Genetics of Pancreatic Cancer

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Genetics of Pancreatic Cancer

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Professor of Medicine
University of Pittsburgh Medical Center
Overview of the Talk

- Background on pancreatic cancer
- Genetics Primer
- Review how pancreatic cancer develops
- Background on cancer screening
- What is the goal of PC screening?
- Who should be screened for PC?
- How should PC screening be performed?
- Current results of PC screening
- Approach to PC screening in 2013

Cancer is a common disease

1 in 3 people will develop cancer in their lifetime

About 1.4% chance lifetime risk of developing pancreatic cancer

(1 in 71 people in US)
Pancreatic Cancer: Epidemiology

- Incidence
  - In the US in 2013: 45,220 new diagnoses
  - About 1.4% life-time risk of developing
- Fourth leading cause of cancer related mortality in the United States
- Over 90% of tumors are adenocarcinomas
- Most epidemiology studies report a 2 to 3-fold increased risk for PC in smokers
- Greatest risk factors for PC are hereditary disorders
Pancreatic Adenocarcinoma

What Is Genetics?

- The branch of biology that studies heredity and variation in organisms
- How traits are passed down through families and why we are different from each other
Chromosomes

The nucleus of the cell houses chromosomes
- Chromosomes are stick-like structures that contain our genetic information
- Humans have a total of 46 chromosomes that are divided into 23 pairs
- The first 22 pairs are the same for everyone
- The last pair is called the sex chromosomes
  - Females have two X chromosomes
  - Males have one X chromosome and one Y chromosome

Genes

- Each chromosome contains many genes
- Genes are made up of DNA
- Our genes determine what we look like, how we develop and grow, and how our body works
Mutations

- If the letter code of a gene has a spelling mistake, our body cannot read the letter code correctly and the protein it codes for cannot work correctly, which may lead to disease.
- This type of spelling mistake is called a mutation.
- Mutations can be acquired- almost all mutations in a tumor are this type.
- Mutations can also be inherited from one of your parents.

Inheritance

- Just as we have two copies of each chromosome, we also have two copies of each gene.
- We get one copy from our mom and one copy from our dad.
- If a gene has a mutation, that can also be passed down through families.
- These mutations are inherited in different ways.
Autosomal Dominant Inheritance

- A person with an autosomal dominant condition has one working copy of the gene and one non-working copy.
- That person has a 50-50 chance of passing on the non-working copy to their child.
Autosomal Recessive Inheritance

- A person with an autosomal recessive condition has two non-working copies of a gene.
- In order for a child to have a recessive condition, both parents must have one non-working copy of the gene.
  - A person with one non-working copy of a gene is called a carrier.
  - Two carriers have a 1 in 4 (25%) chance of having a child with the recessive condition.
Multifactorial Inheritance

- Most diseases are not caused by changes in single genes
- Usually, they are the result of gene-gene and gene-environment interactions
- These types of conditions are considered multifactorial because they are caused by many factors
- Some examples of multifactorial conditions: heart disease, cancer, diabetes, and birth defects

What is a Genetic Counselor?

- Genetic counselors are part of the health care team
- Help families learn about how conditions are passed down through a family
- Help families deal with feelings about how these conditions affect their family
- Ask questions about family health and pregnancy history
  - Family history is a major tool for genetic counselors
- Talk with families about available genetic tests, recurrence risks and treatment and prevention of certain diseases
- Provide resources and referrals
Family History

- A pedigree, or family history, is a drawing of a family tree using different symbols that records health information.

- A pedigree can be a useful way to track diseases through families.
  - For genetic conditions, a pedigree can be helpful in determining the inheritance pattern.
  - For multifactorial conditions, a pedigree can be helpful in assessing risk because families share genes, behaviors, and environments.

A Pedigree

http://www.accessexcellence.org
Why did my loved one or friend get pancreatic cancer?
Pancreatic Adenocarcinoma: Precursor Lesions

- Pancreatic Intraepithelial Neoplasias (PanINs) (~85% of adenocarcinomas)
- Intraductal Papillary Mucinous Neoplasms (IPMNs) (10-15%)
- Mucinous cystic neoplasms (<5%)

Genetic Progression Model of Pancreatic Adenocarcinoma

Can we screen for pancreatic cancer?
Definition of Cancer Screening

- **Screening**: Testing in setting of asymptomatic general population
- **Surveillance**: Testing in asymptomatic high-risk individuals
- **Diagnostic**: Testing in setting of symptoms

