sophisticated imaging procedures able to detect the presence of cancer in an altered gland affected by chronic involvement, a screening test is not recommended^[14].

Similarly to other cancers, such as colon cancer, pancreatic adenocarcinoma may be present in the same family^[12]. It should be pointed out that subjects from families with a history of pancreatic cancer have an inherited predisposition of developing the disease, and subjects having familial pancreatic cancer may have at least two first-

Table 1 Major molecular markers in pancreatic ductal adenocarcinoma and their roles in screening

Marker	Implication of mutation	Diagnosis
EGF/EGFR	Constitutive activation of mitogen-activated protein kinase pathway	Screening for the patients more likely to respond to EGFR inhibitors
TGF- α	Promotes metastasis Brings about epithelial mesenchymal transition	
VEGF/VEGFR	Tumor cell invasion and migration promoting tumor progression Lymphangiogenesis and lymphatic metastasis	Good diagnostic tool especially in combination with Cx43
FGF	Cell proliferation, migration, and invasion	Serum FGF-BP1 can be used as a marker for high-risk premalignant lesions
MMPs	Digestion of extracellular components Cell dissociation and subsequent invasion	MMP-2 in pancreatic juice Serum MMP-9 Plasma MMP-7 levels help to distinguish between PC and CP
miRNAs	Invasive capacity Metastasis and maintenance of cancer	Plasma miRNA profiling for blood-based biomarkers

EGF: Endothelial growth factor; EGFR: Endothelial growth factor together with its receptors; TGF- α : Tumor growth factor- α ; VEGF: Vascular endothelial growth factor; VEGFR: Vascular endothelial growth factor and its receptor; FGF: Fibroblast growth factor; MMPs: Metalloproteinases; PC: Pancreatic carcinoma; CP: Chronic pancreatitis.

degree relatives with this disease, probably demonstrating autosomal dominant transmission^[13]. A computer-based risk assessment tool has recently been developed and it has been shown to provide an accurate risk assessment for relatives with familial pancreatic cancer^[16]. In addition, several studies have been carried out in patients with familial pancreatic cancer^[17-23]; screening relatives from families in which pancreatic cancer is familial has a significant diagnostic yield, particularly in relatives > 65 years of age, confirming prior studies showing that magnetic resonance cholangiopancreatography as an initial screening modality is safe and effective^[23].

One of the few currently known pre-neoplastic lesions is that of an intraductal papillary mucinous neoplasm (IPMN). If this lesion is located in the main duct (IPMN types 1 and 3), the treatment is surgical resection; on the other hand, if the lesion is located in the branch duct (IPMN type 2), the treatment depends on the size; if the diameter is less than 1 cm, therapeutic monitoring with MRI or CT scan once a year is sufficient. Monitoring is indicated every 6-12 mo if the diameter is between 1 and 2 cm; lesions between 2 and 3 cm should be monitored every 3-6 mo while, if the lesion is greater than 3 cm, or it is smaller but with the presence of high risk stigmata or symptoms, surgery is indicated^[24]. Nevertheless, the diagnosis of IPMNs is usually incidental and therefore, a screening strategy in the general population is not possible; in fact, clinical symptoms are often vague or absent, and there is rarely an increase of serum amylase and lipase^[25].

FUTURE PERSPECTIVES

The future of screening for pancreatic ductal adenocarcinoma is represented by the OMICs (genomic, proteomic, metabolomic). In particular, with regard to genomic, there are two studies which correlate the genetic alterations of pancreatic cells and the genetic alterations in the genome of the cells of the immune system. Baine *et al.*^[26] have studied the peripheral blood mononuclear cells from pancreatic cancer patients and matched healthy controls,

