Hereditary pancreatic cancer

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Identity

Alias: Familial pancreatic cancer

Inheritance

It has been estimated that as many as 10% of pancreatic cancers have a hereditary basis; five genetic syndromes have been identified that are associated with the familial aggregation of pancreatic cancer; these include:

The second breast cancer syndrome (BRCA2), the familial atypical multiple mole melanoma (FAMMM), the Peutz-Jeghers Syndrome, the hereditary pancreatitis and the hereditary non-polyposis colorectal cancer (HNPCC) syndrome.

Most kindreds with familial pancreatic cancer, however, do not fall into one of these well-defined syndromes and these are referred to simply as "family pancreatic cancer."

Clinics

Note

A generally accepted definition of familial pancreatic cancer is a kindred in which at least a pair of first-degree relatives (sibling-sibling or parent-child) have been diagnosed with pancreatic cancer; several large registries have been established to define the patterns of inheritance and genetic basis for the familial aggregation of pancreatic cancer in these kindreds; the National Pancreas Tumor Registry (NFPTR) is the largest such registry; over 260 familial pancreatic cancer kindreds have enrolled in this registry and studies of these kindreds has revealed that when followed prospectively, apparently healthy, first-degree relatives of patients with familial pancreatic cancer have an 18-fold increased risk of developing pancreatic cancer; when there are three or more family members with pancreatic cancer in a kindred, the first-degree relatives of the index patient with pancreatic cancer have a 56-fold increased risk of developing pancreatic cancer.

Each of the five clinically recognized syndromes associated with the familial aggregation of pancreatic cancer has its own unique clinical findings.

Second breast cancer syndrome: the BRCA2 tumor suppressor gene is located on chromosome 13q and carriers of germline BRCA2 mutations have a significant lifetime risk of developing breast cancer (30-85%) at a young age; they are also at risk for bilateral breast cancer; BRCA2 is also associated with an increased risk of male breast cancer, ovarian cancer, prostate cancer and pancreatic cancer; the lifetime risk of pancreatic cancer in carriers of germline BRCA2 mutations is approximately 10%; germline BRCA2 mutations are particularly common amongst individuals of Ashkenazi Jewish heritage because of a founder effect.

Familial atypical multiple mole melanoma (FAMMM) syndrome has an autosomal dominant mode of transmission; most cases are caused by germline mutations in the p16 tumor suppressor gene on chromosome 9p; individuals affected with FAMMM develop multiple melanocytic nevi, some of which can be atypical; they also are at increased risk of developing melanoma and pancreatic cancer; the lifetime risk of pancreatic cancer in individuals with germline p16 mutations is about 20%.

The Peutz-Jeghers Syndrome is inherited in an autosomal dominant mode; it has recently been shown to be caused by germline mutations in the STK11/LKB1 gene on chromosome 19p; individuals with this syndrome typically develop multiple mucocutaneous melanin macules, harmartomatous gastrointestinal polyps and they have an increased risk of developing cancers of the gastrointestinal tract; it has been estimated that the lifetime risk of pancreatic cancer in patient with the Peutz-Jeghers Syndrome is approximately 30%.
Hereditary pancreatic cancer has an autosomal dominant mode of transmission; it is caused by germline mutations in the cationic trypsinogen gene (called PRSS1) on chromosome 7q35; affected individuals develop recurrent episodes of pancreatitis at a young age and they have an elevated lifetime risk of developing pancreatic cancers that approaches 40%. The hereditary nonpolyposis colorectal cancer (HNPCC) syndrome is caused by germline mutations in one of the DNA mismatch repair genes (such as hMLH1 on chromosome 3p and hMSH2 on chromosome 2p); in addition to colorectal neoplasmia, affected family members have an increased risk of developing pancreatic cancer; the pancreatic cancers that arise in patients with HNPCC often have a distinct histologic appearance referred to as "medullary" histology.

The ataxia-telangectasia and familial adenomatous polyposis syndromes have also been associated with an increased risk of developing pancreatic cancer, however, these associations are not well-established.

Treatment
Currently, there are no effective methods to screen individuals at-risk for early pancreatic cancer; several studies are underway to examine the effectiveness of endoscopic ultrasound (EUS) in the early detection of pancreatic cancer.

Prognosis
Prognosis will depend on the stage of the disease at diagnosis more than it does on hereditary susceptibility.

Genes involved and proteins

**BRCA2**
Location: 13q12.3
DNA/RNA
Description: gene spanning more than 70kb of genomic DNA; the coding sequence comprises 27 exons (11 395 nucleotides).
Protein
Description: the corresponding protein has 3 418 amino acid residues (384 kDa).
Function: the Brca2 protein binds to Rad51 and serves as an important co-factor in the Rad51-dependent DNA repair of double strand breaks; the Brca2 protein may also have transcription activation potential.
Mutations
Germinal: more than 300 unique germ-line mutations have been reported; the 6174 delT mutation is particularly common in Jewish subjects.
Somatic: acquired mutations in BRCA2 rare in pancreatic cancer.

**p16**
Location: 9p21

DNA/RNA
Description: the coding sequence comprises 3 exons: this locus gives rise to 2 distinct transcripts from different promoters (p16 and p16(ARF)).
Protein
Description: the corresponding protein, called cyclin-dependent kinase inhibitor-2A, has 156 amino acid residues.
Function: cyclin-dependent kinase inhibitor 2A binds to CDK4 and inhibits the ability of CDK4 to interact with cyclinA thereby inducing a G1 cell cycle arrest.

**Mutations**
Germinal: germ-line mutations are associated with the FAMMM Syndrome.
Somatic: virtually all invasive pancreatic carcinomas show inactivation of the p16 gene; forty percent by homozygous deletion, 40% by an intragenic mutation coupled with loss of heterozygocity (LOH) and 15% by hypermethylation of the p16 promoter.

**STK11**
Location: 19p13.3
DNA/RNA
Description: gene spanning 23kb of genomic DNA, the coding sequence comprises 9 exons (1446bp).
Protein
Description: the corresponding protein has 433 amino acid residues.
Function: serine threonine protein kinase 11.

**Mutations**
Germinal: almost all germline mutations are predicted to disrupt the function of the kinase domain.
Somatic: approximately 4% of sporadic pancreatic cancers have somatic inactivation of STK11.

**PRSS1**
Location: 7q35
DNA/RNA
Description: the coding sequence comprise 5 exons (800bp).
Protein
Description: trypsin, which is active in the pancreas, in inactivated by cleavage; mutations which abrogate this cleavage site can result in autodigestion and pancreatitis.

**Mutations**
Germinal: the arg117-to-his mutation (R117H) is the most common mutation identified to date.

**hMLH1**
Location: 3p21.3
DNA/RNA
Description: the coding sequence comprises 2484b.
**Protein**

Description: MLH1 forms a complex with other DNA mismatch repair gene; functions in DNA mismatch repairs.

**Mutations**

Germline: one of at least 5 known human mismatch repair genes associated with the hereditary non-polyposis colorectal cancer syndrome; the neoplasms that develop in these patients typically show microsatellite instability.

**hMSH2**

**Location:** 2p22-p21

**DNA/RNA**

Description: the MSH2 locus covers approximately 73kb and contains 16 exons.

**Protein**

Description: MSH2 functions in DNA mismatch repair.

**Mutations**

Germline: one of at least 5 known human mismatch repair genes associated with the hereditary non-polyposis colorectal cancer syndrome; the neoplasms that develop in these patients typically show microsatellite instability.

**References**


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