BRCA and Pancreatic Cancer

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Head, Pancreatic Tumor Section
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Objectives

• What is the pancreas?
• What is pancreatic cancer?
• What are the factors that affect pancreatic cancer risk?
  • Risk for pancreatic cancer in BRCA carriers.
• How can we beat pancreatic cancer in BRCA carriers?
  • Research update in early detection strategies.
  • Research update in chemoprevention.
What is the pancreas?
Exocrine and Endocrine Pancreas Secretion

- Acini
- Islet
- Stellate Cell (Vitamin A Containing Cell)

**ENZYMES**

- Nutrients Digestion and Absorption
- Insulin and Hormone Nutrients Metabolism
- Diabetes Mellitus Metabolic Syndrome
- Pancreatitis
- Pancreatic Cancer

Source: AGA Teaching Slide, Modified by VLW Go
### 10 Leading Cancer Types for Estimated Deaths by Sex in the US 2008

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>90,810</td>
<td>71,030</td>
</tr>
<tr>
<td>Prostate</td>
<td>28,660</td>
<td>40,480</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>24,260</td>
<td>25,700</td>
</tr>
<tr>
<td>Pancreas</td>
<td>17,500</td>
<td>16,790</td>
</tr>
<tr>
<td>Leukemia</td>
<td>12,460</td>
<td>9,250</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>12,570</td>
<td>9,370</td>
</tr>
<tr>
<td>Esophagus</td>
<td>11,250</td>
<td>7,470</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>9,950</td>
<td>5,650</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>9,790</td>
<td>5,840</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>8,100</td>
<td>3,500</td>
</tr>
<tr>
<td>All sites</td>
<td>294,120</td>
<td>271,530</td>
</tr>
</tbody>
</table>

### Female

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung &amp; bronchus</td>
<td>31%</td>
</tr>
<tr>
<td>Prostate</td>
<td>10%</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>8%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>6%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>4%</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>4%</td>
</tr>
<tr>
<td>Esophagus</td>
<td>4%</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>3%</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>3%</td>
</tr>
<tr>
<td>Uterine corpus</td>
<td>3%</td>
</tr>
<tr>
<td>Brain &amp; other nervous system</td>
<td>2%</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>2%</td>
</tr>
<tr>
<td>All sites</td>
<td>100%</td>
</tr>
</tbody>
</table>

**SOURCE:** American Cancer Society, Inc., Surveillance Research, 2008
Pancreatic Cancer

Survival rate 5 years after diagnosis

Source: American Cancer Society
## Pancreatic cancer

<table>
<thead>
<tr>
<th>Stage</th>
<th>Characteristics</th>
<th>Medium Survival (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>&lt;2cm</td>
<td>24.1</td>
</tr>
<tr>
<td>IB</td>
<td>&gt;2cm</td>
<td>20.6</td>
</tr>
<tr>
<td>IIA</td>
<td>Beyond pancreas</td>
<td>15.4</td>
</tr>
<tr>
<td>IIB</td>
<td>Regional nodes</td>
<td>12.7</td>
</tr>
<tr>
<td>III</td>
<td>Celiac/SMA involvement</td>
<td>10.6</td>
</tr>
<tr>
<td>IV</td>
<td>metastasis</td>
<td>4.5</td>
</tr>
</tbody>
</table>

Pancreatic Cancer

- 80% advanced stage at diagnosis.
- Resistant to current therapy.
  - Median survival with gemcitabine (6 months).
- Early detection and an agent(s) that can prevent or augment current treatment is urgently needed.
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- How can we beat pancreatic cancer in BRCA carriers?
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  - Research update in chemoprevention.
Pancreatic Cancer
World-wide Age-standardized Mortality Rates

Publications.cancerresearch.uk
Pancreatic cancer
Risk Factors

• Age, gender, race
• Body mass index
• Pancreatitis
• Smoking
• Family history
• Genetic syndromes
Annual Pancreatic Cancer Incidence Rates by Age, Race, and Sex.
Cigarrete smoking

- Smokers have 2-3X increase in pancreatic cancer.
- Implicated in about 30% PC.
- Promotion of pancreatic cancer in FPC patients.
- Risk decreases when smoking stops (49% within 2 years).

