Hereditary Pancreatic Cancer

The lifetime risk of pancreatic cancer among men and women in the United States is ~1.4% and most cases of pancreatic cancers are sporadic (1). However, an estimated 10% of cases may be due to an underlying hereditary cause (2,3). Although our knowledge and the genetic testing options for hereditary pancreatic cancer have increased in recent years, the underlying genetic cause for clusters of pancreatic cancer in many families is still unclear.

Hereditary pancreatic cancer can be divided into several distinct categories: 1) known hereditary cancer syndromes mainly defined by risk for other cancers which include an increased risk of PC; 2) known hereditary disease which causes inflammation of the pancreas leading to an increased risk of PC; 3) familial pancreatic cancer (a clustering of pancreatic cancer in 2 or more first degree relatives) in which the underlying genetic cause is not yet known (4).

Genetic testing is available for the following:

**Hereditary Cancer Syndromes**

**Hereditary Breast and Ovarian Cancer (HBOC)**
HBOC is caused by mutations (genetic changes) in the BRCA1 and BRCA2 genes and is associated with significantly increased risks of breast, ovarian, and prostate cancer. Mutations in the BRCA2 gene are the most common genetic cause for familial pancreatic cancer. Individuals with BRCA2 mutations have a 4-8% lifetime risk to develop pancreatic cancer.

**Familial Atypical Multiple Mole Melanoma Syndrome (FAMMM)**
FAMMM is caused by mutations in the CDKN2A (p16) gene (2,3). Individuals with a CDKN2A mutation develop multiple moles (including many that are atypical or “dysplastic”) and have an increased risk of developing melanoma including melanoma at an earlier than average age and multiple melanomas. CDKN2A mutations are associated with a ~10-19% lifetime risk of PC (2,3,4,7).

**Familial adenomatous polyposis (FAP)**
FAP is caused by mutations in the APC gene and is associated with the development of 100s to 1000s of colon polyps and an almost 100% risk of developing colorectal cancer if risk reducing surgery is not performed. Individuals with FAP also have an increased risk to develop osteomas, fibromas, a benign eye finding known as CHRPE, desmoid tumors, and polyps/cancer in the small bowel or stomach. Individuals with FAP have a 2-4% increased risk to develop pancreatic cancer.
Lynch Syndrome/ Hereditary Non-polyposis Colorectal Cancer (HNPCC)
Lynch syndrome is caused by mutations in the MLH1, MSH2, MSH6, PMS2, and EPCAM genes (3,12). Individuals with Lynch syndrome have a significantly increased risk of developing colon, uterine and ovarian cancer as well as some increased risk to develop other gastrointestinal, urinary tract cancers and sebaceous skin cancers. The link between pancreatic cancer and Lynch syndrome is less clear but recent data suggest that individuals with Lynch syndrome may have a ~3-4% lifetime risk of PC (3,12).

Peutz-Jeghers Syndrome (PJS)
PJS is a rare hereditary cancer syndrome involving multiple polyps throughout the gastrointestinal tract, dark blue to brown spots or “freckling” on the lips, hands, feet, and in the mouth, and increased risk for cancers within and outside of the gastrointestinal tract (e.g. colorectal, breast, gynecologic, stomach) (2,3). Individuals with PJS have a lifetime risk of ~11-36% to develop PC (2,3).

PALB2 gene/ATM gene
Mutations in the PALB2 gene and ATM gene are associated with an increased risk of pancreatic and female breast cancers. These genes have been identified and studied more recently, so the risks for other types of cancers and the exact cancer risks are not well defined at this time (9,10,11).

Hereditary Diseases Associated with an Increased Risk of Pancreatic Cancer

Hereditary Pancreatitis (HP)
HP is a rare genetic disease characterized by recurrent episodes of severe pancreatitis (inflammation of the pancreas), often beginning in the teenage years, and leading to chronic pancreatitis in late adolescence to early adulthood (2,3). HP is primarily due to mutations in the PRSS1 (cationic trypsinogen) gene or SPINK1 gene (2,3). Individuals with hereditary pancreatitis have a ~25-40% lifetime risk of PC (2,3). Smoking is associated with a further increase in risk and younger age of onset of PC (2,3).

Cystic Fibrosis (CF)
CF is a genetic disease that is due to mutations in the CFTR gene and is characterized by chronic obstructive lung disease and pancreatic insufficiency (2). Individuals with CF may have an increased risk of pancreatic cancer and may be diagnosed at young ages (2).

Referral for Genetic Counseling:
Consider being evaluated by a genetic counselor if you have a personal and/or family history that includes any of the following:

- Multiple cases of pancreatic cancer on the same side of the family
- A combination of related cancers on the same side of the family (e.g. pancreatic/breast/ovarian, pancreatic/melanoma, or pancreatic/colon/uterine/ovarian)
- Multiple related new primary cancers in one individual (e.g. pancreatic/melanoma, pancreatic/breast)
- Ashkenazi Jewish ancestry and pancreatic cancer
- Pancreatic cancer and multiple and/or early onset gastrointestinal polyps including greater than 15 gastrointestinal polyps or greater than 5 hamartomatous polyps

**Screening for Individuals at Increased Risk:**

Routine population screening for pancreatic cancer is not useful due the limitations of the available screening and the fact that pancreatic cancer is rare (2,3). However, some data suggest that screening may prove valuable in individuals at high risk by detecting cancers at an earlier, treatable stage (2,3). The optimal screening method for pancreatic cancer is still unclear due to the risks and limitations of each of the available methods. However, consideration of screening, particularly in the setting of a research study, is recommended for individuals with a significantly increased risk to develop pancreatic cancer. We provide referrals for appropriate individuals to discuss pancreatic cancer screening and clinical trial options with our pancreatic experts.

Please contact the Smilow Cancer Genetics and Prevention Program at 203-200-4362 if you would like further information or to schedule an appointment.
References: