# Review

# Pancreatic cancer – More familial than you thought

M. Tascilar [a], A.C. Tersmette [a], G.J.A. Offerhaus [a]
and R.H. Hruban [b,*]

[a] *Department of Pathology, the Academic Medical Center, Amsterdam, The Netherlands*
[b] *The Departments of Pathology and Oncology, The Johns Hopkins Medical Institutions, Baltimore, MD, USA*

## 1. Introduction

Although pancreatic cancer accounts for only 2% of new cancer cases, it is the fifth leading cause of cancer-related death in Western countries. The high mortality rate is mainly caused by the fact that most cases are detected at a stage when curable resection is not an option anymore and prognosis is poor [45,55].

The etiology of pancreatic cancer is poorly understood. Several putative risk factors have been described, such as cigarette smoking, high-fat diet, chronic pancreatitis, diabetes mellitus and remote history of partial gastrectomy [3,20,23,28,36,38,52,59]. Of these cigarette smoking has the strongest positive association with pancreatic cancer.

Recently, it has been suggested that a family history of pancreatic cancer is a risk factor for pancreatic cancer, and Henry Lynch has estimated that as many as 10% of pancreatic cancers are familial [32]. There have been a number of isolated case reports of the aggregation of pancreatic cancer in families suggesting a hereditary susceptibility for pancreatic cancer, however chance aggregations or shared environmental exposure could also cause this clustering [8,35,44].

In order to overcome the problems caused by the small numbers inherent to case reports, several groups have studied extended families with pancreatic cancer clustering and these studies have suggested an autosomal dominant pattern of inheritance to the pancreatic cancers in some of these families [1,7,18,32,34]. The pathology, sex-ratio, age of onset and prognosis of these patients were comparable to patients with sporadic pancreatic cancer [34].

In addition, several registries have been established to learn more about the role of inheritance in the etiology of pancreatic cancer. These include the National Familial Pancreatic Tumor Registry (NFPTR), established at The Johns Hopkins University, Baltimore, USA in 1994 (http://pathology.jhu.edu/pancreas), and the European Registry for Hereditary Pancreatitis and Pancreatic Cancer (EUROPAC) of the European Study Group for Pancreatic Cancer (ESPAC) [11,18].

Detailed examination of the pancreatic cancer-prone families in these registries has yielded important information on the epidemiology and genetics of this disease. DNA from these individuals can be used for genetic linkage, molecular genetics and finally cloning of a putative cancer causing gene. If a gene is identified as responsible for the familial aggregation of pancreatic cancer, it could form the basis for the development of a screening program for pancreatic cancer and eventually gene-based therapies.

## 2. The National Familial Pancreatic Tumor Registry (NFPTR)

To date, more than 446 families have been registered in the NFPTR. In this registry "familial pancreatic cancer" is defined as pedigrees in which two or more first degree relatives are affected with pancreatic cancer. The term "sporadic pancreatic cancer" is used to designate those families without two affected first-degree

relatives. In a preliminary analysis, we prospectively followed 153 familial pancreatic cancer families from this registry looking at new cancers in family members who were healthy at the time of entry into the registry [41]. Remarkably, we observed a 18-fold increased risk of pancreatic cancer in the 1100 first degree relatives of patients with pancreatic cancer. This risk of apparently healthy family members prospectively developing pancreatic cancer increased to 57-fold if three or more family members had pancreatic cancer at the time of entry into the registry.

There was no obvious relationship with smoking behaviour.

This preliminary analysis shows that the risk of pancreatic cancer is indeed considerably increased among first degree relatives in families in which at least two first degree relatives had previously developed pancreatic cancer. Moreover, the incidence of non-pancreatic cancer, such as breast, colon and lung cancer, also appears to be increased in these families [18]. In a recent report Vaittinen et al. confirmed the above-mentioned association between pancreatic cancer and various other cancers in an analysis of familial risks in discordant cancers of offspring and parents using the Swedish nation-wide Family-Cancer Database [54].

Importantly, these data strongly support the hypothesis that there is a genetic basis for the aggregation of pancreatic cancer in some families.

## 3. Genetic alterations in sporadic pancreatic cancer

A large number of genes have been identified which play a role in the formation of sporadic pancreatic cancer. These genes are important for our understanding of familial pancreatic cancer, because, as Knudson described years ago for retinoblastoma, the same genes are often responsible for familial and sporadic forms of a cancer [24,25]. Germline mutations in some of the genes that are known to play a role in the sporadic pancreatic carcinogenesis appear to play a role in the development of some familial pancreatic cancers.

