Pancreatic cancer and diabetes: it goes both ways

Fred Gorelick
Departments of Medicine and Cell Biology
Yale University
February 2018
Disclosure

Grant support:
NIH (NIDDK RO1 and PO1): Acute pancreatitis
VA Merit Award: Acute pancreatitis

Data Safety monitoring boards:
GLP-1 agonists and prevention of cardiovascular disease (AstraZeneca)
Indomethacin vs stents for the prevention of post-ERCP pancreatitis (NIH NIDDK)

No intellectual or financial conflicts of interest with this presentation
Pancreatic cancer and diabetes: *it goes both ways*

1. Long-standing diabetes mellitus (DM) increases the risk of developing pancreatic cancer

2. Pancreatic cancer can induce DM (independent of direct islet destruction)
Diabetes and Pancreatic Cancer

Two relationships

1. Diabetes increases PaCa risk

Diabetes → Cancer

2. PaCa increases diabetes risk

Diabetes ↑ → Cancer ←
Diabetes and Pancreatic Cancer
Two relationships

1. Diabetes increases PaCa risk

2. PaCa increases diabetes risk

How might diabetes cause cancer?
Multiple mechanisms may contribute to the effects of DM on pancreatic cancer (PC) risk

- High insulin $\rightarrow$ insulin-like growth factor receptors that can promote cancer
- Obesity: cancer-promoting pro-inflammatory state
- Intracellular lipids promotes neoplasia
- Poor glycemic control $\rightarrow$ abnormal protein glycosylation can activate RAG, a receptor linked to pancreatic cancer
- Glucose $\rightarrow$ EMT
- Insulin $\rightarrow$ pancreatic stellate cells $\rightarrow$ fibrosis

Yang J AJP. 2016; Andersen D. Diabetes, 2017; Rahn Cancer Lett 2018
The pancreatic portal system exposes about 50% of acinar cells to high levels of endocrine hormones

From Gorelick and Shoendorf, AGA GTP: pancreatic physiology and disease
Diabetes is associated with an exocrine pancreatopathy

**Phenotype:** Type I diabetes >>> Type II

- Reduced pancreatic mass
- Occasional mild to moderate pancreatic insufficiency
- Preliminary histology
  - Fibrosis (arrowheads)
  - Acinar cell atrophy
  - Vasculopathy
  - Lack of inflammation
  - Lack of duct involvement/calcification

- Mechanism unclear: 1) reduced levels islet hormones, 2) high exogenous insulin
- Since fibrosis appears to predispose to carcinoma, could this be an unrecognized risk for PC in diabetes?

Sonmoon Mohapatra, Pancreas, 2016
High insulin levels may stimulate pancreatic fibrosis through IGF-R1

Human pancreatic tissues

- A, B: Normal
- D, E: T2DM

Figure G: Collagen deposition (% total area)

- Normal: 0 - 2
- T2DM: 4 - 12

* Significant difference

- Yang AP, 2016
Anti-diabetic agents may affect risk of developing PaCa

<table>
<thead>
<tr>
<th>Type of therapy</th>
<th>No. of cases/ no. of controls</th>
<th>Adjusted OR (95% CI)/ P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>147/88</td>
<td>5.04 (2.38-10.7)/&lt;.001</td>
</tr>
<tr>
<td>Ever</td>
<td>112/21</td>
<td></td>
</tr>
<tr>
<td>Insulin secretagogues</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>171/84</td>
<td>1.74 (0.80-3.77)/.160</td>
</tr>
<tr>
<td>Ever</td>
<td>84/22</td>
<td></td>
</tr>
<tr>
<td>Metformin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>138/32</td>
<td>0.41 (0.19-0.87)/.020</td>
</tr>
<tr>
<td>Ever</td>
<td>117/74</td>
<td></td>
</tr>
<tr>
<td>TZDs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>204/87</td>
<td>1.65 (0.71-3.87)/.245</td>
</tr>
<tr>
<td>Ever</td>
<td>51/19</td>
<td></td>
</tr>
</tbody>
</table>

GLP1 agonists (incretins) and pancreatic cancer
• Most studies have not identified a relationship
• Risk if present decreases over first year (suggesting pre-existing tumor effect)

Li, Gastroenterology 2009
Bodmer, Am J Gastroenterol 2012
Li, Diabetes Res 2012
Azoulay BMJ, 2016
Boniol, Diabetes Care, 2018
Diabetes and Pancreatic Cancer

