Hereditary Aspects of Pancreatic Cancer

Genetic Risk Assessment and Counseling for Familial Pancreatic Cancer

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Risk Factors For Pancreatic Cancer

- Smoking
- Age
- Race
- Gender
- Obesity
- Diabetes
- Chronic Pancreatitis
- Family History
Family History

- 5-10% of patients with pancreatic cancer will have a family member with the disease.

- Patients with pancreatic cancer are 1.9-13 times more likely to have a family history of pancreas cancer.

- Pancreatic Cancer Cohort Consortium (PanScan) 2010:
  - Risk to 1st degree relatives is 1.76 times higher

What Percentage of Cancer is Thought to be Hereditary?

- 60-85% Sporadic
- 10-30% combination
- 5-10% hereditary
“Sporadic” Pancreatic Cancer:

MI Smoker
d.71

77

75

54

50

Pancreas Cancer

“Familial” Pancreatic Cancer:

MI Smoker
d.71
d.85

77

75

54

50

Pancreas Cancer
"Hereditary" Pancreatic Cancer:  

When to Suspect a Hereditary Cancer Syndrome

- Cancer in two or more close relatives (on the same side of the family).
- Early age at diagnosis.
- Multiple primary tumors.
- Bilateral or multiple rare tumors.
- Constellation of cancers consistent with known cancer syndrome (e.g., breast and ovary).
- Lack of other known risk factors.
- Multiple generations affected (vertical transmission).
Autosomal Dominant Inheritance

Father with mutation on one chromosome

Each child has a 50% chance of inheriting an autosomal dominant disorder

Family History

- Current age or age at death
- Age at diagnosis of cancer
- Type and location of primary cancer(s), stage, laterality, treatment
- Second cancer: metastasis or new primary
- Environmental exposures
- Ethnicity/Race
- Other risk factors/significant health conditions
Guidelines for Considering Genetic Testing

- Patient has a reasonable likelihood of carrying an altered cancer susceptibility gene.
- Genetic test result can be adequately interpreted.
- Results will impact medical management or aid in the diagnosis of a hereditary cancer syndrome.

Genetic Testing: Technical Considerations

- It is a blood test.
  - DNA from peripheral WBCs is analyzed.
- Next generation sequencing panels allow analysis of numerous genes with a single test, at one low price.
  - Sensitivity for each gene tested is >99%.
Interpreting Test Results

1. Positive for a deleterious mutation

2. No mutation detected
   - Mutation previously identified in the family
     - True negative
   - No known mutation in the family
     - Inconclusive

3. Uncertain clinical significance
   - Approximately 10% of all genetic tests

Inconclusive Negative Results

- Does not rule out genetic predisposition
  - Cancer in family could be caused by mutation(s) not detected by current tests
  - Cancer in family could be caused by another gene that was not tested
  - Tested person could have sporadic cancer. Another affected family member may need to be tested
Benefits of Genetic Testing

- Identifies high-risk individuals
- Identifies non-carriers in families with a known mutation (i.e. general population risk)
- Allows early detection and prevention strategies
- May relieve anxiety (positive or negative)

Risks and Limitations of Genetic Testing

- Does not detect all mutations
- Uncertain test results
- Continued risk of sporadic cancer
- Efficacy of interventions sometimes unproven
- Psychosocial issues
Psychosocial and Ethical Issues in Cancer Predisposition Testing

- Anxiety/fear
- Guilt
- Self-esteem
- Depression
- Stigmatization
- Grief and/or loss
- Family dynamics
- Right to know/right not to know
- Sharing of information
- Coercion
- Privacy
- Reproductive decisions
- Testing of minors

Genetic Testing: Cost and Insurance Coverage

- The cost of genetic testing has decreased dramatically over the past few years due to the development of massively parallel sequencing (next generation sequencing panels). Self-pay price ranges from $300-500 depending on lab.
- The vast majority of insurers cover at least some portion of genetic testing.
- Medicare will cover genetic testing if strict guidelines are met. Medicaid coverage varies.
- Most laboratories offer pre-verification services before committing to the cost of genetic testing.
Genetic Testing: Discrimination and the Law

- Genetic discrimination:
  - Social or economic based on one’s inherited predisposition to disease.
    - Increased cost or denied access to insurance.
    - Loss of employment, education or other opportunities.
  - Fact vs. Fiction?