James et al *Cancer* 2004; Bueno de Mesquita et al. *Int J Ca*, 1991
Pancreatic Cancer

Sporadic (~85%)

Known Genetic Syndromes (~5%)

Familial Pancreatic Cancer (~10%)

Pancreatic Cancer

Known genetic syndromes

- Heritable Breast Ovary Cancer (BRCA2)*
- Hereditary Pancreatitis (PRSS1)
- HNPCC/Lynch II (hMSH2 and hMLH1)
- Peutz Jeghers Syndrome (STK11/LKB1)
- (FAMMM) Familial Atypical Multiple Mole Melanoma Syndrome: p16 (CDKNA2)
- Cystic Fibrosis

*The most common associated genetic abnormality found in families with two or more affected relatives
Expected Pancreatic Cancer Incidence per 100,000 in the General U.S. Population

# FDRs with Pancreatic Cancer

## Risk of Pancreatic Cancer

### Genetic syndromes

<table>
<thead>
<tr>
<th>Individuals</th>
<th>Risk</th>
<th>Age 50</th>
<th>Age 70</th>
</tr>
</thead>
<tbody>
<tr>
<td>No History</td>
<td>1</td>
<td>0.05%</td>
<td>0.5%</td>
</tr>
<tr>
<td><strong>BRCA 2</strong> (Breast-Ovarian)</td>
<td>3.5-10</td>
<td>0.5%</td>
<td>5%</td>
</tr>
<tr>
<td><strong>P16</strong> (FAMMM)</td>
<td>20-34</td>
<td>1%</td>
<td>10-17%</td>
</tr>
<tr>
<td>Familial(1-3)</td>
<td>14-32</td>
<td>0.8-1.6%</td>
<td>8-16%</td>
</tr>
<tr>
<td><strong>PRSS1</strong> (Pancreatitis)</td>
<td>50-80</td>
<td>2.5%</td>
<td>25-40%</td>
</tr>
<tr>
<td><strong>STK11/LKB1</strong> (Peutz-Jeghers)</td>
<td>132</td>
<td>6.6%</td>
<td>30-60%</td>
</tr>
</tbody>
</table>
BRCA and Pancreatic Cancer

- **BRCA2 and Pancreatic Cancer**
  - Present in 17-19% of patients with at least 2 or more affected individuals
  - Present in 5-10% of patients with pancreatic cancer without family history
    - 1% Ashkenazi Jews

- **BRCA1 and Pancreatic Cancer**
  - ?-RR 2-fold
Sporadic Cancer
(Two acquired mutations)

2 normal 1 damaged 2 damaged

Hereditary Cancer

1 damaged 2 damaged

Tumor Develops
Pancreatic Oncogenesis

**Normal duct**
- Low cuboidal cells
- Single cell layer

PanIN-1A
- Elongated cells
- Mucin production

PanIN-1B
- Papillary architecture

PanIN-2
- Nuclear abnormalities: e.g. enlargement, some loss of polarity, crowding

PanIN-3
- Budding into lumen
- Severe nuclear atypia
- Mitosis, some abnormal

Adenocarcinoma
- Invasive growth
- Marked stromal reaction (desmoplasia)

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**Genes and Protein Levels**

- **ERBB2, EGFR**
- **KRAS**
- **INK4A**
- **TP53**
- **SMAD4/DPC4**
- **BRCA2**
- Telomerase

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**Telomere length**

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Pancreatic Oncogenesis

# genetic alterations

Pancreatic Oncogenesis
Signaling pathways and processes

Components of Pancreatic Cancer

Clinical Presentation

Symptoms

- Painless jaundice
- Dark urine, light stool
- Pancreatitis
- Abdominal pain/back pain
- Weight loss
- Loss of appetite
Clinical Pancreatic Oncology

Objectives

• What is the pancreas?
• What is pancreatic cancer?
• What are the factors that affect pancreatic cancer risk?
  • Risk for pancreatic cancer in BRCA carriers.
• How can we beat pancreatic cancer in BRCA carriers?
  • Research update in early detection strategies.
  • Research update in chemoprevention.
Pancreatic cancer

Why screen?