Important Issues on Cancer Screening

- The goal of cancer screening is to decrease the risk of dying from that cancer
  - Indolent disease
    - Patient will never die from this cancer
    - Unnecessary treatment
  - Lead-time bias
  - Not useful if cancer found at a untreatable stage
- Test must be acceptable to patients and PCP
Lead-Time Bias
Indolent Disease

Ideal Diagnostic Goals for Pancreatic Cancer

- **Short-term**
  - Finding a tumor at an early stage
    - “Localized” tumor, node negative (Stage I or 2A)
    - Identify long-term survivors (> 3 yrs)

- **Long-term**
  - Identification of advanced precursor lesions
    - PanIN-3 lesion
    - Mucinous cystic lesion with high malignant potential
Stage Distribution and 5-year Relative Survival by Stage at Diagnosis for 2001-2007, All Races, Both Sexes

<table>
<thead>
<tr>
<th>Stage at Diagnosis</th>
<th>Stage Distribution (%)</th>
<th>5-year Relative Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localized</td>
<td>8</td>
<td>21.5</td>
</tr>
<tr>
<td>Regional</td>
<td>27</td>
<td>8.6</td>
</tr>
<tr>
<td>Distant</td>
<td>53</td>
<td>1.8</td>
</tr>
<tr>
<td>Unknown (unstaged)</td>
<td>13</td>
<td>4.2</td>
</tr>
</tbody>
</table>

Adapted from NCI’s SEER Cancer Statistics Review

Can we screen the general population for PC?

- Screen 100,000 asymptomatic individuals
  - Age-adjusted incidence rate was 12.0 per 100,000 men and women per year*
- Apply a biomarker with a 100% sensitivity and 99% specificity
  - Detect all 12 PC cases
  - ~1,000 false positive studies
- Not feasible to screen population, must enrich

*Rates based on cases diagnosed in 2004-2008 from 17 SEER geographic areas
Is surveillance of PC reasonable?

- Screen enriched population of 10,000 asymptomatic individuals
  - Age-adjusted incidence rate was 120 per 100,000 men and women per year*
- Apply a biomarker with a 100% sensitivity and 99% specificity
  - Detect all 12 PC cases
  - ~100 false positive studies
- Practical to do surveillance for PC

*Rates based on cases diagnosed in 2004-2008 from 17 SEER geographic areas

Who are candidates for PC surveillance?
Definition of Hereditary Pancreatic Cancer

- Recognized genetic syndromes with a known germline mutation expressing PC
- 2 or more cases of PC with at least a pair of FDR.
  - Also known as Familial Pancreatic Cancer

Five to 10% of PC related to hereditary factors

- Study from Louisiana (Falk et al. 1988)
  - Patients with pancreatic cancer
    - OR = 1.86 (1.42-2.44) any cancer
    - OR= 5.25 (2.08-13.21) with history of PC
- Study in French Canadians (Ghadirian et al. 1991)
  - 13-fold difference
    - 7.8% of PC patients with positive FH
    - 0.6% of controls with positive FH
- UPMC PAGER registry (unpublished data)
  - 619 PC cases
    - 33 with FDR: 5.3%
    - 50 with FDR or SDR: 8.1%
**Syndromes Associated with Pancreatic Adenocarcinoma**

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial Atypical Multiple Mole Melanoma (FAMMM)</td>
<td>p16</td>
</tr>
<tr>
<td>Familial Breast and Ovarian Cancer</td>
<td>BRCA1 BRCA2</td>
</tr>
<tr>
<td>Fanconi anemia, breast cancer</td>
<td>PALB2</td>
</tr>
<tr>
<td>Familial Adenomatous Polyposis</td>
<td>APC</td>
</tr>
<tr>
<td>Hereditary Non-polyposis Colon Cancer (HNPCC)</td>
<td>MLH1 MSH2</td>
</tr>
<tr>
<td>Peutz-Jeghers syndrome</td>
<td>STK11/LKB1</td>
</tr>
<tr>
<td>Hereditary Pancreatitis</td>
<td>PRSS1</td>
</tr>
<tr>
<td>Cystic Fibrosis</td>
<td>CFTR</td>
</tr>
</tbody>
</table>

**What is the risk for these pancreatic cancer-prone families?**

- Germline mutation known
- 3 or more members in pancreatic cancer-prone families
- 2 or more members?
- Early age onset PC
### Syndromes Associated with Pancreatic Adenocarcinoma

