Genetics of Pancreatic Cancer

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Genetics of Pancreatic Cancer

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Icahn School of Medicine at Mount Sinai
#2 Cause of Cancer Death by 2020
Inherited Syndromes
Predisposing to Pancreatic Cancer

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer BRCA1, BRCA2, PALB2</td>
<td>2-10 increased</td>
</tr>
<tr>
<td>FAMMM CDKN2A/P16</td>
<td>15-65</td>
</tr>
<tr>
<td>Peutz-Jeghers Syndrome STK11</td>
<td>130</td>
</tr>
<tr>
<td>Lynch Syndrome MLH1, MSH2, MSH6, PMS2, EPCAM</td>
<td>8</td>
</tr>
<tr>
<td>Hereditary pancreatitis PRSS1</td>
<td>69</td>
</tr>
<tr>
<td>Familial Polyposis APC</td>
<td>5</td>
</tr>
<tr>
<td>Ataxia Telangectasia ATM</td>
<td>increased</td>
</tr>
</tbody>
</table>

Age of Onset

PC age onset: 65.6
Corrected age -3.23 yrs
p = .001

PC age onset: 57.9
Corrected age -5.63 yrs
p = .005

PC age onset: 62.7
Corrected age -3.19 yrs
p = .002

PC age onset: 65.1
Corrected age -5.63 yrs
p = .005

PC age onset: 65.5
Corrected age -.61 yrs
p = .65

PC age onset: 69.4
Corrected age +.78 yrs
p = .49

McWilliams et al. CGH 2006
Incidence of Pancreatic Cancer by Number of Affected First Degree Relatives

10-15% of patients with pancreatic cancer have a familial aggregation or an inherited predisposition

<table>
<thead>
<tr>
<th>Number of FDRs</th>
<th>Standardized Incidence Ratio</th>
<th>Incidence (per 100,000 in the US Population)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General U.S. (reference)</td>
<td>-</td>
<td>9</td>
</tr>
<tr>
<td>1</td>
<td>4.5 x</td>
<td>41</td>
</tr>
<tr>
<td>2</td>
<td>6.4 x</td>
<td>58</td>
</tr>
<tr>
<td>3 or more</td>
<td>32.0 x</td>
<td>288</td>
</tr>
</tbody>
</table>

Klein AP et al. Cancer Research 2004; 64; 2634-2638

Familial Pancreatic Cancer

- Families with at least two first-degree relatives diagnosed with pancreatic cancer
- 2 or more FDR with pancreatic cancer
- 1 FDR with pancreas cancer, ≤ 50 years old
- 2 or more second degree relatives with pancreatic cancer, one at an early age
Human Cell Formation

- **Oocyte**
  - 22 autosomal chromosomes
  - 2 X chromosome

- **Zygote**
  - 46 chromosomes

- **Sperm**
  - 22 autosomal chromosomes
  - 1 Y chromosome
  - 1 X chromosome

MITOSIS

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Two Kinds of Gene Mutations

- Somatic Mutations → Sporadic Cancer
- Germ Line Mutations → Inherited Syndrome
Somatic Mutations
(Sporadic Disease)

2 normal copies of the gene in every cell

One copy mutated in cell
(1st hit acquired)

Second copy mutated in cell
(2nd hit also acquired)

Germline Mutation
(Inherited Disease)

One copy mutated in every cell
(1st hit acquired)

Second copy mutated in cell
(2nd hit also acquired)
Smoking…

is the major known risk factor for this cancer

- associated with ~ 30% of all cases
- results in *accelerated* tumor progression

- Smokers have YOUNGER onset
- Dose-dependent

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**Incidence Ratios for Pancreatic Cancer by Cigarette Smoking Status for Those with At Least One First-Degree Relative (FDR) with Pancreatic Cancer**

<table>
<thead>
<tr>
<th>Smoking Status</th>
<th>Standardized Incidence Ratio (95% Confidence Intervals)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smokers</td>
<td>19.2 (7.7 – 39.5)</td>
</tr>
<tr>
<td>Non Smokers</td>
<td>6.25 (1.70 – 16.0)</td>
</tr>
</tbody>
</table>

Klein AP et al. Cancer Research 2004; 64; 2634-2638
Other risk factors...

