Pancreatic ductal adenocarcinoma epidemiology and risk assessment: Could we prevent? Possibility for an early diagnosis

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INTRODUCTION

It is estimated that pancreatic ductal adenocarcinoma (PDAC) will become the second leading cause of cancer-related deaths by 2030.1 Currently, only 15%–20% of patients have operable disease at the time of diagnosis. Operability and survival are better in patients with smaller lesions, however, preoperative diagnosis of T1 carcinoma (<20 mm) is rare (<5%), in an analysis of 13,131 PDAC cases, only 3.11% were staged as stage T1a.2 There is therefore great interest in prevention by identifying and minimizing environmental risk factors and in earlier diagnosis which holds the promise of improved outcomes.

EPIDEMIOLOGY

PDAC presents in general at a median age of 70 years. Pancreatic cancer is recognised as having a complex multistep etiology with the interaction between genetic susceptibility and environmental toxins. Both acquired and germline genetic variants are implicated in the failure to repair DNA. Exposure to toxic factors that cause DNA damage (e.g., smoking) and inflammation accelerate this process. The most consistently mutated genes are KRAS, CDKN2A, TP53, and SMAD4/DPC4.3

SPORADIC PANCREATIC DUCTAL ADENOCARCINOMA

The majority of PDAC cases are sporadic with no known genetic predisposition. Tobacco smoking, alcohol, and obesity are known modifiable risk factors. A recent study estimated that approximately 36% of pancreatic cancers in men and 39% in women are linked to lifestyle factors, including tobacco smoking and being overweight which increases the risk by 20%.4 New onset of diabetes (NoD) in subjects >50 years has also been documented as a high-risk factor in sporadic PDAC.5 Compared with the age-matched general population, subjects older than 50 years with NoD have a 6–8 fold higher probability of being diagnosed with PDAC within 3 years of meeting criteria for diabetes.5 This group is estimated to be approximately 1 million people/year in the USA and accounts for approximately 25% of those diagnosed with PDAC.5 In addition, chronic pancreatitis (CP) has long been recognised as a risk for PDAC. A recent Danish epidemiological

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study showed a hazard ratio of 6.9 to develop PDAC in patients with CP compared to controls.[6] Finally, recent genome-wide association studies have identified blood type A and B as associated with increased risk, but a dozen of other loci was also identified. However, the risk of any one of these alleles is relatively small, with odds ratios ranging from 0.88 (slightly protective) to 1.26 (slight risk) and hence none of these sites have yet provided the critical insights into pancreatic cancer risks.[7]

**HEREDITARY PANCREATIC DUCTAL ADENOCARCINOMA**

It is estimated that up to 10% of PDAC has an inherited basis. Familial pancreatic cancer is defined as kindreds with at least two first-degree relatives with pancreatic cancer with an as yet unidentified genetic abnormality.[8,9] In contrast, hereditary pancreatic cancer implies patients with inherited cancer syndromes with a known germline mutation associated with an increased risk of pancreatic cancer. These gene mutations include syndromes such as Lynch syndrome (MLH1, MLH2, MLH6, PMS2), familial breast and ovarian cancer (BRCA1 and BRCA2), familial adenomatous polyposis (FAP), familial atypical multiple mole melanoma (CDKN2A), Peutz–Jeghers (STK11/LKB1) but also hereditary pancreatitis (HPs) (PRSS1, SPINK1, ATM). In HPs, patients have an autosomal dominant disorder with estimated 80% phenotypic penetrance which typically results in recurrent pancreatitis with subsequent CP.[10] Overall, mutations in the cationic trypsinogen gene (R122H, N291), which cause the disease in 60%–70% of kindreds, are suggested to enhance trypsin activity within vesicular compartments of the pancreatic acinar cells.[10] However, a definite cause-and-effect relationship is yet to be established. More importantly, this group has an age-accumulated risk, which starts to rise between 40 and 50 years of age with an ethnic deviation (Ashkenazi Jews and African American > Caucasians). At the age of 70 years, the accumulated risk is 40%–70%.

**PREVENTION**

There are known environmental/lifestyle factors that could be avoided. High-risk patients, in particular, should be recommended to avoid smoking and alcohol given its risk to increase PDAC. Other life style factors such as obesity (and subsequent diabetes), nickel exposure, lack of physical activity, and calorie intake are also known factors that increase the incidence of PDAC.[10] Public health measures to reduce smoking and achieve a healthy body mass index would contribute to a reduction in the incidence of PDAC.

**BIOMARKERS**

Carbohydrate antigen 19-9 (CA19-9) is the most widely known and used biomarker. However, diagnostic performance in isolation is modest.

