Early Lessons from the Jefferson Pancreas Tumor Registry (JPTR)

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Jefferson Pancreas Tumor Registry
Co-Investigators

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- Avi Nevlar, MD, Senior Surgical Resident, Tel Aviv, Israel
- Jennifer Brumbaugh, MA, JPTR Web Master, Thomas Jefferson University
- Jonathan Brody, PhD, Professor and Director of Surgical Research, Thomas Jefferson University
- Jordan Winter, MD, FACS, Associate Professor, Sidney Kimmel Medical College
- Charles J. Yeo, MD, FACS, Professor and Chairman of Surgery, Sidney Kimmel Medical College of Thomas Jefferson University

No relevant conflicts of Interest to disclose

OUR TEAM- Jefferson Pancreas, Biliary & Related Cancer Center
Background: Pancreatic Cancer

American Cancer Society*:
- **53,070** new cases
- **41,780** deaths in 2016
- PC (all types) now the third leading cause of cancer-related death in the U.S.
- Pancreatic ductal adenocarcinoma accounts for the majority of cases.

Pancreatic Cancer Terminology

- Pancreatic ductal adenocarcinoma (garden-variety)
- PanIN lesions (Pancreatic Intraepithelial Neoplasia)...microscopic; PanIN-1 to 3; precursors
- IPMNs (Intraductal Papillary Mucinous Neoplasms)...macroscopic; low grade to high grade dysplasia and cancer
- Islet cell and acinar cell cancer (rare)
- Mucinous cystadenocarcinoma (uncommon)

Survival*

Combining all Pathologic Stages:
- One-year survival rate 20%
- Five-year survival rate ~6%
- Median survival: 6 months

Following Surgical Resection:
- Median survival 12 – 22 months
- Five-year survival 10 - 40%

* American Cancer Society, 2016; Rahib, 2014
Risk Factors Associated with PC

- **Genetic factors** - ~5% of cases have inherited germline gene mutations
- **Family history** - in 5–10% of cases, 2 or more family members will have PC, suggesting similar gene mutations (K-ras, BRCA1 & 2)
- **Inherited predisposition** - six high-risk familial syndromes have been identified

Six High-Risk Syndromes

- Hereditary pancreatitis
- Hereditary nonpolyposis colorectal cancer
- Hereditary breast & ovarian cancer
- Familial atypical multiple mole melanoma (FAMMM)
- Peutz-Jeghers syndrome
- Ataxia-telangectasia

These conditions increase PC risk 20-100 fold depending on the condition

Other Documented PC Risk Factors

<table>
<thead>
<tr>
<th>Life-style Factors:</th>
<th>Occupational Exposure to Carcinogens:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cigarette smoking (dose-response)</td>
<td>2-naphthylamine, benzidine, gasoline products, PCBs, dry cleaning agents, DDT</td>
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<tr>
<td>Environmental tobacco smoke exposure (ETS and second hand smoke)</td>
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<table>
<thead>
<tr>
<th>Race/Ethnic Factors:</th>
<th>High-Risk Occupations:</th>
</tr>
</thead>
<tbody>
<tr>
<td>African-American men and women</td>
<td>Dry cleaning, chemical plant work, sawmills, electrical equipment manufacturing workers, miners, metal workers</td>
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<tr>
<td>Native female Hawaiians</td>
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<tr>
<td>Ashkenazi Jewish heritage (due to BRCA 1 &amp; 2 genes)</td>
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<table>
<thead>
<tr>
<th>Medical Conditions:</th>
<th>Height:</th>
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<tbody>
<tr>
<td>Diabetes Mellitus</td>
<td>Relative risk 1.8 (CI 1.31-2.52) when comparing tallest to shortest height categories, for men and women. For every 2.54 cm above average height, PC risk increased 6-10%</td>
</tr>
<tr>
<td>Chronic pancreatitis</td>
<td></td>
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<td>ABO blood type</td>
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<table>
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<tr>
<th>Dietary Factors:</th>
<th>Previous Surgery:</th>
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<tr>
<td>High fat/cholesterol</td>
<td>Cholecystectomy</td>
</tr>
<tr>
<td>Obesity</td>
<td></td>
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<tr>
<td>Nitrosamines in food</td>
<td></td>
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<tr>
<td>Heavy alcohol use</td>
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Pancreatic Ductal Adenocarcinoma (PDA):
- Over 50,000 new cases annually in U.S.
- 4th leading cause of cancer death in U.S… but VERY underfunded by the NIH—receives 2% of funding
- Average age at presentation = 60-65 years
- Majority present with unresectable (locally advanced or disseminated) disease
- After successful resection, median survival approaches 2 years

