Overview

- Background: what are genes?
- Risk factors for pancreatic cancer
- What does this mean for family members?
Genetics - Human Cell Formation

Oocyte
22 autosomal chromosomes
2 X chromosome

Zygote
46 chromosomes

Sperm
22 autosomal chromosomes
1 Y chromosome
1 X chromosome

MITOSIS

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)

Germline Mutation (Inherited Disease)

One copy mutated in every cell (born with 1st hit)

Second copy mutated in cell (2nd hit needed to develop disease)
**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

**Smoking...**

is the major known risk factor for this cancer

- associated with ~ 30% of all cases
- results in **accelerated** tumor progression
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></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 Factors</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic Pancreatitis</td>
<td>13</td>
</tr>
<tr>
<td>Red Meat (men)</td>
<td>1.29</td>
</tr>
<tr>
<td>Processed Meat (men and women)</td>
<td>1.19</td>
</tr>
<tr>
<td>Obesity (BMI&gt;40)</td>
<td>1.49 (men), 2.76 (women)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.8-2.0</td>
</tr>
<tr>
<td>Alcohol (≥ 3 drinks/day)</td>
<td>1.22</td>
</tr>
<tr>
<td>Cholecystectomy</td>
<td>1.23</td>
</tr>
<tr>
<td>Partial Gastrectomy</td>
<td>1.54</td>
</tr>
</tbody>
</table>

## Inherited Syndromes Predisposing to Pancreatic Cancer

<table>
<thead>
<tr>
<th>Gene</th>
<th>Increased Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast + Ovarian Cancer</td>
<td>BRCA1, BRCA2</td>
</tr>
<tr>
<td>FAMMM</td>
<td>CDKN2A/p16</td>
</tr>
<tr>
<td>Peutz-Jeghers Syndrome</td>
<td>STK11/LKB1</td>
</tr>
<tr>
<td>Lynch Syndrome</td>
<td>MLH1, MSH2, MSH6, PMS2, EPCAM</td>
</tr>
<tr>
<td>Hereditary pancreatitis</td>
<td>PRSS1/SPINK1</td>
</tr>
<tr>
<td>Other</td>
<td>PALB2, ATM</td>
</tr>
</tbody>
</table>

### Familial Pancreatic Cancer

- Families with at least two first-degree relatives who have been diagnosed with pancreatic cancer
Breast and Ovarian Cancer Syndrome (BRCA)

- Breast Cancer
- Ovarian Cancer
- Prostate Cancer
- Pancreas Cancer
- Germline Mutation: BRCA 2, BRCA 1

Familial Atypical Multiple Mole Melanoma Syndrome (FAMMM)

- Multiple
  - Nevi
  - Dysplastic Nevi
  - Melanomas
- Pancreas Cancer
- Head and Neck: Squamous Cell Cancer
- Germline Mutation: CDKN2A (p16)

Vinarsky et al., Head and Neck 2009
Peutz-Jeghers Syndrome

- Hamartomatous GI Polyps
- Mucocutaneous Pigmentation
- Lifetime Pancreas Cancer Risk ~36%
- Germline Mutation: STK11

Hereditary Pancreatitis

- Severe episodes of pancreatitis beginning at a young age (14 yrs)
- ~40% will develop pancreas cancer
- Prophylactic total pancreatectomy is considered as pancreas is non-functional
- Germline mutation: PRSS1 (cationic trypsinogen gene) / SPINK1
Lynch Syndrome (Hereditary Non-Polyposis Colon Cancer Syndrome)

- Colon 63%
- Endometrium 8% (28% Women)
- Gastric 6%
- Pancreaticobiliary 4%
- Genitourinary 2%
- Ovary 1% (3% Women)
- Small Bowel 1%
- Brain (glioblastoma)
- Skin (sebaceous)

Can we prevent patients from developing pancreatic cancer?

(Or catch it at a treatable phase?)
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

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
Pancreas Cancer Screening Options

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

Magnetic Resonance Imaging (MRI)
- Non-invasive
- Unable to biopsy
- Patient tolerance

Can we incorporate genetic testing into risk stratification?

High-risk program
- Unaffected individuals with family history of cancers
- Affected individuals with family history of cancers, young age onset of cancer

Family History Is Important!
- 3 generation family tree
- Asked questions about cancers in the family

Incorporated family history and genetic testing into risk stratification

Lucas et al. Cancer 2014
Medical History
Physical Examination
Family History

Average Risk:
• 1 affected family member >55 years
• No affected family members

Moderate Risk:
• ≥2 first-, second-, or third-degree affected relatives
• 1 affected first-degree relative <55
• Not meeting criteria for average- or high-risk

High Risk:
• ≥3 first-, second-, or third-degree affected relatives
• ≥2 affected first-degree relatives
• Genetic syndrome associated with pancreatic cancer

n = 17
n = 12
n = 1
n = 3
n = 1
n = 4
n = 3
n = 1

Lucas et al. Cancer 2014
Can we incorporate genetic testing into risk stratification?

37 unaffected individuals
  • 7/37 (18.9%) had gene mutations

32 affected individuals
  • 7/32 (21.9%) had gene mutations

*Large number of Ashkenazi Jewish individuals

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

Patient
67 years old

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

Pancreas (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

PATIENT CASE #2

= BRCA2 6174delAG

Patient 1

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

Pancreas (40) d. 46

BRCA2 neg

BRCA2 neg

27 years old

31 years old

33 years old
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

Patient

Pancreas (78)

Pancreas (68)

Breast and Kidney

4 41

d. 87  d. 70
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
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
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

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FAMILY HISTORY

- Breast (45)
- Melanoma (59)
- Lung (60s) d. 60s
- Breast (40) d. 40
- Leukemia (60s) d. 50s
- Larynx (80s) d. 80s
- Pancreas (66) d. 69
- Diabetes (90s) d. 96
- Lung (50s) d. 59
- Prostate d. 55
- Kidney (70s) d. 80s
- Patient 64 years old
Patient #3

RECOMMENDATIONS

• Genetic testing
  • Test sister first

GENETIC TESTING
Patient #3

RECOMMENDATIONS

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

MRI and EUS = Cystic changes
Irregular Ducts
GENETIC TESTING

Patient #2

Breast (45)
Melanoma (59)
Pancreas (66)
d. 69

Leukemia (60s)
d. 60s

Larynx (80s)

Diabetes d. 50s

Diabetes (p10) d. 96

Lung (50s)
d. 59

Kidney (70s)
d. 80s

Prostate d. 55

IPMN

Patient #3

SURGICAL INTERVENTION
(Sister)

- Prophylactic hysterectomy and oophorectomy
Patient #3
PATHOLOGY RESULTS
(Sister)

- Ovarian papillary serous 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!

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