Recently, as a result of advancements in genomics, large numbers of genetic alterations have been identified. Therefore, several gene mutations of PDAC, including genetic, epigenetic, noncoding RNA, metabolomics, and microbiome signatures have been identified. A recent metabolomic study identified a metabolic signature of 9 metabolites plus CA19-9 with an accuracy over 90% and a negative predictive value of 99% in differentiating CP from PDAC.[11] In an exploratory study Schultz et al.,[12] reported a micro-RNA panel with sensitivity and specificity of 85% and 99% respectively in differentiating PDAC from CP. Circulating tumor cells, cell-free circulating tumor DNA and exomes can be detected in body fluids and could potentially be used as an early diagnostic tool for PDAC. Prospective studies are required to delineate the role of these biomarkers in early diagnosis.

**SCREENING**

The need for early detection is evident but remains challenging. Population level screening is not feasible at this time due to several factors including the overall low incidence of PDAC (lifetime risk of 1.3% in the general population), the lack of simple, safe, inexpensive, sensitive, and noninvasive tests and unlike other gastrointestinal malignancies such as colorectal cancer the lack of a well-defined readily dealt with premalignant lesion. To date, screening has predominantly been performed in study settings on high-risk individuals (HRIs) with genetic predisposition. Criteria were recently formulated by the international cancer of the pancreas-screening consortium which overall includes patients with first degree affected family members with or without gene mutations.[13]

Yearly screening is recommended from 50 years of age apart from in HPs where screening is recommended.
from the age of 40. Screening is not currently recommended for CP.\textsuperscript{[14]}

Genetic high-risk groups, however, account for a minority of PDAC. There is great interest in developing screening methodologies of use in sporadic PDAC. Patients with NoD are of interest for screening as approximately 50% of patients with PDAC develop diabetes before the diagnosis of their PDAC. Identification of the HRIs in this cohort would provide an enriched pool for definitive testing. A recent study developed a risk model for NoD. In this model using a 1% predicted risk of PDAC as the threshold for definitive testing, would result in 6.19% of the entire NoD population undergoing the definitive test but would identify almost 50% of PDAC in the cohort with a number needed to screen of 38.\textsuperscript{[15]}

Combining this risk model with novel biomarkers could potentially further reduce the numbers undergoing definitive testing and increase the diagnostic yield.

**TYPE OF IMAGING FOR SCREENING**

For screening, several studies were performed comparing different imaging modalities, endoscopic ultrasound (EUS), and magnetic resonance imaging (MRI) were found to be the best modalities.\textsuperscript{[16]} EUS was especially more accurate in finding solid lesions which is relevant in PDAC as smaller lesions, especially <1 cm, have the best survival up to 78%. As EUS and MRI are complementary, many units alternate screening/investigations using EUS and MRI.\textsuperscript{[17]} In addition, EUS enables biopsy acquisition (fine needle aspiration/biopsy) in cases where lesions are found. Ancillary EUS techniques such as contrast and elastography may be useful in this setting as well these techniques are discussed in more detail elsewhere in this issue.

**POTENTIAL OF SCREENING**

The goal of screening using imaging such as EUS is to find small lesions as smaller lesions are associated with better survival.\textsuperscript{[18]} It is suggested that early detection of PDAC in high-risk patients is likely to increase long-term survival by as much as 30%–40%.\textsuperscript{[19]} However, studies have yet to show survival improvement in PDAC screening with imaging. Therefore, the development of specific biomarkers long before the development of PDAC and the establishment of consortia such as the “Pancreatic Cancer Detection Consortium,” are expected to be the way forward for adequate screening.

A more holistic approach in the form of screening programs is needed to unravel PDAC, as it is a complex condition, involving multifaceted genetics as well as environmental (and hence potentially modifiable) risk factors. Such programs should not only appreciate this complexity of the disease but also need to assess the effect of targeted preventive treatment, usage of (better) biomarkers and imaging for monitoring the disease and the aim to create better predictive models of the natural history of PDAC.

**CONCLUSION**

Due to its presentation at late stage with locally advanced or metastatic disease, earlier identification through screening is an attractive proposition for PDAC. Although concerns remain as to whether earlier detection would confer any survival benefit, evidence is accruing in favour of the utility of screening in HRIs. More work needs to be done to enable screening in large moderate risk groups such as NoD through the use of risk modeling and biomarkers. Such enriched groups could then be the subject of definitive testing such as with EUS. The ultimate goal of such development is to devise a screening methodology applicable on a population level.

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