Genetics of Pancreatic Cancer

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Topics

- Is family history a risk factor for pancreatic cancer?
- Why we study families with pancreatic cancer
- New discoveries in genetics of pancreatic cancer: What does it all mean?
Pancreatic Cancer: Risk Factors

Avoidable Risk Factors

Proportion of Cancer Deaths Linked to Avoidable Risk Factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Proportion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tobacco</td>
<td>29–31 percent</td>
</tr>
<tr>
<td>Diet</td>
<td>20–50 percent</td>
</tr>
<tr>
<td>Infections:</td>
<td>10–20 percent</td>
</tr>
<tr>
<td>- bacteria, viruses</td>
<td></td>
</tr>
<tr>
<td>Ionizing and UV light</td>
<td>5–7 percent</td>
</tr>
<tr>
<td>Occupation</td>
<td>2–4 percent</td>
</tr>
<tr>
<td>Pollution:</td>
<td>1–5 percent</td>
</tr>
<tr>
<td>- air, water, food</td>
<td></td>
</tr>
</tbody>
</table>


Pancreatic Cancer: Risk Factors

- **Smoking**: Cigarette smokers are two or three times more likely than nonsmokers to develop pancreatic cancer.
- **Age**: Most pancreatic cancers occur in people over the age of 60.
- **Dietary**: Diets low in fruits and vegetables can increase risk of developing pancreatic cancer.
- **Being male**: More men than women are diagnosed with pancreatic cancer.
- **Being African American**: African Americans are more likely than Asians, Hispanics, or whites to get pancreatic cancer.
- **Family history**: The risk for developing pancreatic cancer triples if a person's mother, father, sister, or brother had the disease.

Genes and/or Shared environment?
10% of pancreatic cancer patients have a first degree relative with pancreatic cancer

- The same proportion, 10%, is seen for other major cancers (breast, colon, prostate, lung)
- Susceptibility genes have been identified for some subsets of these cancers
- Similarly, pancreatic cancer may have susceptibility genes

Genetics and Your Family History

- Is family history a risk factor for pancreatic cancer?
- Why we study families with pancreatic cancer
- New discoveries in genetics of pancreatic cancer: What does it all mean?
In the clinic, knowing about your family history is one way to:

- Identify who is at risk
- Refer for genetic risk counseling and possibly genetic testing
- Recommend who needs checkups more often

Family-based Research

- Patient provides family history information: at least three generations is helpful
- Family members can be invited into the study
- Even deceased relatives are important!
- DNA from blood, combined with the family history structure, helps to “connect the dots”
Three-Generation Family Tree

1. First degree relatives
2. Second degree
3. Third degree

German/Polish

Pancreas Ca, dx 62
d. 70

Pancreas Ca, dx 62

Pancreas Ca, dx 54

English/Irish

d. 80
d. 85

Diabetes, dx 45
59

Pancreas Ca, dx 54

Dx 58
NS

Dx 79
NS

Dx 87

Working definition:
Families in which at least two first degree relatives have been diagnosed with pancreatic cancer.

Familial Pancreatic Cancer

Mayo 627

Dx 79
NS

Dx 58
NS

Dx 58
S

Dx 79
NS

Dx unk
NS

NS = Nonsmoker
S  = Smoker

Hruban and Petersen, 1997
Family history of some cancers is associated with younger age of onset of pc


Hereditary Disorders and Genes Associated with Pancreas Cancer

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hereditary Pancreatitis</td>
<td>PRSSI (Cationic trypsinogen)</td>
</tr>
<tr>
<td>Familial Atypical Multiple Mole Melanoma Syndrome (FAMMM)</td>
<td>P16 (CDKN2A)</td>
</tr>
<tr>
<td>BRCA2</td>
<td>BRCA2</td>
</tr>
<tr>
<td>Hereditary Colorectal Cancers</td>
<td>APC, MSH2, MLH1</td>
</tr>
<tr>
<td>Peutz-Jeghers Syndrome</td>
<td>STK11/LKB1</td>
</tr>
<tr>
<td>Fanconi Anemia genes</td>
<td>FANCC, FANCG</td>
</tr>
<tr>
<td>Syndrome</td>
<td>Gene(s)</td>
</tr>
<tr>
<td>----------------------------------------------</td>
<td>----------------</td>
</tr>
<tr>
<td>Hereditary breast and ovarian cancer</td>
<td>BRCA1</td>
</tr>
<tr>
<td></td>
<td>BRCA2</td>
</tr>
<tr>
<td>Familial atypical mole and melanoma</td>
<td>CDKN2A</td>
</tr>
<tr>
<td>Hereditary pancreatitis</td>
<td>PRSS1</td>
</tr>
<tr>
<td>Hereditary nonpolyposis colorectal cancer</td>
<td>MLH1</td>
</tr>
<tr>
<td>(Lynch syndrome)</td>
<td>MSH2</td>
</tr>
<tr>
<td></td>
<td>MSH6</td>
</tr>
<tr>
<td></td>
<td>PMS2</td>
</tr>
<tr>
<td></td>
<td>EPCAM</td>
</tr>
<tr>
<td>Peutz Jeghers Syndrome</td>
<td>STK11</td>
</tr>
</tbody>
</table>