Two relationships

1. Diabetes increases PaCa risk

Diabetes → Cancer

2. PaCa increases diabetes risk

Diabetes ↑ Cancer ←
New Onset Diabetes: most common in pancreatic cancer

- Aggarwal, Pancreas, 2013
- Also He, Shi and Wu. Curr Med Res Opinion, 2018
Observations suggesting that pancreatic cancer (PC) can cause diabetes mellitus (DM)

- DM in most PC
- DM precedes PC presentation by months to years
- DM appears with small or undetectable tumors
- DM can improve after pancreatic resection
- PC cells can induce insulin-resistance in hepatocytes
- Skeletal muscle from PC patients exhibits insulin resistance
- PC secretes adrenomedullin (reduces insulin secretion)
- PC exosome induces fat cell lipolysis

Aggarwal, Gastro 2012; Sah, Nat Rev Gastro Hepatology 2014; Sagar, Gut, 2016
Diabetes precedes pancreatic cancer
*Positive CT scan occurs late in disease*

CT screening for PaCa after onset type II DM: **not effective**

S. Chari, Gastroenterology, August 2005; Pannala Lancet Oncol 2009
Rising FBS and falling BMI typify PC

Pannala: AJGastro 2009
Pancreatic cancer: Type 3c diabetes mellitus (T3cDM)

- **Key feature:** presence of diabetes secondary to exocrine pancreatic disease
- **Most common definition***
  - **MAJOR CRITERIA**
    - Pancreatic exocrine insufficiency
    - Pathologic pancreatic imaging
    - Absence of T1DM auto-antibodies
  - **MINOR CRITERIA**
    - Absent PP secretion
    - Lack of insulin resistance
    - Impaired beta-cell function

*Ewald and Hardt: World J Gastro 2013
Duggan and Conlon Pract Gastro 2017; Andersen et al: Lancet, 2017*
Type 3cDM causes about 10% of adult diabetes; about 10% is associated with pancreatic cancer.

**A**

Distribution of T1DM, Type2DM, and Type 3cDM

- T2DM: 80%
- T1DM: 12%
- T3cDM: 8%

**B**

Distribution of causes of Type3cDM

- Chronic pancreatitis: 76%
- Pancreatic resection: 3%
- Cystic fibrosis: 4%
- Hemochromatosis: 8%
- Pancreatic neoplasia: 9%
## Distinct features of diabetes reflect varied etiologies

<table>
<thead>
<tr>
<th>Parameter</th>
<th>T1DM</th>
<th>T2DM</th>
<th>T3cDM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoglycemia</td>
<td>common</td>
<td>rare</td>
<td>rare</td>
</tr>
<tr>
<td>Peripheral insulin sensitivity</td>
<td>Normal or decreased</td>
<td>Decreased</td>
<td>Normal or increased</td>
</tr>
<tr>
<td>Hepatic insulin sensitivity</td>
<td>Normal or decreased</td>
<td>Decreased</td>
<td>Normal or decreased</td>
</tr>
<tr>
<td>PP levels</td>
<td>Normal or low</td>
<td>Normal or high</td>
<td>Normal or low</td>
</tr>
<tr>
<td>Etiology</td>
<td>autoimmune</td>
<td>Obesity, age</td>
<td>Pancreatic exocrine disease</td>
</tr>
</tbody>
</table>

T4DM (gestational) not included

Duggan and Conlon Pract Gastro 2017; Andersen et al: Lancet, 2017
Diabetes and Pancreatic Cancer
Two relationships - Summary

1. Diabetes increases PaCa risk

Diabetes ➔ Cancer

- Longstanding diabetes, especially with insulin use
- DM associated factors (e.g. obesity)
- Exocrine pancreatic fibrosis
- Metformin may be protective

2. PaCa increases diabetes risk

Diabetes ← Cancer

- Recent onset (<36m) DM frequent (~40%) in PC
- PC resection can cause regression of DM
- PC can release factors that affect insulin secretion and sensitivity
- Not useful for screening (yet)
PC presentation is increased soon after initiating incretin therapy then decreases: reflection of bias and not drug effect

- Similar effects were observed with other non-insulin drugs
- Opposite effects with insulin (risk increased with time
- Likely protopathic bias: drug is prescribed for a disease that has not been detected