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REVIEW ARTICLE

An update on familial pancreatic cancer and the management of asymptomatic relatives

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Abstract
Families of patients with pancreatic adenocarcinoma (PC) often ask about their own risk of developing this disease. There is now a sufficient body of evidence to inform relatives of their relative risk of developing PC. The purpose of this review is to provide practical advice for the clinician when confronted with questions about the risk of PC in relatives, and the role of genetic testing and screening in high-risk individuals.

Introduction

The importance of this topic is underscored by the dismal prognosis of pancreatic adenocarcinoma (PC), with an overall 5-year survival of $<5\%$ [1,2]. The best chance of reducing the high mortality of PC is the identification of individuals at risk and the development of screening tests for early diagnosis and treatment [3]. The proof that early detection prolongs life is still wanting.

The majority of PC cases are sporadic, with no known inherited predisposition. It has been commonly stated that familial PC (FPC) is responsible for 10% of cases of PC [4]. More recent prospective studies from Sweden and Germany, using strict criteria of confirmation by histology and medical records, suggest that the familial proportion of PC is only 1.9–2.7% [5,6]. Nevertheless, family history of PC remains an important risk factor for developing PC.

Familial pancreatic cancer is one of several clinical settings in which an inherited predisposition to PC can be found. These include hereditary pancreatitis, cystic fibrosis and defined familial cancer syndromes [7] (Table I), for which the gene mutations and lifetime risk of cancers have been estimated [8]. Aside from these syndromes, which account for the minority of FPC cases, the major gene(s) responsible for the inheritance patterns of PC remains to be identified. The inheritance pattern is probably autosomal dominant with variable penetrance [7].

Definition of familial pancreatic cancer

There is no agreed definition of FPC, although the one most widely accepted is kindreds with two or more family members who have been diagnosed with pancreatic cancer and who are first degree relatives [8] and who are not part of a familial cancer syndrome. The familial aggregation of PC is not just due to hereditary predisposition, but is also influenced by variable gene penetrance (not all gene carriers will develop PC), environmental factors, family size and chance.

Presentation of familial pancreatic cancer

Although an early age of onset of PC would be expected in these families, it has not been proven [9,10]. The manner of presentation is similar to those with sporadic PC. Even in the context of a national registry where there were 25 incipient cases of PC, 22 presented with metastatic disease at the time of presentation [11]. This is remarkable because the individuals were aware of the signs and symptoms of PC through their experiences with family members who died of pancreatic cancer. Thus FPC, like sporadic cancer, is usually diagnosed with symptomatic and advanced disease.

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Table I. Clinical syndromes and diseases with defined gene alterations, the chromosome locus and cumulative lifetime risk of developing pancreatic adencarcinoma.

Syndrome/disease	Gene(s)	Locus	Lifetime risk
Hereditary breast/ovarian cancer	BRCA2	13q	5%
FAMM melanoma syndrome	CDKN2A	9p	19%
Cystic fibrosis	CFTR	7q	25%
Peutz-Jeghers syndrome	STK11	19p	35%
Hereditary pancreatitis	PRSS1, SPINK 1	7q, 5q	40%
Familial adenomatous polyposis	APC	5q	?
Hereditary non-polyposis colon cancer	DNA MMR	2p, 3p	?

FAMM, familial atypical multiple mole; MMR, mismatch repair.

Risk of pancreatic cancer in first degree relatives

First-degree relatives of patients with FPC form a high-risk group of individuals. Two recent publications have helped to quantify the relative risk of developing PC in first degree relatives.

The first major prospective study of incipient PC occurring in FPC kindreds comes from the John Hopkins Medical Institutions, Baltimore, using the National Familial Pancreas Tumor Registry [9]. They estimated risk by comparing observed new cases of PC during the observation period with expected numbers based on the United States population-based Surveillance, Epidemiology and End Results (SEER) program data. They found that the risk of PC among 191 sporadic kindreds was not significantly greater than expected, with an incidence rate of 24.5 cases per 100 000 per year. Overall there was an 18-fold risk of PC among first degree relatives in FPC kindreds, which equates with an incidence of 76 cases per 100 000 per year. In the subset of FPC kindreds with 3 or more affected first degree relatives there was a 57-fold increased risk of PC with an incidence of 310 cases per 100 000 per year.