SIR indicates standardized incidence ratio; RR, relative risk.


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**Genetics and Your Family History**

- Is family history a risk factor for pancreatic cancer?
- Why we study families with pancreatic cancer
- New discoveries in genetics of pancreatic cancer: What does it all mean?
Who is at risk for pancreatic cancer?

Genetics provides a clue...
Chromosomes, DNA, and Genes

Cell
Nucleus
Chromosomes
Gene
Protein

How do geneticists study cancer?

NORMAL

CANCER
Is There A Genetic Connection Between Melanoma and Pancreatic Cancer?

• **Methods:**
  - 1,537 pancreatic adenocarcinoma patients
  - Mutation analysis of CDKN2A gene

• **Results:**
  - 9 (0.6%) carried germline mutations in CDKN2A
  - Carriers were more likely to have:
    - Family history of pancreatic cancer (p= 0.003); carrier rate 3.3%
    - Family history of melanoma (p= 0.03); carrier rate 5.3%
    - Personal history of melanoma (p= 0.01)

Germline Mutations in CDKN2A Among 1,537 Unselected Unrelated Pancreatic Cancer Patients

<table>
<thead>
<tr>
<th>Pt</th>
<th>Sex/ Age</th>
<th>Family history of pancreatic cancer</th>
<th>Family history of melanoma</th>
<th>Personal history of melanoma</th>
<th>Exon</th>
<th>Protein</th>
<th>Genetic change</th>
<th>Protein change</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F 61</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>1A</td>
<td>p16</td>
<td>-34G&gt;T</td>
<td>N/A</td>
<td>Initiation codon</td>
</tr>
<tr>
<td>2</td>
<td>M 74</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>1A</td>
<td>p16</td>
<td>47T&gt;G</td>
<td>L16+R</td>
<td>AAC p16</td>
</tr>
<tr>
<td>3</td>
<td>F 65</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>1A</td>
<td>p16</td>
<td>71G&gt;C</td>
<td>R24&gt;P</td>
<td>AAC p16</td>
</tr>
<tr>
<td>4</td>
<td>F 58</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>2</td>
<td>p16</td>
<td>192G&gt;C</td>
<td>L64-L</td>
<td>AAC p14ARF</td>
</tr>
<tr>
<td>5</td>
<td>M 66</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>2</td>
<td>p16</td>
<td>238-251 del 404-417 del</td>
<td>R105fs P135fs</td>
<td>makes a hybrid p16/p14 protein after frameshift</td>
</tr>
<tr>
<td>6</td>
<td>M 65</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>2</td>
<td>p16</td>
<td>283 del 449 del</td>
<td>V95fs G150fs</td>
<td>frameshift</td>
</tr>
<tr>
<td>7</td>
<td>M 45</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>2</td>
<td>p16</td>
<td>318G&gt;A</td>
<td>V106&gt;G A162&gt;T</td>
<td>AAC p14ARF</td>
</tr>
<tr>
<td>8</td>
<td>M 67</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>2</td>
<td>p16</td>
<td>457G&gt;T</td>
<td>D153fs</td>
<td>Affects splicing in p16/p14ARF</td>
</tr>
<tr>
<td>9</td>
<td>M 57</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>2</td>
<td>p16</td>
<td>457G&gt;T</td>
<td>D153fs</td>
<td>Affects splicing in p16/p14ARF</td>
</tr>
</tbody>
</table>

* M= male, F=female, age (years) at diagnosis of pancreatic cancer, AAC = amino acid change


Genetic susceptibility to pancreatic cancer

Sporadic ~85%
Young onset (<60) sporadic ~20%
Familial pancreatic cancer ~10%
Known cancer genes (~5%)
PanScan - a GWAS