• Pancreatic cancer is a deadly disease once symptoms develop.
• 5%-20% yield from screening high risk individuals.
• Patients and doctors prefer screening to waiting for symptoms or prophylactic removal of the pancreas.
Pancreatic cancer
Problems with screening?

• Not covered by insurance.
• Firm evidence that it saves lives is still lacking.
• Best/ideal screening method is unknown.
PRECURSOR LESIONS OF PANCREATIC ADENOCARCINOMA

PanIN: Pancreatic Intraductal Neoplasia
MCN: Mucinous Cystic Neoplasm
IPMN: Intraductal Papillary Mucinous Neoplasm
Pancreatic cancer
Methods of early detection?

- Imaging
- Molecular markers
  - Blood
  - Pancreatic juice
  - Urine
# Pancreatic cancer screening

## Which imaging modality?

<table>
<thead>
<tr>
<th>Modality</th>
<th>Issues</th>
</tr>
</thead>
</table>
| Multidetector CT | • Suboptimal for early pancreatic neoplasia  
                  |     • Concern for repeat radiation exposure               |
| MRI/MRCP       | • No data on accuracy and yield  
                  |     • High cost                                           |
| ERCP           | • Invasive – Risk of pancreatitis                           |
| EUS            | • Highly operator dependent  
                  |     • Poor interobserver variability                       |

Topazian et al. Gastrointest Endosc, 2007
### Yield of screening in high risk individuals

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Modality</th>
<th>Diagnostic yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saunders et al</td>
<td>100</td>
<td>EUS</td>
<td>22%</td>
</tr>
<tr>
<td>Canto et al</td>
<td>78</td>
<td>EUS</td>
<td>10%</td>
</tr>
<tr>
<td>Canto et al</td>
<td>36</td>
<td>EUS</td>
<td>5.3%</td>
</tr>
<tr>
<td>Poley et al</td>
<td>17</td>
<td>EUS</td>
<td>18%</td>
</tr>
</tbody>
</table>

Protocol for High-Risk Assessment, Screening and Early Detection of Pancreatic Cancer at Moffitt Cancer Center

Jason Klapman, MD
Principal investigator
IRB #14482
Study Design

- Eligibility Criteria
  - Pts with at least 1 FDR from a familial PC kindred with at least 2 members affected
    - Age >40 or 10yrs younger than youngest affected
  - PJS patients age>30
  - Familial Pancreatitis patients
  - FAMMM
  - FAP
  - Pt’s with BRCA2 (Esp if FMHx of Pancreatic cancer)
  - Willingness to undergo EUS/FNA and Surgical Eval for abnormal EUS/FNA
  - Willingness to under Ct scans if screening abnormal
Study Design

• Exclusion Criteria
  – Age<18
  – Medical Contraindications to endoscopy or obstruction of GI tract
  – Personal History of Pancreatic Adenocarcinoma
  – Previous partial/complete resection of the pancreas for adenocarcinoma
  – Prior partial or total gastrectomy with B2 or Roux-En-Y anastamosis
Patient Recruitment

- Established patients/relatives of patients at Moffitt
- Tumor registry
- Lifetime cancer screening and prevention center
- Direct referrals from affiliate network
- Self-referred
Endoscopic Ultrasound (EUS)

- Originally developed as an alternative diagnostic imaging modality of the pancreas
- Technological advances have broadened the field of Endoscopic Ultrasound
  - EUS-guided Fine-Needle Aspiration (FNA)
  - EUS-guided FNA of a pancreatic cancer in 1992
EUS Equipment

- Radial Echoendoscopes
EUS-guided FNA

- **Safety**
  - Outpatient procedure
  - EUS alone has similar risk profile to standard endoscopy
  - EUS-guided FNA adds 1% risk of pancreatitis
Linear Echoendoscopes
High-Risk Individual Identified

- Consent For Pancreatic Screening Protocol
- Genetic Counseling

Total Cancer Care Protocol/Lifetime Cancer Database

Screening EUS Exam

- Normal
  - Repeat EUS in 1 yr
- Abnormal (Mass/Cyst)
  - EUS-Guided FNA

Invasive or pre-invasive neoplasm

- Pancreatic and Chest CT
  - Resectable
  - Surgical referral
  - Unresectable
  - Referral to Oncology
- Benign
  - Repeat EUS/FNA 6 months
- Indeterminate
  - Repeat EUS 3 Months
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  • Research update in chemoprevention.
What Will It Take To Establish A Chemopreventive Agent For Pancreatic Neoplasia?