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Increased PDAC risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current cigarette use</td>
<td>1.7-2.2</td>
</tr>
<tr>
<td>Current pipe or cigar use</td>
<td>1.5</td>
</tr>
<tr>
<td>&gt; 3 alcoholic drinks per day</td>
<td>1.2-1.4</td>
</tr>
<tr>
<td>Chronic pancreatitis</td>
<td>13.3</td>
</tr>
<tr>
<td>BMI &gt; 40 kg/m², male</td>
<td>1.5</td>
</tr>
<tr>
<td>BMI &gt; 40 kg/m², female</td>
<td>2.8</td>
</tr>
<tr>
<td>Diabetes mellitus, type 1</td>
<td>2.0</td>
</tr>
<tr>
<td>Diabetes mellitus, type 2</td>
<td>1.8</td>
</tr>
<tr>
<td>Cholecystectomy</td>
<td>1.2</td>
</tr>
<tr>
<td>Gastrectomy</td>
<td>1.5</td>
</tr>
<tr>
<td>Helicobacter pylori infection</td>
<td>1.4</td>
</tr>
</tbody>
</table>


Can we prevent patients from developing pancreatic cancer?

(Or catch it at a treatable stage?)
Pancreatic Intraepithelial Neoplasia (PanIN)

- Small intraductal lesions formed by abnormal proliferation of ducts
- Pan-IN demonstrate varying degrees of dysplasia
  - PanIN-1, PanIN-2, and PanIN-3
- Some pancreatic cancers arise from PanIN, but not all PanIN become cancers
- Unable to visualize clearly on imaging

Hruban et al. Mod Path 2003.
Terhune et al. CEBP 1998.
Mucinous Cystic Neoplasms & Intraductal Papillary Mucinous Neoplasms

Mucinous Cystic Neoplasm (MCN)
- Ovarian stroma, possibly arising from ovarian rests within pancreas
- Invasive carcinoma 6-36%

Intraductal Papillary Mucinous Neoplasm (IPMN)
- Branch duct vs main duct
  - Different risk of malignancy
  - Branch Duct: ~25%
  - Main Duct: ~70%

Tanaka et al. Pancreatology 2006

What about clinical genetic testing for asymptomatic individuals?
History, physical exam, family history, genetic testing

Average risk:
- <1 family member with PC >55 years old

History, physical exam, family history, genetic testing

Moderate risk:
- ≥ 2 first-, second-, or third-degree with PC
- <1 first-degree with PC <55 years old
- Not meeting criteria for high risk

History, physical exam, family history, genetic testing

High risk:
- ≥ 3 first-, second-, or third-degree with PC
- ≥ 2 first-degree with PC
- >1 first-and 1 second-degree with PC; 1 at < 55 years old
- Genetic syndrome with PC

Basic blood tests, additional testing if indicated

EUS or MRI CA 19-9 and OGTT

EUS and MRI CA 19-9 and OGTT

Any abnormal testing:
EUS
(if not already done) (+/- FNA and ERCP)

Pre-Genetic Testing Screening Stratification

Post-Genetic Testing Screening Stratification

BRCA2 Mutation
BRCA1 Mutation
No Mutation
Incorporating Genetic Testing for Pancreatic Cancer into Clinical Practice

Three-generation pedigree
- Personal and family history
- Genetic counselors

Limited use previously for pancreatic cancer
- Exception: BRCA1/2 gene mutations

Since 2013
- Technology advances
- $$
- Patent issues
- VUS vs pathologic mutation
  https://www.supremecourt.gov/opinions/12pdf/12-398_1b7d.pdf

Summary of Consensus Statements for High Risk Individuals – Who to Screen?

- 3 or more affected blood relatives, with at least one affected FDR
- 2 affected family members, with at least one affected FDR
- All Peutz-Jeghers
- P16 carriers with one affected FDR
- BRCA2 carriers with one affected FDR
- BRCA2 carriers with 2 affected family members
- PALB2 carriers with 1 affected FDR
- Mismatch repair gene mutations (Lynch syndrome) with one affected FDR

Summary of Consensus Statements for HRIs – How to Screen?

▶ Initial screening should include:
  – EUS (87.3%), MRI/MRCP (73.5%), CT (26.5%), abd US (14.3%), ERCP (2%)

▶ When previous screening did not detect an abnormality that met criteria for shortening of the interval or surgical resection, follow-up screening should include:
  – EUS (79.6%), MRI/MRCP (69.4%), CT (22.4%), abd US (4.1%), ERCP (2%)

Summary of Consensus Statements for HRIs – Targets of Screening?