PanScan 1
- 2000 pairs

PanScan 2
- 3,850 pairs

GWAS Results: ABO Blood Group
**ABO Blood Groups and Cancer**

- **Gastric Cancer** - well established
  - Increased risk for blood group A
- **Pancreatic Cancer** - Possibly risk with ABO

<table>
<thead>
<tr>
<th>Disease</th>
<th>ABO allele</th>
<th>↑ Risk</th>
<th>$\chi^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duodenal ulcer</td>
<td>O</td>
<td>1.40</td>
<td>200</td>
</tr>
<tr>
<td>Stomach cancer</td>
<td>A</td>
<td>1.25</td>
<td>49</td>
</tr>
<tr>
<td>Stomach ulcer</td>
<td>O</td>
<td>1.82</td>
<td>37</td>
</tr>
<tr>
<td>Pernicious anemia</td>
<td>A</td>
<td>1.50</td>
<td>17</td>
</tr>
<tr>
<td>Pancreas cancer</td>
<td>A</td>
<td>1.27</td>
<td>8</td>
</tr>
</tbody>
</table>

Summary of GWAS Main Findings

- **Chromosome 13q22.1** - 2 SNPs: rs9543325 ($P=3.27 \times 10^{-11}$; per allele odds ratio, OR 1.26, 95% CI=1.18-1.35) and rs9564966 ($P=5.86 \times 10^{-8}$; per allele OR 1.21, 95% CI=1.13-1.30) map to a non-genic region.

- **Chromosome 1q32.1** – 5 SNPs map to NR5A2 [Nuclear receptor subfamily 5, group A, member 2]; the strongest signal was rs3790844 ($P=2.45 \times 10^{-10}$; per allele OR 0.77, 95% CI=0.71-0.84).

- **Chromosome 5p15.33** – 1 SNP maps to CLPTM1L-TERT; rs401681 ($P=3.66 \times 10^{-7}$; per allele OR 1.19, 95% CI=1.11-1.27); gene is associated with multiple cancers.
Genetic susceptibility is heterogeneous

Genetic polymorphisms (ABO) and GxE interactions

Sporadic ~70%

Young onset (<60) sporadic ~20%

Familial pancreatic cancer <10%

Known genetic syndromes ~3%

How do we find new genes that confer susceptibility to familial PC?

Pancreatic Cancer Genetic Epidemiology (PACGENE) Consortium

Funded by NCI grant R01 CA97075

- Prospective accrual of FPC kindreds
- Whole genome scan
- Linkage analysis

To date:
- 36,546 screened
- 2,853 with +FHx enrolled (19,075 mbrs)
- 6,594 family enrolled

New familial pancreatic cancer gene: PALB2

- 96 FPC patients screened for PALB2 mutations (90 Caucasian)
- Average onset age: 66.7 years (in non PALB2 kindreds, 65.3)
- Previous published study: no mutations in 1,084 normal controls.

ATM gene mutations predispose some families to pancreatic cancer

- Ataxia telangiectasia mutated (ATM) gene, a serine/threonine kinase
- Coordinates DNA double-strand break repair
- Causes AT (autosomal-recessive)
- Associated with an increased risk of cancer, particularly lymphoma and leukemia


Selected subjects enrolled in familial PC registries of PACGENE

Whole Genome sequencing

Whole exome sequencing

10 subjects from 6 families

22 subjects from 10 families

Filter/Candidates

ATM


Functional ATM variants

Table 2. Summary of heterozygous deleterious ATM variants found in patients with pancreatic cancer

<table>
<thead>
<tr>
<th>Variant</th>
<th>Pancreatic cancer type</th>
<th>Nucleotide (genomic)(^a)</th>
<th>Nucleotide (cDNA)(^b)</th>
<th>Amino acid (protein)(^b)</th>
<th>Type</th>
<th>Number of affected individuals sequenced</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Familial(^d)</td>
<td>g.chr1:1107711896A&gt;T</td>
<td>c.8266A&gt;T</td>
<td>p.R2756X</td>
<td>Nonsense</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>Familial(^d)</td>
<td>g.chr1:1107603810G&gt;A</td>
<td>c.170G&gt;A</td>
<td>p.W52X</td>
<td>Nonsense</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>Familial(^d)</td>
<td>g.chr1:110764719G&gt;T</td>
<td>c.3214G&gt;T</td>
<td>p.E1072X</td>
<td>Nonsense</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>Familial(^d)</td>
<td>g.chr1:1107601848G&gt;A</td>
<td>c.6095G&gt;A</td>
<td>p.R2032K</td>
<td>Missense</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>Familial(^d)</td>
<td>g.chr1:110769309G&gt;T</td>
<td>IVS41-1G&gt;T</td>
<td>sp</td>
<td>Splice site</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td>Familial(^d)</td>
<td>g.chr1:110760218delG</td>
<td>c.3801delG</td>
<td>fs</td>
<td>INDEL</td>
<td>1</td>
</tr>
</tbody>
</table>

- 4/166 (2.4%) carried deleterious ATM mutations. 0/190 controls. P=0.046
- For probands\(\geq 3\) in family: 4.6%
- ATM contributes to the genetic heterogeneity of familial pancreatic cancer

Where are genes for inherited pancreatic cancer?