The second publication is an extension of this study, and involved quadrupling the follow-up [11]. There were 5179 individuals from 838 kindreds (370 FPC kindreds) followed for 14 128 personal years. The standardized incidence rates (as above) of PC were 4.5 (confidence interval (CI) 0.54–16.3) for one first degree relative with PC, 6.4 (CI, 1.8–16.4) for two first degree relatives and 32 (CI, 10.4-74.7) for three or more first degree relatives. This translates to an estimated incidence of pancreatic cancer of 41, 58 and 288 per 100 000, respectively, compared with the reference of 9 per 100 000 in the general US population.

Cigarette smoking and the risk of PC

A number of environmental factors are thought to further increase the risk of PC in individuals from FPC kindred. Cigarette smoking is an independent, significant risk factor; it is the most important identified risk factor and is more so in men and younger FPC members [10]. Other risk factors are reviewed elsewhere [8]. An interaction between family history and smoking was first reported in 2001 [9,12]. More recent work has determined that smoking increases the risk of PC in FPC kindred fourfold, and that it hastens the onset of the disease by 10 years [10]. This is important because it influences the timing of screening. Smoking cessation reverses this risk, but takes at least a decade to do so.

Identification of high-risk individuals

The key step in estimating the risk of PC in an individual is the analysis of the family tree over at least three generations. If the individual (or proband) appears to be at increased risk, then it is appropriate to involve a clinical genetics service. A formal pedigree analysis will be undertaken, allowing a more accurate estimation of risk. In addition the individual should have access to genetic counselling that should include a discussion about the role of genetic testing, registries and screening.

Genetics of FPC and role of gene testing

Familial pancreatic cancer may be a genetically heterogeneous disorder caused by mutations in different oncogenes and/or modifier genes, but recent segregation studies suggest that FPC may be caused by a single major gene [13]. Although an FPC gene has not been identified, a PC susceptibility locus has been mapped to chromosome 4q32-34 in a large kindred with an autosomal dominant inheritance pattern [14]. This is a unique locus, not associated with the recognized familial cancer syndromes. Advances like this offer hope that gene testing will have a clinical role in the future.

There are a number of benefits of gene testing including defining personal cancer aetiology, determining the risk to siblings and offspring, and aiding decision making around screening, surveillance and treatment. However, the real value of gene testing is only when treatment is based on genetic information. There are also potentially important clinical, psychological and social consequences to gene testing that should only be considered after genetic counselling. While gene testing is possible it is not always advisable

and there remain a number of key questions about how well gene testing actually measures what it purports to measure (analytical validity) and the clinical validity (how well it predicts PC) and utility (likelihood that a positive result lead to improved outcome) of individual tests.

There are a number of known oncogenes and tumour suppressor genes that are either activated or inactivated in the progression from precursor lesions to PC [15]. The current understanding of the genetics of pancreatic cancer has been reviewed recently [2,16]. The role of gene testing in individuals thought to have one of the recognized familial cancer syndromes (Table I) is well established. The situation is much less clear for individuals from FPC kindreds. The current position is that gene testing outside of controlled studies should be avoided because we do not know the relevant germline mutations in FPC [3]. Consideration should be given to the storage of serum for subsequent gene testing when more is known about the genetics of FPC.

Registration

The registration of individuals at high risk is important. The collection of FPC kindreds offers an important opportunity to evaluate pathogenesis, natural history, biomarkers, underlying gene alterations, new diagnosis, treatment and chemoprevention strategies. In addition, knowledge gained from the study of FPC might be useful in improving the diagnosis, management and prognosis of sporadic PC. There are a number of established registries around the world, and advice can be sought for the registry most appropriate for the individual concerned.

Screening and surveillance

Although there are no established standards for defining a high-risk population for screening it would be reasonable to consider it when the family history reveals two or more first degree relatives with PC, especially if the individual is a smoker and/or has chronic pancreatitis.