- Identify and characterize potential chemopreventive agents.
- Establish ‘proof of concept’ in early phase trials.
- Identify the individuals who will benefit.
- Prove benefit in phase III trial.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Trial</th>
<th>Site</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT00094445* Dhillon et al.47</td>
<td>Curcumin (in advanced pancreatic cancer)</td>
<td>MD Anderson Cancer Center, USA</td>
<td>Phase II Published results for first 25 patients (biological effect in some patients)</td>
</tr>
<tr>
<td>NCT00192842*</td>
<td>Curcumin and gemcitabine (in advanced pancreatic cancer)</td>
<td>Rambam Health Care Campus, Israel</td>
<td>Phase II</td>
</tr>
<tr>
<td>NCT00486460*</td>
<td>Curcumin, gemcitabine and celecoxib (in advanced pancreatic cancer)</td>
<td>Tel-Aviv Sourasky Medical Center, Israel</td>
<td>Phase III</td>
</tr>
<tr>
<td>Goel et al.31</td>
<td>Curcumin (in advanced pancreatic cancer)</td>
<td>Kyoto University, Japan</td>
<td>Phase II</td>
</tr>
<tr>
<td>NCT00198081*</td>
<td>Celecoxib (prevention in patients with premalignant pancreatic lesions)</td>
<td>Indiana University School of Medicine, USA</td>
<td>Phase II</td>
</tr>
<tr>
<td>NCT00985777*</td>
<td>Vitamin E delta-tocotrienol (in resectable pancreatic cancer)</td>
<td>H. Lee Moffitt Cancer Center and Research Institute, USA</td>
<td>Phase I</td>
</tr>
<tr>
<td>NCT00882765*</td>
<td>Genistein (in resectable pancreatic cancer)</td>
<td>Jonsson Comprehensive Cancer Center at UCLA, USA</td>
<td>Phase II</td>
</tr>
</tbody>
</table>

*Source: [www.clinicaltrials.gov](http://www.clinicaltrials.gov).
Food-Genome Interface

Vitamin E Tocotrienols
Food Sources

Palm  Rice  Wheat  Barley  Rye  Oat

Mo Malafa, MD
## Nutrition and Pancreatic Cancer Protection

- **Increasing vegetable, fruit, and cereal consumption may protect against pancreatic cancer**

<table>
<thead>
<tr>
<th>Studies</th>
<th>Benefit</th>
<th>No Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prospective</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Case Control</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Cohort</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

Mo Malafa, MD
Pancreatic Cancer
Whole grain decreases risk

- Risk of pancreatic cancer reduced by nearly 50% with whole grain consumption.

- How?
  - Bioactive food components?

Natural Vitamin E Compounds

<table>
<thead>
<tr>
<th></th>
<th>R1</th>
<th>R2</th>
<th>R3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha (α-)</td>
<td>CH₃</td>
<td>CH₃</td>
<td>CH₃</td>
</tr>
<tr>
<td>Betta (β-)</td>
<td>CH₃</td>
<td>H</td>
<td>CH₃</td>
</tr>
<tr>
<td>Gamma (γ-)</td>
<td>H</td>
<td>CH₃</td>
<td>CH₃</td>
</tr>
<tr>
<td>Delta (δ-)</td>
<td>H</td>
<td>H</td>
<td>CH₃</td>
</tr>
</tbody>
</table>
Tocotrienols in Pancreatic Cancer
Preclinical studies

• Delta-tocotrienol was the most effective vitamin E compound against pancreatic cancer.
• Mice receiving delta-tocotrienol showed pancreatic tumor growth inhibition.
• Adequate levels of delta-tocotrienol in the pancreas of mice was achieved with well tolerated oral dosing.
Tocotrienols in Pancreatic Cancer

Preclinical identification of biomarkers

• δ-Tocotrienol preclinical studies demonstrated specific PD effects.
  – Decreased tumor cell proliferation.
  – Increased tumor cell apoptosis.