analyzing them by means of whole genome cDNA microarray. They found that 383 genes were significantly different between pancreatic cancer patients and healthy controls, and 65 had at least a 1.5 fold change in expression. Pathway analysis revealed that many of these genes fell into the pathways responsible for hematopoietic differentiation, cytokine signaling, and natural killer cell and CD8+ T-cell cytotoxic response. Unsupervised hierarchical clustering analysis identified an eight-gene predictor set, consisting of *SSBP2*, *Ube2b-rs1*, *CA5B*, *F5*, *TBC1D8*, *ANXA3*, *ARG1* and *ADAMTS20* capable of distinguishing pancreatic cancer patients from healthy controls with an accuracy of 79% (sensitivity 83% and specificity 75%). In the future, these data may help in diagnosing pancreatic cancer earlier. In the same way, De Monte *et al.*^[27] have identified the complex interaction involving cells, such as stromal and immune cells, and tumor cells in the tumor microenvironment. The result of this is an alteration of the T-cells which, instead of producing cytokines effective in fighting cancer, produce cytokines capable of promoting further progression of the disease; this lymphocyte derangement has been called “deviant lymphocytes” by the authors. The authors also identified the molecules involved in this mechanism which will allow the development of therapies to curb this activity. Antibodies are already available for some of these molecules and they are capable of blocking their activity. Most important, in a series of patients undergoing surgery, the authors also showed the existence of a correlation between the quantity of “deviant cells” present in the tumor and patient survival showing the possibility of stratifying pancreatic cancer patients into two categories having a better or a worse prognosis.

The other aspect of the future of screening for pancreatic ductal adenocarcinoma is the proteomic; in particular, it is interesting to evaluate studies with large populations whether (or not) cancer cells secrete proteins whose levels rise early in serum or in pancreatic juice.

Presently, as shown in the Table 1, the major molecular markers in pancreatic ductal adenocarcinoma evaluated in clinical practice are the following: endothelial growth

factor together with its receptors (EGFR) involved in the activation of the mitogen-activated protein kinase pathway and used as a screening test for patients who are that more likely to respond to EGFR inhibitors: (1) tumor growth factor- α , which promotes metastasis and brings about epithelial mesenchymal transition; (2) vascular endothelial growth factor and its receptor, which indicate tumor cell invasion and migration promoting tumor progression, lymphangiogenesis and lymphatic metastasis and seem to be a good diagnostic tool, especially in combination with Cx43; (3) fibroblast growth factor, which is involved in cell proliferation, migration and invasion, and can be used as a marker for high-risk premalignant lesions; (4) metalloproteinases, which are markers of the digestion of extracellular components, cell dissociation and subsequent invasion found in the pancreatic juice, in serum or in plasma and help to distinguish between pancreatic adenocarcinoma and chronic pancreatitis; and (5) miRNAs which represent a marker of invasive capacity, metastasis and maintenance of cancer, and may be an aid for developing blood-based biomarkers^[28]. However, the clinical studies are largely disappointing regarding the routine use of these markers^[29-31].

Finally, it should be remembered that the last OMIC is metabolomic. Neoplastic cells have an accelerated metabolism; this results in an increase of the concentration of some biochemical components in serum, and these changes may be used as markers of pancreatic cancer. Bathe *et al.*^[32] have studied the variations of these biochemical components in patients with pancreatic cancer. In the pancreatic cancer group, as compared to benign cases, the serum concentrations of glutamate and glucose were the most elevated on multivariate analysis. In benign cases, creatine and glutamine were most abundant. To examine the usefulness of this test, a comparison was made to age- and gender-matched controls with benign lesions which mimicked cancer, also checking for the presence of jaundice and diabetes; the results were encouraging because the metabolic profile in patients with pancreatic cancer was distinguishable from patients with benign pancreatic lesions.

In conclusion, the primary prevention of pancreatic cancer is based on the assessment and elimination of major risk factors: smoking, high fat diet, diet rich in meat and low in vegetables and folate, occupational exposure, and obesity^[33,34]. Presently, secondary prevention is limited to patients at risk for familial cancer and a screening plan should be established based on the implementation of an annual MRI or EUS.

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