Others:
- FANCC (9q)
- CFTR (7q)
- PJS (19p)
- MMR (2p, 3p)
- APC (5q)
- PALLD (4q)

At least 3 other genomic regions involved

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Genetics and Your Family History

- Is family history a risk factor for pancreatic cancer?
- What does it all mean?
- New discoveries in genetics of pancreatic cancer
Sporadic ~70%

Known genetic syndromes ~3%

Hereditary pancreatitis, FAMMM, etc.

Familial pancreatic cancer <10%

BRCA2, p16, PALB2, etc.

Young onset (<60) sporadic ~20%
CFTR

Genetic polymorphisms and GxE interactions
(DNA Repair, ABO, CLPTM1L-TERT, NR5A)

Genetic susceptibility to pancreatic cancer

Five PACGENE sites contributed germline DNA samples from 518 unrelated cases affected with pancreatic adenocarcinoma.

Tested individuals were affected with pancreatic cancer (PC) and all came from kindreds with 2+ PC.

160 individuals were from kindreds that met criteria for FPC; the remainder were Non-FPC.

Testing performed on BRCA1, BRCA2 (including analysis of deletions and rearrangements), CDKN2A, and PALB2.

Mutation frequencies in subset of patients who had had all 4 genes tested

---

### Pancreatic Cancer Cases Tested for All Four Genes

<table>
<thead>
<tr>
<th>Gene</th>
<th>FPC (N=154)</th>
<th>Non-FPC (N=336)</th>
<th>FPC (N=154)</th>
<th>Non-FPC (N=336)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1</td>
<td>2.0</td>
<td>0.6</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>BRCA2</td>
<td>3.3</td>
<td>3.0</td>
<td>0</td>
<td>0.9</td>
</tr>
<tr>
<td>CDKN2A</td>
<td>2.6</td>
<td>0.9</td>
<td>5.2</td>
<td>1.2</td>
</tr>
<tr>
<td>PALB2</td>
<td>0.7</td>
<td>0.3</td>
<td>0</td>
<td>2.1</td>
</tr>
<tr>
<td>Total (probability of a mutation in any of the four genes)</td>
<td><strong>7.8</strong></td>
<td><strong>4.8</strong></td>
<td><strong>5.2</strong></td>
<td><strong>4.2</strong></td>
</tr>
</tbody>
</table>

FPC: Familial Pancreatic Cancer (2+ affected first degree relatives in kindred)

Non-FPC: Two affected blood relatives in kindred, not first degree
BRCA1 and BRCA2 germline mutations are frequently demonstrated in both high-risk pancreatic cancer screening and pancreatic cancer cohorts. Cancer, April 2014 epub ahead of print.

- High risk genetics/prevention setting for PC
- N=37 high risk unaffected individuals
  - 7 (18.9%) positive
- N=32 patients affected with PC
  - 7 (21.9%) positive
- High proportion of Ashkenazi Jewish (AJ) population; recommended that BRCA1/2 testing should be considered in AJ PC patients even with no family history of breast or ovarian cancer

Figure 2. Risk stratification of the unaffected pancreatic ductal adenocarcinoma screening cohort who underwent genetic testing at the study institution is shown. Risk stratification before genetic testing identified 20 patients at average risk, 13 patients at moderate risk, and 4 patients at high risk. Of the 4 high-risk patients, 3 (75%) were BRCA2 carriers. One moderate-risk patient was found to carry a BRCA2 mutation. A total of 3 of 20 average-risk patients (15%) were found to have BRCA1 mutations. All BRCA1/2 mutation carriers were reclassified into a high-risk screening protocol.
Conclusions

- Research has shown that there are individuals at increased risk for developing pancreatic cancer
- Genetic susceptibility is heterogeneous
- Limited genetic testing is available
- Our work continues to better understand the genetics and to help patients

Collaborators & Acknowledgments

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