• RNAi and chemical inhibitors confirmed the essential role of specific biomarkers (p27, caspase 8) in δ-tocotrienol MOA.
Transgenic Mouse Model of Pancreatic Cancer

- LSL-KRAS\textsuperscript{G12D};PDX-1-Cre mice
  - PDX – developmental transcription factor, targets to pancreatic progenitor cells
  - KRAS\textsuperscript{G12D} mutation commonly found in human pancreatic ductal adenocarcinoma, constitutive activation
- By 9 months ~30% of ducts show PanIN-1B/-2 lesions and ~5% signs of PanIN-3 lesions
- By 15 months virtually every animal develops invasive pancreatic ductal adenocarcinoma

Hingorani et al., *Cancer Cell*, 4:437, 2003
The hypothesis

• Vitamin E delta-tocotrienol will activate cell death and decrease proliferation of pancreatic neoplastic cells thereby resulting in the inhibition or delay of pancreatic tumor growth.
Phase I Study of Vitamin E δ-Tocotrienol in Pancreatic Neoplasia

- Single center, open label, dose-escalation study.
- Approximately 32 patients with pancreatic tumors undergoing surgery will be enrolled.
- Oral route of administration.
Phase I Study of Vitamin E δ-Tocotrienol in Pancreatic Neoplasia

Eligibility
Resectable Pancreatic Tumor

δ-tocotrienol

Day: 0
Pre-treatment Biopsy and blood draw

15 days
Post-treatment tissue and blood draw

Mo Malafa, MD
Phase I Study of Vitamin E δ-Tocotrienol in Pancreatic Neoplasia

• Objectives:
  – Primary:
    1. Phase II dose = Biologically Effective Dose (BED).
    2. Safety and tolerability (5.6X the predicted BED).
  – Secondary:
    1. Pharmacokinetics.
    2. Pharmacodynamics in blood, pancreatic tumor tissue, and adjacent resected tissues.
    3. Biodistribution of δ-tocotrienol in blood, pancreatic tumor tissue, and adjacent resected tissues.
Phase I Study of Vitamin E δ-Tocotrienol in Pancreatic Neoplasia

• **Outcomes:**
  - **Primary:**
    1. Biologically Effective Dose (BED) defined as dose which significantly induces apoptosis and reduces proliferation in pancreatic neoplastic cells.
  - **Secondary:**
    1. Activation of caspase 8 and 3.
    2. Induction of p27.
    3. Inhibition of cFLIP, pMAPK, pAKT.
• **Other** (DCE-MRI, PET scan, etc).

Mo Malafa, MD
Phase I Study of Vitamin E \( \delta \)-Tocotrienol in Pancreatic Neoplasia

Presurgical biomarker trial

• **Advantages:**
  – Rapid.
  – Rationale.
  – Cost effective.
  – Patients are not terminal or heavily pretreated.

• **Disadvantage:**
  – ? Biomarkers will translate to meaningful clinical outcomes (increase patient survival).

Mo Malafa, MD
Pancreatic Cancer
Population At-Risk

- Heritable syndromes (10%-15%).
- Incidental pre-neoplastic pancreatic tumors on body imaging (? 2.6% of CT Scans).
- Pancreatic cancer patients after curative resection (70% relapse rate).
Strategy For Investigating δ-Tocotrienol In Pancreatic Cancer

Phase 0/I ‘Proof of Concept’ trials in:
• Patients undergoing surgical resection.
• Patients who have had resection.
• Healthy subjects.

Phase II/III trials in:
• Patients with resected Pancreatic Ca.

Phase III trials in:
• Heritable syndromes.
• Incidental pre-neoplastic tumors
"Let food be your medicine" - Hippocrates

Red Palm Oil may have potential anti-cancer properties

Mo Malafa, MD
BRCA and Pancreatic Cancer
Summary

• BRCA 2 is a common mutation in both familial and sporadic pancreatic cancer.

• Individuals with BRCA 2 have 10X risk of developing PC (10/200). BRCA 1 2X risk.

• To fight this risk, the priority should be research in:
  – Early detection
  – Prevention
Acknowledgements

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