Similarly there are no established standards for what constitutes an acceptable screening protocol [2]. The possibilities include the use of tumour markers, but current markers (e.g. Ca 19-9 and CEA) do not have adequate sensitivity for screening. Imaging technologies, including computed tomography (CT), magnetic resonance imaging (MRI) and ultrasound (US) scanning do not have adequate resolution to detect PC precursor lesions. Endoscopic retrograde pancreatography (ERP) is probably too invasive as a primary screening tool. The most promising approach is endoscopic ultrasonography (EUS), but it is highly operator-dependent and not widely available outside major centres. EUS can detect quite subtle changes, abnormal changes associated with pancreatic intraepithelial neoplasia, including parenchymal heterogeneity, echogenic foci and hypoechoic nodules.

There are a number of requirements for screening which EUS appears to fulfill. It is able to detect PC earlier than diagnosis by symptoms, and the risks of EUS are known and probably acceptable. Cost benefit information and proof that EUS screening improves outcome in high-risk individuals are not available.

The first screening study combined both EUS and ERCP in testing 35 members of 13 FPC families at the University of Washington Medical Centre, Seattle [17]. There were 12 (34%) individuals with abnormalities, all of whom had a pancreatectomy. An update on this series shows that a total of 15 patients have had a pancreatectomy (12 total, 3 partial) [8]. Histology revealed no invasive cancer, but they were all found to have dysplasia PanIN II ($n=5$) and PanIN III ($n=10$). This group went on to perform a decision analysis on EUS screening [18]. It was concluded that EUS-based screening of FPC kindreds is cost-effective, although the benefit appears to be limited to populations with a pre-test probability of pancreatic dysplasia of 16% or greater and in individuals under 70 years of age. The degree of dysplasia was not specified.

The second important screening study used EUS alone as the primary screening tool in 38 high-risk asymptomatic individuals at the Johns Hopkins Medical Institution, Baltimore and the Mayo Clinic, Rochester [19]. Abnormalities found on EUS were then screened with EUS-guided fine-needle aspiration for cytology, ERCP and CT scanning. There were six pancreatic masses identified (one invasive ductal adenocarcinoma, one benign intraductal papillary mucinous neoplasm (IPMN), two serous cystadenomas and two non-neoplastic masses) and seven other incidental symptomatic gastrointestinal findings. Of the six masses, only two were clinically significant pancreatic neoplasia, giving a clinically significant yield of 5% (2/38) or 1:20.

These studies demonstrate that screening with EUS is feasible and can detect significant asymptomatic pancreatic neoplasms; however, a number of questions remain to be answered. At what age and comorbidity should screening not be performed? Does PanIN II warrant a pancreatectomy? What are the significance and natural history of EUS-detected chronic pancreatitis-like abnormalities?

The following are acceptable guidelines for screening high-risk individuals [20]:

- Primary screening should be undertaken using EUS after genetic counselling.
- Screening should be done in an expert centre as success is operator dependent.
- Screening should not be done unless pancreatectomy would be considered for dysplasia/early cancer.

- Screening is less useful if there is concurrent chronic pancreatitis or significant alcohol history.
- Screening should be initiated at 50 or 10 years before the earliest age of onset of PC in a family member.
- Annual surveillance is reasonable.

Less invasive and more sensitive approaches to screening are required. The potential exists in the future for the use of genomic or proteomic biomarker analyses of pancreatic juice, serum, urine or stool samples.

Treatment

When an abnormality is found on screening there is a choice between ongoing surveillance, until a mass develops, or obtaining a tissue diagnosis. The Washington group obtain the latter by a laparoscopic distal pancreatectomy [21]. The role of prophylactic pancreatectomy cannot be recommended in asymptomatic high-risk individuals without evidence of dysplastic pancreatic lesions, given the significant morbidity of the procedure and the unknown penetrance in the different settings of inherited PC [3]. The management of patients with a PanIN II lesion is uncertain because the natural history is unknown. Patients with a PanIN III lesion and no mass can be offered continuing surveillance or a total pancreatectomy, because of the multifocal and widespread nature of precursor lesions [8]. Patients must be informed of the risks and consequences of total pancreatectomy. Preoperative education by a diabetologist is advisable.

Prevention

The most important preventative measure is to stop smoking. Assistance for this should be offered. Chemoprevention is a promising concept in this field, but not more than that. When an effective agent is available, gene testing will assume a critical role in the management of high-risk individuals.

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