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Relative Risk of PC</th>
<th>Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial Atypical Multiple Mole Melanoma (FAMMM)</td>
<td>13-22 fold</td>
<td>p16</td>
</tr>
<tr>
<td>Familial Breast and Ovarian</td>
<td>&lt; 5 fold</td>
<td>BRCA1 or 2</td>
</tr>
<tr>
<td>Fanconi Anemia, Breast CA</td>
<td>Unknown</td>
<td>PALB2</td>
</tr>
<tr>
<td>FAP</td>
<td>5 fold</td>
<td>APC</td>
</tr>
<tr>
<td>Hereditary Non-polyposis Colon Cancer (HNPCC)</td>
<td>1.5-9 fold</td>
<td>MLH1, MSH6, MSH2, PMS2</td>
</tr>
<tr>
<td>Peutz-Jeghers Syndrome</td>
<td>Up to 100 fold</td>
<td>STK11/LKB1</td>
</tr>
<tr>
<td>Hereditary Pancreatitis</td>
<td>53 fold</td>
<td>PRSS1</td>
</tr>
<tr>
<td>Cystic Fibrosis</td>
<td>2.6 to 32 fold</td>
<td>CFTR</td>
</tr>
<tr>
<td>Ataxia-telangiectasia</td>
<td>~ 2-fold</td>
<td>ATM</td>
</tr>
</tbody>
</table>

### Frequency of Germline Mutations in familial PC kindreds

<table>
<thead>
<tr>
<th>2 FDR</th>
<th>&gt;2 FDR</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA2 1,2</td>
<td>5-6%</td>
</tr>
<tr>
<td>p16 3</td>
<td>3%</td>
</tr>
<tr>
<td>Lynch4</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>PALB25</td>
<td>3%</td>
</tr>
<tr>
<td>ATM6</td>
<td>2.4%</td>
</tr>
</tbody>
</table>

1. Murphy et al Cancer Research 2012
6. Nicholas et al Cancer Discovery 2012
No guidelines currently available for genetic testing in hereditary PC kindreds

- Review pedigree
  - If melanoma is present consider testing for FAMMM
  - Look for Amsterdam criteria
  - Look if meets HBOC NCCN guidelines
    - Younger age affected individuals (< 55) consider BRCA2 testing
  - In some instances it may be reasonable to perform testing on a panel of genes
Candidates for PC Surveillance

- Three or more first, second, or third-degree relatives with PC in the same lineage
- Known mutation carrier for BRCA1 or BRCA2 or p16 with at least one first or second-degree relative with pancreatic cancer (Apply to FAP and Lynch Syndrome)
- A member, ideally a verified germline carrier, of a Peutz-Jeghers kindred
- Two relatives in the same lineage (directly connected) affected with pancreatic cancer, at least one a first-degree relative of the candidate
- An affected individual with hereditary pancreatitis

Summary

- Due to its low incidence, not practical to screen for PC in general population
- Surveillance is currently reserved for those patients at high risk for PC development
  - Hereditary risk factors
  - It is premature to recommend screening of asymptomatic new-onset diabetics
    - About 1% of these individuals over the age of 50 would be diagnosed with PC within 3 years (Chari et al. Gastroenterology 2005)
  - Smoking increases risk of PC in the hereditary setting and causes earlier age of onset of disease
How should patients undergo surveillance for pancreatic cancer?

- Biomarker in blood
- Imaging tests
  - ERCP
  - CT
  - EUS
  - MRI

Current Status of Biomarkers: CA 19-9

- Most widely studied biomarker
- Sialyated Lewis\(\text{a}\) antigen associated with circulating mucins
- Commercially available
- Sensitivity and Specificity dependent on cutoff point (Neiderau et al. Pancreas 1992)
  - At 37 U/ml  85% Sens  81% Spec
  - At 250 U/ml  70% Sens  90% Spec
  - At 1000 U/ml  40% Sens  99% Spec
CA 19-9 as Screening Test

- Asymptomatic Korean population
- Study over 6 years of 70,940 individuals
- 1063 (1.5%) had cutoff greater than 37 U/mL
- PPV only 0.9%

Kim et al. J of Gastro and Hepat 2004

Early Diagnosis of Pancreatic Dysplasia

- 14 patients from 3 kindreds with FH
- ERCP abnormal in 7 patients
  - Similar changes to chronic pancreatitis
    - mild side-branch duct irregularities
    - ectasia
    - main-duct strictures
    - clusters of saccular deformities
- 7 patients underwent pancreatectomy
  - All had dysplasia
- All patients with abnormal ERCP had abnormal EUS

Can We Detect Early Pancreatic Cancer?