Early Detection
- Basis
  - The majority of individuals with pancreatic cancer develop symptoms when the tumors are pathologically advanced
- Strategies
  - Screening blood test — the search continues for true PSA
  - Virtual physical: Screening CT scan?
  - Identify high risk groups and screen CT/ERCP/EUS

Current Treatment of PC-1
- Neoadjuvant chemotherapy: locally advanced and borderline resectable cases (with involvement of major blood vessels, SMV, SMA, HA, HV)
- Standard therapy: Gemcitabine, other protocols include gem with abraxane, or multi-drug therapy with Folfirinox (5 drugs)
- Radiation therapy or proton therapy: +/- indication
Current Treatment of PC-2
- **Resectable PC tumors**: PPPD (Mini-Whipple, Classic PD, distal pancreatectomy or total panc).
- Depending on lymph node status from nodes harvested at time of surgery, may also need adjuvant chemotherapy.
- Always recommend and refer patients to available open clinical trials.
- Participating in a clinical drug trial confers greater opportunity for a cure.

Summary of Treatment
- Currently, neoadjuvant therapy followed by surgery, and/or with adjuvant chemotherapy, and/or radiation therapy, results in less than optimal 5 year survival.

Significance of Study
- We need to do a better job at identifying early cases, and persons most at risk due to family history, lifestyle factors, and genetic mutations.
- Working on this problem requires a multi-faceted approach involving: molecular, biochemical, environmental, epidemiological and social investigations.
- *Persons diagnosed with PC have concerns about future cancer risk for family members.*
Jefferson Pancreas Tumor Registry—
Founded 2008

- 2007- Formulated plan to start a pancreas tumor registry at Thomas Jefferson University Hospital, Philadelphia, PA
- Modeled on the Johns Hopkins National Familial Pancreas Tumor Registry (NFPTTR)
- 2008- Study protocol approved by the Jefferson Institutional Review Board
- February 2008 enrollment of patients and families began

Purpose of Study: Three-fold

1) Repository of self-reported information on hereditary conditions, family history of cancer, environmental exposures and occupational risk factors.
2) In conjunction with the ongoing Jefferson Tissue Banking Study, JPTR provides link between gene mutations, family history and precision medicine therapy and
3) Identify High-Risk Non-Affected Family Members for surveillance screening.
Study Design and Methods

- The JPTR is designed as a longitudinal, epidemiological study of persons with pancreas and related cancers and their family members and other relatives. Non-affected family members are welcome to participate.
- All persons 18 years or older, with a diagnosis of pancreas cancer and related cancers (e.g. bile duct, gallbladder, duodenal, ampullary) are invited to participate in the study.
- The study is approved by the Thomas Jefferson University IRB and undergoes continuing review yearly.

Data Collection-1

- Informed consent obtained after discussion of study and goals
- Data for analysis are collected via hard copies of JPTR questionnaires, electronic medical record, operative notes, molecular analysis, and pathology reports.
- Data are entered and variables created in Password-protected Access® database accessible only to study personnel
- Family genograms created using Progeny software available in the public domain.