Protections: State and Federal
- GINA
  - Went into effect May of 2009
  - Health insurance and employment protections.
  - Currently does not cover members of active military.

Genetic Predisposition to Pancreatic Cancer

- High Penetrance Genes
  - Known hereditary cancer predisposition syndromes
  - Hereditary pancreatitis
  - Familial pancreatic cancer (FPC)

- Low Penetrance Susceptibility Variants
  - Ex: ABO blood group
  - Limited knowledge

- Gene-gene interactions and gene-environment interactions
  - Poorly understood
Known Hereditary Cancer Predisposition Syndromes

- **Peutz-Jeghers Syndrome (PJS)**
  - STK11 gene
- **Multiple Endocrine Neoplasia type I**
  - Neuroendocrine PC
  - MEN1 gene
- **Familial Adenomatous Polyposis**
  - APC and MYH genes
- **Familial Melanoma (FM)**
  - CDKN2A/p16
- **Li-Fraumeni Syndrome**
  - TP53 gene
- **Lynch Syndrome (HNPCC)**
  - MLH1, MSH2, MSH6, PMS2, EPCAM
- **Hereditary Breast and Ovarian Cancer (HBOC)**
  - BRCA1 and BRCA2
- **Familial Breast Cancer**
  - ATM, PALB2

Peutz-Jeghers Syndrome

- Often presents as small bowel intussusception
- Melanin pigmentation
- Lifetime risk of *any* cancer is 93%
  - Colon, stomach, small bowel, pancreas, breast, cervix, lung, testicle, ovary.
- Autosomal Dominant (STK-11)
Multiple Endocrine Neoplasia Type 1 (MEN1)

- Includes varying combinations of more than 20 endocrine and non-endocrine tumors.
  - Parathyroid
  - Pituitary
  - Pancreatic Islet Cell
  - Gastrinoma
  - Insulinoma
  - Glucagonoma
- MEN1 (menin) gene
- Autosomal dominant

Familial Adenomatous Polyposis (FAP)

- 100’s to 1000’s colonic adenomas
- Average age of polyp onset is 15 years
- Cancer risk approaches 100%
- Average age of cancer diagnosis is 39 years
- APC gene
  - Autosomal dominant
- MYH gene
  - Autosomal recessive
Familial Melanoma (FM) Syndrome

- Characterized by a dominant pattern of melanoma and dysplastic nevi
- Risk for pancreas cancer is increased (22-fold)
- P16 gene (CDKN2A)
- Genetic testing is controversial

![Image of asymmetry, border irregularity, color, and diameter of melanoma with ¼ inch or 6mm]

Family 1

Family tree showing members with various diagnoses including leukemia, breast, colon, lung, pancreas, and diabetes.
Li-Fraumeni Syndrome

- **TP53 gene**
  - Autosomal dominant
- **90% lifetime risk for cancer.**
  - Childhood: leukemia, sarcoma, adrenocortical carcinoma, brain tumors.
  - Adulthood: leukemia, sarcoma, brain tumors, breast cancer, pancreatic cancer, colon cancer, melanoma, lung cancer, and others.
Lynch Syndrome

- Early but variable age at colorectal and endometrial cancer diagnosis (40-45 years)
- Tumor site in proximal colon predominates (50-70%)
- Other cancers: urinary tract, ovary, stomach, small bowel, pancreas, brain tumors, and sebaceous skin tumors
- DNA mismatch repair genes: MLH1, MSH2, MSH6, PMS2, EPCAM
- Autosomal dominant
Hereditary Breast and Ovarian Cancer Syndrome

- Breast cancer (50-85%)
- Second primary (40-60%)
- Male breast cancer (5-10%)
- Ovarian and fallopian tube cancer (BRCA1 up to 50%)
  (BRCA2 up to 25%)
- Prostate cancer (16-22%)