The genes which have been shown to play a role in the development of sporadic pancreatic cancer include oncogenes, tumor suppressor genes and DNA mismatch repair genes. Activating point mutations in the K-ras oncogene are one of the most common genetic alteration in sporadic pancreatic cancer, 80–90% of the sporadic pancreatic cancers harbour activating point mutations in the K-ras oncogene [19].

Several tumor suppressor genes have also been described to be inactivated in sporadic pancreatic cancer. The p53 tumor suppressor is inactivated in 50–70%, the deleted in pancreatic cancer 4 (DPC4/SMAD4) gene is inactivated in approximately 55%, and the p16/MTS-1 gene is inactivated in approximately 95% of pancreatic cancers [9,46,47]. The BRCA2 gene is inactivated in a small fraction (5–10%) of apparently sporadic pancreatic cancers, and the STK11 gene, responsible for the Peutz–Jeghers syndrome, and the MKK4 gene are inactivated in a small (approximately 4%) proportion of pancreatic cancers [13,15,39,50].

Finally, DNA mismatch repair genes appear to be inactivated in a small fraction (∼4%) of pancreatic cancers. These cancers are remarkable because they appear to have a distinct histologic appearance ("medullary phenotype") and they are often wild-type for the K-ras gene [14].

## 4. Genetic alterations in familial pancreatic cancer

Some of the genetic alterations responsible for the aggregation of pancreatic cancer in families have already been identified and in all cases the genes known to be targeted are the same genes targeted in sporadic pancreatic cancer. These genetic alterations establish a genetic basis for the familial aggregation of pancreatic cancer and other tumor types in some families.

### 4.1. P16/MTS-1 gene

As mentioned above, the p16 tumor suppressor gene is inactivated in a very high percentage (∼95%) of sporadic pancreatic cancers. In these sporadic cancers the p16 gene is inactivated either by homozygous deletions (in 40% of the carcinomas), by mutation of one allele combined with loss of the other allele (in 40%), or by hypermethylation of the p16 promotor region (∼15%) [47].

Germline mutations in the p16 gene are responsible for the development of the Familial Atypical Multiple Mole Melanoma (FAMMM) syndrome, a rare disorder which predisposes affected patients to the development of multiple nevi, melanomas and pancreatic cancer [16,33,34]. Goldstein et al. [16] have demonstrated that germline mutations in the p16 gene, which impaired the p16 protein function in in vitro assays, are associated with a 22-fold increased risk of developing pancreatic cancer in melanoma-prone families.

Moskaluk et al. [37] have recently postulated that mutations affecting the C-terminal end of the p16 protein are associated with a higher penetrance of pancreatic cancer. Now that the gene responsible for the clustering of melanoma and pancreatic cancer in some families has been identified, families with a strong aggregation of pancreatic cancer and melanoma can be tested for germline mutations in the *p16* gene. Careful surveillance of those members with a germline mutation in the *p16* gene should stimulate the development of techniques for early diagnosis for this high risk group and thereby improving survival.

### 4.2. STK11/LKB1 gene

Germline mutations in the *STK11/LKB1* gene have recently been shown to cause the Peutz–Jeghers syndrome (PJS) [17,22]. PJS is a rare syndrome characterized by hamartomatous polyposis of the gastrointestinal tract and by the occurrence of melanin spots on the buccal mucosa and on the lips [21,42]. The Peutz–Jeghers syndrome has been associated with an increased risk of developing cancer, including pancreatic cancer [13].

Su et al. recently reported inactivation of the *STK11/LKB1* gene in 5–6% of the 135 sporadic pancreatic and biliary carcinomas they analyzed. In these cancers, the *STK11/LKB1* gene was inactivated by either homozygous deletions or intragenic sequence mutations combined with loss of the other allele [51]. They also studied a pancreatic cancer obtained from a PJS patient who died from pancreatic cancer and they demonstrated a germline splice site mutation in the *STK11/LKB1* gene in the patient's germline DNA and a loss of the wild type allele in the patient's pancreatic cancer. The *STK11/LKB1* gene was thereby inactivated in this patient's cancer. Thus, just as is true for *p16*, genetic alterations in the *STK11/LKB1* gene contribute to the development of sporadic cancer, and when present in the germline, these alterations may also play a role in the development of familial pancreatic cancer.

### 4.3. BRCA2 gene

As mentioned previously, an increased risk for developing breast cancer has been observed in families in which there is an aggregation of pancreatic cancer [18]. Conversely, it is shown that, in families of patients with breast cancer there is an increased risk of developing pancreatic cancer [53].

Germline mutations in the *BRCA2* gene may explain these associations. Indeed, pancreatic cancers have been reported in many of the *BRCA2* kindred [2, 39]. The increased risk of pancreatic cancer caused by *BRCA2* is not limited, however, to these classical *BRCA2* kindred.