JPTR Questionnaire

- Demographics
- Past medical history (e.g. FH cancer, DM, pancreatitis, inherited syndromes)
- Tobacco exposure (cigarettes, cigars, pipes, ETS)
- 3 generation family genogram- focus on all cancers, DM, smoking hx, pancreas diseases
- Environmental exposure to 20 known carcinogens r/t to PC
- Occupational history (usual job, yrs., type of work)
- Neighborhood-industrial exposure and residential radon
Pedigree of High-Risk Family Showing Pancreas Cancer in Three Generations, NFPTTR

Longitudinal Follow-up

- Annual follow-up is conducted; includes index patients, non-affected family members and, in some cases, next-of-kin, or spouses.
- Publish annual JPTR Newsletter featuring an interesting patient story, success story, an update on the Registry and brief details of new and ongoing research trials at Jefferson.

Pancreas Tumor Registry Update

Six Years After Min-Whipple Procedure, Leonard Brett Is Still Grateful—and Going Strong.

(2015 JPTR Newsletter)
Data Collection- 2 (Sites)

8 Institutions in PA and NJ now collaborate with JPTR:
(Provide questionnaire data only; tumor samples only from TJUH)

- Scranton General Hospital
- Pocono Medical Center
- Reading Hospital
- Lankenau Hospital
- Bryn Mawr Hospital
- Paoli Hospital
- Riddle Hospital
- Inspira Health System in NJ

Results: Current Overall Characteristics of JPTR

2016 JPTR* Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>2016 JPTR*</th>
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<tbody>
<tr>
<td>Total Members:</td>
<td>605</td>
</tr>
<tr>
<td>Sporadic PC</td>
<td>66%</td>
</tr>
<tr>
<td>Familial PC</td>
<td>14%</td>
</tr>
<tr>
<td>Other Conditions</td>
<td>7%</td>
</tr>
<tr>
<td>Controls</td>
<td>14%</td>
</tr>
<tr>
<td>High-Risk Non-Affected</td>
<td>75</td>
</tr>
<tr>
<td>Family Members</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>53%</td>
</tr>
<tr>
<td>Men</td>
<td>47%</td>
</tr>
<tr>
<td>Average Age:</td>
<td>64.6 years</td>
</tr>
<tr>
<td>Age Range</td>
<td>24 – 91 years</td>
</tr>
<tr>
<td>Race:</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>91%</td>
</tr>
<tr>
<td>African-American</td>
<td>3%</td>
</tr>
<tr>
<td>Asian</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Hispanic</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Unknown</td>
<td>14%</td>
</tr>
</tbody>
</table>

* = Consistent w/ national published stats

Results
Part 1: 2015 JPTR Member Survey

- **Mailed:** 150 surveys
- **Completed:** 106 (77%)
- **No response:** 7

**Gender:**
- Men: 55
- Women: 61

**Confirmed Status:** 116/150
- Alive: 83 (72%)
- Deceased: 25 (22%)
- Unknown: 8 (6%)

**Condition:**
- PC, Amp Ca, Duod Ca: 65 (56%)
- IPMN: 13
- Pancreatic Cyst: 13
- Pancreatitis: 5
- Pan. Endocrine Tumor: 5
- Bile duct Ca: 2
- Not Cancer: 11

**Treatment:**
- Surgery: 95 (82%)
- No Surgery: 9
- Surgery + CT: 59
- Surgery + CT + RT: 34
- Chemotherapy Only: 2

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Part 2: Self-Reported Quality of Life Responses

- **Walk Regularly:**
  - Yes = 63 (76%)
  - No = 20

- **Exercise Regularly:**
  - Yes = 38 (46%)
  - No = 42

- **Most Common Exercises:**
  - Aerobics at gym, weight lifting, biking, yoga, golf, tennis

- **Most common persistent symptoms:**
  - Fatigue, bloating, diarrhea, wt. loss, pain, poor appetite