- Autosomal Dominant Transmission
- Small increase in risk of other cancers (e.g. pancreas, melanoma)

Prevalence of BRCA2 in PC

- 7% of apparently sporadic pancreas cancer (Goggins et al. 1996)
- 10% of Ashkenazi Jewish patients with pancreas cancer (Ozcelik et al. 1997)
- 17% of kindreds with three or more relatives affected with pancreas cancer (Murphy et al. 2002)
**BRCA1 and BRCA2 Mutations in the Ashkenazi Jewish Population**

1 in 40 Individuals of Ashkenazi Jewish descent has a BRCA1 or BRCA2 Mutation

- **185delAG**
  - Prevalence = ~1%

- **5382insC**
  - Prevalence = ~0.15%

- **6174delT**
  - Prevalence = ~1.5%

**PALB2**

- Official name “partner and localizer of BRCA2”
- Genome maintenance gene
- PALB2 binds to BRCA2 stabilizing it and anchoring it to structures in the nucleus allowing BRCA2 to repair DNA
**PALB2**

- Sequence Analysis of 20,661 genes: *PALB2* mutated in one proband
- 3 of 96 additional FPC patients sequenced also had truncating *PALB2* mutations
- Co-segregation was observed
  - Two brothers with pancreatic cancer both had same PALB2 stop mutations
- 3 of 4 families also had history of breast cancer
- The cumulative breast cancer risk is now known to be between 40-60%.
- Risk of pancreatic cancer is still uncertain

**Family 3**
ATM

- Well known gene. Causes ataxia telangectasia when recessively inherited.
  - Childhood onset ataxia: unsteady gait, lack of coordinated muscle movements.
  - Telangectasias: tiny red spider veins (dilated blood vessels) of the eyes, ears, cheeks and other sun exposed areas.
  - Increased risk of cancers, primarily leukemia and lymphoma. Individuals with A-T are also sensitive to ionizing radiation

ATM

- Mothers of children with AT appeared to have a higher prevalence of breast cancer than women in the general population.
- ATM also participates in the BRCA1/2 pathway, and is therefore essential to BRCA1/2 mediated DNA repair.
- The cumulative breast cancer risk is now known to be 30%.
- May also increase the risk of other cancers: pancreatic, ovarian, and colon. Risks are still uncertain.
Hereditary Pancreatitis

- **Autosomal dominant disease with 80% penetrance and 40% lifetime risk for PC.**
  - PRSS1 mutations found in ~70% of families.
  - Other genes include SPINK1, CFTR, and CTRC.
  - Risk is often determined by a combination of all of the above genes (multi-genic).
- **Risk is further increased in cases with cigarette smoking.**
Most patients with a strong family history of pancreatic cancer do not fit into one of these recognized syndromes!

Familial Pancreatic Cancer

- Absence of known hereditary cancer predisposition syndrome.
- Autosomal dominant with variable penetrance.
- No consistent definition: at least two 1st degree relatives with PC or three or more relatives of any degree, especially if one is young onset.
Empiric risks of pancreatic cancer

• Based on the number of affected first degree relatives (FDR):
  – One FDR = 4.5-fold
  – Two FDRs = 6.4-fold
  – Three FDRs = 32-fold

Ongoing Gene Discovery Studies

• PacGene
  – Multi-center linkage consortium: Johns Hopkins, Mayo Clinic, Karmanos Cancer Institute, M.D. Anderson Cancer Center, University of Toronto, Dana-Farber Cancer Institute

• PANSCAN
  – Genome Wide Association Studies: The Pancreatic Cancer Cohort Consortium; JHU, MD Anderson, Mayo, Mount Sinai, MSKCC, USCF, Group Health (Seattle WA)
Resources

• National Society of Genetic Counselors
  – [http://www.nsgc.org](http://www.nsgc.org)

• National Cancer Institute
  – [Cancer Genetics Services Directory](http://www.cancer.gov/cancertopics/genetics/directory)