Approximately 7% of the patients with apparently sporadic pancreatic cancers analyzed by Goggins et al. had a germline mutation in the *BRCA2* gene, and Goggins et al. demonstrated that the remaining wild-type allele was lost in the pancreatic cancers that developed in these patients. Remarkably, only one of the five patients with pancreatic cancer and germline *BRCA2* mutations had a family history positive for breast cancer and none of them had a positive family history of pancreatic cancer [15]. The penetrance of this trait is therefore probably low and the inherited basis for some patients with pancreatic cancer would be missed if it were not for our knowledge of this gene.

To date these germline mutations in the *BRCA2* gene are the most frequent described cause of an inherited predisposition to pancreatic cancer. It may prove useful to screen members of families in which there is an aggregation of breast and pancreatic cancer for the presence of germline mutations in the *BRCA2* gene. Those found to carry a germline mutation may benefit of breast cancer screening.

### 4.4. Cationic trypsinogen gene

Pancreatic cancer clustering is also seen in families with a hereditary form of pancreatitis [6,10]. Hereditary pancreatitis is an autosomal dominant disorder caused by point mutations in the cationic trypsinogen gene, *PRSS1*, on chromosome 7q35 [56,57]. These mutations result in a cationic trypsinogen protein which is resistant to auto-inactivation, ultimately resulting in autodigestion of the pancreas. Affected patients have recurrent episodes of pancreatitis that often begin during childhood. Compared with the general population and patients who have chronic pancreatitis of common etiologies who have a somewhat increased cancer risk, patients with hereditary pancreatitis have a cumulative risk of developing pancreatic carcinoma that approaches 40% by the age of 70. The relative risk for the development of pancreatic carcinoma is approximately 50-fold, and the average age of onset is dramatically reduced to 39 years [29].

Considering the high lifetime risk of pancreatic cancer in this group, it is important to recognize patients with hereditary pancreatitis in an early stage, making surveillance of these patients and maybe even prophylactic pancreatectomy an option.

### 4.5. The Hereditary Non-Polyposis Colorectal Cancer Syndrome (HNPCC)

The Hereditary Non-Polyposis Syndrome (HNPCC) is the result of a germline mutation in one of the DNA mismatch repair genes [12,14,26,27,40,49]. Tumors which develop in patients who have a germline mutation in one of the DNA mismatch repair genes show microsatellite instability, which is a change in length of repeated DNA sequences. In a study performed by Goggins et al. [14] approximately 4% of the 82 analyzed pancreatic cancers showed microsatellite instability; these pancreatic cancers appeared to have a distinct, medullary histology. Wilentz et al. [58] followed up on the report by Goggins et al. and demonstrated that pancreatic cancers with a medullary phenotype type were significantly associated with a family history of any cancer in a first-degree relative. Of note, one of the patients included in this study had synchronous pancreatic and colon cancers, which showed microsatellite instability, suggesting that he has HNPCC. Together with the finding that in familial pancreatic cancer kindreds there is an increased risk of colon cancer, these data indicate that HNPCC can be the cause of pancreatic cancer in at least some of the kindreds in which there is a clustering of colon and pancreatic cancer [18].

### 4.6. Other syndromes

Several other inherited syndromes have been suggested to be associated with pancreatic cancer. These include the familial adenomatous polyposis syndrome (FAP), ataxia telangiectasia, Multiple Endocrine Neoplasia 1 (MEN1) syndrome, and glucanoma syndrome [4,31,44,48].

## 5. Conclusion

This last decade has seen a dramatic advance in our understanding of familial pancreatic cancer. The prospective development of new pancreatic cancers in familial pancreatic kindred firmly establishes that "familial pancreatic cancer" is a real entity, and a number of the genes responsible for the familial aggregation of pancreatic cancer have already been identified. Furthermore, as our experience with *BRCA2* has taught us, even some pancreatic cancers which appear sporadic, may in fact be caused by inherited genetic defects.

The genetic alterations which have been associated with familial pancreatic cancer include germline mutations in *p16, STK11, BRCA2, PRSS1,* and in the DNA mismatch repair genes. Screening of individuals for the presence of one of these germline mutation can now be performed when indicated by the family cancer history.

Members of families in which there is an aggregation of pancreatic cancer will also benefit from efforts to develop a new screening test for early pancreatic cancer. At present, screening for familial pancreatic cancer can be approached only at a clinical level. The use of endoscopic ultrasound (EUS), magnetic resonance imaging (MRI), ERCP, and even molecular analysis of brush cytology and pancreatic juice obtained during ERCP may all be of value, but the efficiency of each technique needs to be established in this patient population [5].

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