- 37 high risk patients screened with EUS
  - 31 from kindreds with 3 or more cases of PC
- 6 pancreatic masses detected
  - One T2N1 adenocarcinoma
  - One benign IPMN
  - 4 non-neoplastic masses

Canto et al. Clin Gastroenterol Hepatol 2004

Can We Detect Early Pancreatic Cancer?

- A prospective controlled study of screening EUS and CT followed by ERCP in 78 at-risk relatives and 149 control subjects
- High prevalence of chronic pancreatitis-like changes
  - 72% by EUS
  - 68% by ERCP
- 10% of these high-risk individuals treated by subtotal pancreatectomy had IPMNs
  - one of these had carcinoma-in-situ

Yield of First-Time EUS in Screening High Risk Individuals

- 44 individuals
  - About half from families with known genetic syndromes
- 3 pancreatic cancers (2- stage IIB, 1-stage Ia) (7%)
- 7 IPMNs (16%) diagnosed by clinical appearance on EUS

Poley et al. AM J Gastro 2009

<table>
<thead>
<tr>
<th>Study Site</th>
<th>Study Population</th>
<th>Initial Imaging Modality</th>
<th>Diagnostic Yield Significant Abnormality#</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(subjects/%highest-risk*)</td>
<td>Surgical</td>
<td>Surgical + Clinical</td>
</tr>
<tr>
<td>JHMI (2004)</td>
<td>38 84% HRI</td>
<td>EUS</td>
<td>2 (5.3%)</td>
</tr>
<tr>
<td>JHMI (2006)</td>
<td>78 100% HRI</td>
<td>CT + EUS</td>
<td>7 (9.0%) 7+11 (23%)</td>
</tr>
<tr>
<td>Univ. of Amsterdam (2009)</td>
<td>44 53% HRI</td>
<td>EUS</td>
<td>3 (7.8%) 3+7 (23%)</td>
</tr>
<tr>
<td>MSKCC (2011)</td>
<td>109 42% HRI</td>
<td>MRI</td>
<td>4 (3.7%) 4+3 (6.4%)</td>
</tr>
<tr>
<td>German Familial PC Registry (2009, 2011)</td>
<td>72 42% HRI</td>
<td>EUS + MRI</td>
<td>4 (5.5%) 4+5 (12.5%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>341</strong></td>
<td></td>
<td><strong>20 (5.9%)</strong> <strong>44 (12.9%)</strong></td>
</tr>
</tbody>
</table>

*HRI defined as 3 or more cases of PC or known germ-line mutation carrier
#Defined as PanIN 3 lesion, cancer, IPMN or MCN
Case of PC surveillance
Follow up EUS March 2010

EUS June 2010 Nodule
Summary

- EUS can identify small tumors or premalignant cysts
  - Up to 23% of detected lesions are significant abnormalities
  - 30 to 40% lesions detected were benign
- Cystic lesions may be a marker of risk of PC
- There is no data at this time demonstrating that surveillance of PC decreases the risk of dying from this disease
  - Likely significantly more people found at a resectable stage
    - Over 80% at our site (compared to ~35% from SEER)
    - Should translate into a survival advantage
- Choice of imaging study of some debate
  - Favor EUS
Prevention of Pancreatic Cancer

- Avoid smoking
- Healthy diet high in fruits and vegetables
- Regular exercise
- Weight reduction if necessary
- Increased Intake of Vitamin D (total of 2000 IU)
- Baby aspirin a day if no contraindication

Approach for Management of Asymptomatic High-Risk Individuals

- Counseling about limitations of surveillance
- EUS- based on expert opinion should be done in centers with active research (Canto Gut 2013)
- When to start?
- If EUS abnormal discuss at multi-disciplinary clinic
- Role of MRI is being defined
- Research studies
  - Collect serum, plasma, pancreatic juice
  - Molecular based technologies
Summary

• The possibility now exist to identify high risk individuals based on family history
• Role of genetic testing is not known outside of known genetic syndromes associated with an increased PC risk
• These patients are appropriate candidates for surveillance based on expert opinion.
Questions?

Thank you for your participation!

Pancreatic Cancer Action Network
www.pancan.org

If you have questions, please contact our Patient and Liaison Services (PALS) program at (877) 272-6226 or e-mail pals@pancan.org.