▶ Resectable carcinoma is a potential target for early detection and treatment

▶ Detection and treatment of multifocal PanIN-3 should be considered a success of a screening/surveillance program

▶ Detection and treatment of IPMNs with high-grade dysplasia should be considered a success of a screening/surveillance program

▶ Detection and treatment of invasive cancer – T1N0M0 should be considered a success of a screening/surveillance program
Cancer Screening Definitions

Screening
• Testing healthy, asymptomatic people in the general population

Surveillance
• Testing healthy, asymptomatic people in a high-risk population

Diagnostic Testing
• Testing when people have symptoms

Pancreas Cancer Testing Options

Endoscopic Ultrasound (EUS)
• Requires sedation
• Invasive procedure
• Ability to biopsy abnormalities

Magnetic Resonance Imaging (MRI)
• Non-invasive
• Unable to biopsy
• Patient tolerance
PATIENT PRESENTATION - 1

- Sex: Male
- Age: 61
- Ashkenazi Jewish: Yes
- Cigarette Use: Discontinued (minimal use in past)
- Alcohol Use: Occasional
- Diabetes Mellitus: No
- Pancreatitis: No
- Cancer Hx: None
- Past Medical Hx: None

- Physical Exam
  - Normal

- Laboratory Exam
  - Normal, except CA 19-9

FAMILY HISTORY

Prostate (70s) Pancreas (70s) d. 78

Patient 61 years old

Prostate (40) d. 46

27 years old 31 years old 33 years old
RECOMMENDATIONS

• EUS
• MRI
• Genetic testing

Endoscopic Ultrasound
GENETIC TESTING

Prostate (70s) Pancreas (70s) d. 78

Patient 1

Pancreas (40) d. 46

= BRCA2 6174delAG

27 years old 31 years old 33 years old

SURGICAL INTERVENTION

• Total pancreatectomy
PATHOLOGY RESULTS

- Pancreatic adenocarcinoma with adjacent IPMN and multifocal PanIN2

GENETIC TESTING

= BRCA2 6174delAG

- Prostate (70s) Pancreas (70s) d. 78

Patient 1

- Pancreas (40) d. 46

- BRCA2 neg 31 years old
- BRCA2 neg 33 years old

27 years old
PATIENT CASE #2

PATIENT PRESENTATION - 2

- Sex: Male
- Age: 73
- Ashkenazi Jewish: Yes
- Cigarette Use: 2nd hand smoke
- Alcohol Use: Occasional
- Diabetes Mellitus: Yes
- Pancreatitis: No
- Cancer History: None
- Past Medical History: hypertension, cholesterol, ulcerative colitis

- Physical Exam
  - Normal

- Laboratory Exam
  - Normal
FAMILY HISTORY

RECOMMENDATIONS

- EUS
- MRI
- Genetic testing
Endoscopic Ultrasound

CEA was 121.47 NG/ML and cytology from the FNA revealed rare atypical glandular cells with dysplastic changes
Magnetic Resonance Imaging

Cystic lesion in the pancreatic neck/body and is oblong shaped, measuring 3.4 x 1.3 x 1.1 cm.
**SURGICAL INTERVENTION**

- Distal pancreatectomy

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**PATHOLOGY RESULTS**

- Two *intraductal papillary mucinous neoplasms* (IPMNs), predominantly involving branch ducts.

- The IPMN is lined by gastric foveolar type epithelium with up to *severe dysplasia*.

- No invasive carcinoma seen.
PATIENT CASE #3

54 yo niece:
Imaging: 5 mm IPMN, few other small 2-3 mm cysts
Colonoscopy: tubular adenoma ascending colon

55 yo niece:
Imaging: normal pancreas
Genetic testing: too expensive
Colonoscopy: 2011 4 tubular adenomas, 2014 2 tubular adenomas
Patient #3
INITIAL CONSULT

- Sex: Male
- Age: 65
- Ashkenazi Jewish: Yes
- Cigarette Use: Discontinued (smoked for 36 years; 1.5 ppd)
- Alcohol Use: 2-3 vodka/week
- Diabetes Mellitus: Yes (64 years old)
- Pancreatitis: No
- Cancer Hx: None
- Past Medical Hx:
  - GERD (35 years old)
  - Colon polyps (64 years old)
  - Barrett’s Esophagus (64 years old)

Physical Exam
Normal

FAMILY HISTORY
Patient #3

RECOMMENDATIONS

- Genetic testing
  - Test sister first

GENETIC TESTING

PATIENT 3

= BRCA2 6174delAG
Patient #3

RECOMMENDATIONS

- Laboratories (normal)
- EUS (secretin protocol)
- MRI (secretin protocol)

MRI and EUS

= Cystic changes
Irregular Ducts
GENETIC TESTING

Patient #3
SURGICAL INTERVENTION
(Sister)

- Prophylactic TAH-BSO
Patient #3

PATHOLOGY RESULTS
(Sister)

• Ovarian adenocarcinoma

Summary

• Several genetic syndromes contribute to the risk of pancreatic cancer

• Smoking is the largest identifiable and modifiable risk factor

• Pre-cancerous lesions can be identified before the development of pancreatic cancer

• Genetic counseling and testing is an important part of pancreatic cancer screening, prevention and management

• More work is required to understand the genetics of pancreatic cancer
Thank you for your participation.

If you have questions, please contact Patient Central at (877) 272-6226 or e-mail patientcentral@pancan.org.

www.pancan.org