PANCREATIC CANCER RESEARCH

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Early detection → Prevention → Novel treatments
PANCREATIC CANCER RESEARCH

Early detection

Kras mutation and chronic pancreatitis

Chronic Pancreatitis

Source: Nat Rev Cancer 2010 Nature Publishing Group
Pancreatic cancer Early Detection
What are the limitations?

- There are no available methods (imaging, biomarkers) to detect preneoplastic lesions (PanINs).
- It is difficult to differentiate pancreatic cancer from chronic pancreatitis.
- The incidence of pancreatic cancer in the general population is low (1:10,000)

Window of opportunity for Early detection

- $T_1$: (average of 11.7 ± 3.1 years)
- $T_2$: (average of 6.8 ± 3.4 years)
- $T_3$: (average of 2.7 ± 1.2 years)

Index lesion

Lung
Liver
Liver
Risk Factors

- Age
- Tobacco
- New Onset Diabetes
- Chronic Pancreatitis
- Genetic Susceptibility

Risk Assessment

<table>
<thead>
<tr>
<th>HEREDITARY</th>
<th>Risk Factor</th>
<th>RR/OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family History</td>
<td>1 FDR (pooled analysis)</td>
<td>1.76</td>
</tr>
<tr>
<td></td>
<td>Pair of FDR PC (Familial PC)</td>
<td>6.79</td>
</tr>
<tr>
<td></td>
<td>Pair of FDR PC (Familial PC) with a young onset case (&lt;50)</td>
<td>9.31</td>
</tr>
<tr>
<td></td>
<td>Three FDRs PC (Familial PC)</td>
<td>32</td>
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<tr>
<td>Mutations</td>
<td>BRCA2 carrier</td>
<td>3.5</td>
</tr>
<tr>
<td></td>
<td>STK11/LKB1 carrier</td>
<td>132</td>
</tr>
<tr>
<td></td>
<td>PALB2 carrier</td>
<td>2.2</td>
</tr>
<tr>
<td></td>
<td>BRCA1 carrier</td>
<td>2.2</td>
</tr>
<tr>
<td></td>
<td>PRSS1 (Hereditary pancreatitis)</td>
<td>53</td>
</tr>
<tr>
<td></td>
<td>CDKN2A</td>
<td>13-38</td>
</tr>
<tr>
<td></td>
<td>HNPCC</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>ABO</td>
<td>1.2</td>
</tr>
<tr>
<td></td>
<td>CFTR</td>
<td>1.4</td>
</tr>
<tr>
<td></td>
<td>13q22.1</td>
<td>1.26</td>
</tr>
<tr>
<td></td>
<td>MMR def</td>
<td>3.4-8</td>
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<tr>
<td></td>
<td>Li Fraumeni patients</td>
<td>7</td>
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<table>
<thead>
<tr>
<th>SPONTANEOUS</th>
<th>Risk Factor</th>
<th>RR/OR</th>
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<tbody>
<tr>
<td>Active smoking</td>
<td>1.74</td>
<td></td>
</tr>
<tr>
<td>Type II Diabetes</td>
<td>1.8</td>
<td></td>
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<tr>
<td>New onset Diabetes</td>
<td>2.9</td>
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</tr>
<tr>
<td>Type II Diabetes (+15 yrs)</td>
<td>1.4</td>
<td></td>
</tr>
<tr>
<td>BMI&gt;35</td>
<td>1.55</td>
<td></td>
</tr>
<tr>
<td>Heavy alcohol consumption (+6 drinks/day)</td>
<td>1.46</td>
<td></td>
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</table>
Pancreatic Cancer High Risk Clinic
MD Anderson Cancer Center

1) RISK ASSESSMENT

2) SCREENING
For patients with high risk:
* Blood work: Biomarkers and glucose
* State-of-the-Art imaging: Pancreas specialized-MRI
* Endoscopic Ultrasound with Elastography

3) BIOSPECIMENS COLLECTION (blood and urine)
Platform for discovery/ validation of:
* Serum/urine biomarkers (tumor circulating cells, exosomes, autoantibodies)
* Novel molecular imaging methods for advanced PanINs detection.

DEVELOPMENT OF PANCREATIC CANCER- HIGH RISK CLINIC
New discoveries for Early Detection

Glypican-1 identifies cancer exosomes and detects early pancreatic cancer

Sonia A. Melo, Linda B. Luecke, Christoph Kahlert, Agustin F. Fernandez, Seth T. Gammon, Judith Kaye, Valerie S. LeBlue, Elizabeth A. Mittendorf, Juergen Weitz, Nuh Rahbari, Christoph Reissfelder, Christian Pilarsky, Mario F. Fraga, David Pihnica-Worms & Raghu Kalluri

Affiliations | Contributions | Corresponding author
Use of aspirin for pancreatic cancer prevention

- Regular use of aspirin was associated with reduced risk of pancreatic cancer.
- The effect was found only after 5 years of use.

Use of metformin for pancreatic cancer prevention

- Use of metformin was associated with a significant lower risk of pancreatic cancer in several studies.
Use of Vitamin D for Pancreatic Cancer Prevention

- Higher intakes of vitamin D have been associated with lower risk for pancreatic cancer.

Targets for cancer therapy

Chemotherapy

MM-398

- Liposomal form of Irinotecan
- Improves delivery of drug to attach tumor cells.
- Recently approved for pancreatic cancer.
- Given in combination with 5-Fluorouracil.
**Targets for cancer therapy**

Drugs that target Stroma

- **PEGPH20**
  - PEGylated form of recombinant human hyaluronidase
  - Targets the tumour stroma
  - Improves delivery of other drugs

*Hingorani, Br J. Cancer, 2013*
Targets for cancer therapy

Drugs that target the immune system

IMMUNOTHERAPY
The next generation of cancer treatment

Monoclonal Antibodies
Antibodies can be produced that target and destroy cancer cells.

Cancer Vaccines
Listeria vaccines: Immune system boosting

Nonspecific Immunotherapies
Immunomodulatory agents Checkpoint Inhibitors
**Checkpoint Inhibitors**

- Patients whose tumors were unable to repair DNA damage, were more likely to respond to the checkpoint inhibitors than those with tumors proficient in DNA repair.

- The worse the tumor cells were at repairing DNA, the better the patients fared on anti-PD-1 therapy!

- The higher the number of mutations in a tumor, the better the patients responded to anti-PD-1 therapy!
**RECENT DISCOVERIES**

* Role of specific type of immune cells in pancreatic cancer initiation and progression

* Novel targets for pancreatic cancer immunoprevention

**CURRENT INTERESTS**

* Role of the immune system in pancreatic cancer initiation and development.

* Targeting specific immune pathways in pancreatic cancer patients.

* Understand the role of the gut bacteria in pancreatic cancer initiation, progression and response to therapies.
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