- **Used Medical Marijuana for Symptoms:**
  - Yes = 4
  - No = 85

- **Would have surgery again?**
  - Yes = 84 (88%)
  - No = 5

- **Would have Chemo again?**
  - Yes = 46 (78%)
  - No = 13

- **Would have RT again?**
  - Yes = 30 (82%)
  - No = 4

- **Ability to Do Activities of Daily Living:**
  - 3.8 (1-4, 1 = poor, 4 = excellent)

- **How Would You Rate Your Overall Quality of Life?**
  - 3.2 (1-4, 1 = poor, 4 = excellent)
Translating Clinical Epidemiology into Basic Science Research

- As an example of how clinical epidemiology can inform biological studies, the JPTR (Dr. Avi Nevlar) looked at a specific tumor suppressor gene (WEE1) at the HuR binding site for polymorphisms (normal variations in ~ 1% of population).
- HuR is a RNA binding protein important in normal cell function and upregulated in cancers.

WEE1 is a cell cycle regulator and a tumor suppressor gene

Adapted from Richard Wheeler, 2008

WEE1 (TSG) Polymorphisms (SNPs & INDELS) in an RNA Binding Site (HuR):

<table>
<thead>
<tr>
<th>Resected Population Subset</th>
<th>Genotype Frequency</th>
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<tbody>
<tr>
<td>JPTR-TJUH Resected Patients (n = 99)</td>
<td>53% 41% 6%</td>
</tr>
<tr>
<td>PDA Only-resected Patients (n = 87)</td>
<td>53% 42% 5%</td>
</tr>
<tr>
<td>Resected Index Case with 1st Family Member</td>
<td></td>
</tr>
<tr>
<td>with GI/Gyn/Breast/Bladder/</td>
<td></td>
</tr>
<tr>
<td>Blood/Prostate Cancers (n = 43)</td>
<td>40% 48% 12%</td>
</tr>
<tr>
<td>Resected Index Case with 1st Family Member</td>
<td>24% 59% 18%</td>
</tr>
<tr>
<td>with CRC/Gastric/Ovary/Endometrial Cancers</td>
<td></td>
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<tr>
<td>(n = 17)</td>
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Intergroup Analysis: Index Cases with 12T/12T allele or 12T/12T enrichment were significantly more likely to have 1st-Relatives with Lynch-type cancers (ORs 2.4 & 4.3, p = 0.009) compared to cases without family history.
E.g.: JPTR High-Risk Family Genogram

Summary: Current JPTR Activities

• All patients w/ PC or related conditions are eligible to join the Registry
• Send an Annual Newsletter that includes a follow-up survey aimed at identifying survival and other new cancers in the member or family
• Current Research studies in which the JPTR is a collaborator:
  1. ACS grant- (Drs. Lavu, Brody, others)
  2. Ongoing Quality of Life and Survival Study- (Drs. Winter, T. Yeo, C. You, others)
  3. Molecular Studies- correlating FH w/ specific gene mutations and cell signaling factors that promote cancer development.
     - Looking for new ways to turn off these mechanisms.
     (Drs. Brody, Winter, J. Coritzo, A. Nevlar, many others, and other institutions)

Conclusions: JPTR Lessons Learned

• Early data from the JPTR indicate a remarkable survey response rate, as well as a high degree of satisfaction with treatment choices.
• Persistent unpleasant symptoms remain a problem for many survivors.
• The JPTR has identified a cohort of high-risk non-affected persons who are potentially candidates for surveillance screening.
• Ongoing studies will determine the clinical implications and the biochemical significance of the WEE1 polymorphisms.
• Lastly, if you build it, they will come.....
JPTR and Pancreas, Biliary and Related Cancer Center

- “11th Annual Pancreatic and Related Cancers Patient Symposium”
- November 5, 2016 at Jefferson.
- Complimentary Program: Breakfast, short talks on PC topics and current research, “Whipple friendly lunch”, Q & A session, and Survivor Photo
- About 300 survivors and families attend!!!

2014 Pancreas Cancer Symposium Survivor Photo

References