Risk Factors for Pancreatic Cancer, what will be the #2 Cause of Cancer Death Four Years from Now

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Yale Cancer Center
Potential Conflicts of Interest

I disclose epidemiology consulting work with Pfizer Inc., Daiichi-Sankyo Inc. and Imerys Inc. None of this consulting work is related to the material presented in this talk.

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Figure 1. Trends in Age-adjusted Cancer Death Rates* by Site, Males, US, 1930-2014

*Per 100,000, age adjusted to the 2000 US standard population. †Mortality rates for pancreatic and liver cancers are increasing.

Note: Due to changes in ICD coding, numerator information has changed over time. Rates for cancers of the liver, lung and bronchus, uterus, and colon and rectum are affected by these coding changes.


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Figure 2. Trends in Age-adjusted Cancer Death Rates* by Site, Females, US, 1930-2014

*Per 100,000, age adjusted to the 2000 US standard population. Uterus refers to uterine cervix and uterine corpus combined. The mortality rate for liver cancer is increasing. Note: Due to changes in ICD coding, numerator information has changed over time. Rates for cancer of the liver, lung and bronchus, uterus, and colon and rectum are affected by these coding changes.


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Pancreatic Cancer, United States, 2017

Fourth most frequent cause of cancer death (after lung, breast/prostate, colorectal)

53,700 cases, 43,100 deaths/year, males and females fairly close (28,000 vs. 25,700)

Incidence rates increasing about 1.3% per year

1.5% lifetime risk in general population

1-year relative survival 20-30%, 5-year relative survival 5% (probably less)

Surgical resection is the only substantial treatment, but only about 20-25% of patients qualify. Resection gives about 2-3 years of survival on average.
Reducing Mortality of Pancreatic Cancer

Primary Prevention

Identify modifiable risk factors:
   Gain general acceptance of modifying them

Identify chemopreventive substances:
   Identify population subgroups where benefits outweigh harms
   Gain general subgroup acceptance of using them

Secondary Prevention

Identify biomarkers of developing disease

Identify signs and symptoms of developing disease

In both cases, determine time course before diagnosis
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Risk factors: Approximately 20% of pancreatic cancers are attributable to cigarette smoking; incidence rates are about twice as high for smokers as for never smokers. Use of smokeless tobacco products also increases risk. Other risk factors include a family history of pancreatic cancer and a personal history of chronic pancreatitis, diabetes, obesity, and possibly high levels of alcohol consumption. Individuals with Lynch syndrome and certain other genetic syndromes, including BRCA1 and BRCA2 mutation carriers, are also at increased risk.
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Also: ABO blood group, Jewish ancestry; probably colonization by Helicobacter pylori.
# Risk of Pancreatic Cancer for ABO Non-O vs O Blood Group

Prevalence in US of group O = 44.0%, therefore PAR% for non-O blood group is:

\[
(1 - 0.440) \times (1.41 - 1) / 1 + (1 - 0.440) \times (1.41 - 1) = 19\%
\]

comparable to cigarette smoking.

<table>
<thead>
<tr>
<th>First Author, Year (Reference No.)</th>
<th>No. of Non-O Cases</th>
<th>No. of Non-O Controls</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guleria, 2005 (34)</td>
<td>6</td>
<td>112</td>
<td>1.29 (0.25, 6.60)</td>
</tr>
<tr>
<td>Rai, 1972 (30)</td>
<td>3</td>
<td>2,866</td>
<td>0.49 (0.10, 2.44)</td>
</tr>
<tr>
<td>Walther, 1956 (5)</td>
<td>9</td>
<td>1,255</td>
<td>1.92 (0.59, 6.25)</td>
</tr>
<tr>
<td>Newell, 1974 (18) (whites)</td>
<td>10</td>
<td>647</td>
<td>0.69 (0.30, 1.59)</td>
</tr>
<tr>
<td>Moniwa, 1960 (29)</td>
<td>45</td>
<td>14,430</td>
<td>1.06 (0.62, 1.79)</td>
</tr>
<tr>
<td>Rizzuto, 2011 (15)</td>
<td>71</td>
<td>76</td>
<td>1.35 (0.80, 2.30)</td>
</tr>
<tr>
<td>Vioque, 1991 (33)</td>
<td>56</td>
<td>119</td>
<td>1.51 (0.94, 2.42)</td>
</tr>
<tr>
<td>Iodice, 2010 (11,12)</td>
<td>64</td>
<td>8,156</td>
<td>2.14 (1.36, 3.38)</td>
</tr>
<tr>
<td>Engin, 2012 (37)</td>
<td>93</td>
<td>239</td>
<td>1.11 (0.72, 1.71)</td>
</tr>
<tr>
<td>Newell, 1974 (18) (blacks)</td>
<td>67</td>
<td>1,954</td>
<td>1.34 (0.91, 1.98)</td>
</tr>
<tr>
<td>Macafee, 1964 (19)</td>
<td>63</td>
<td>5,805</td>
<td>1.07 (0.75, 1.54)</td>
</tr>
<tr>
<td>Nakao, 2011 (7)</td>
<td>147</td>
<td>1,037</td>
<td>1.57 (1.19, 2.07)</td>
</tr>
<tr>
<td>Annese, 1990 (32)</td>
<td>145</td>
<td>3,801</td>
<td>1.70 (1.29, 2.24)</td>
</tr>
<tr>
<td>Gong, 2012 (24)</td>
<td>479</td>
<td>513</td>
<td>1.16 (0.89, 1.54)</td>
</tr>
<tr>
<td>Risch, 2010 (9)</td>
<td>214</td>
<td>375</td>
<td>1.22 (0.94, 1.58)</td>
</tr>
<tr>
<td>Greer, 2010 (35)</td>
<td>186</td>
<td>397,047</td>
<td>1.66 (1.29, 2.14)</td>
</tr>
<tr>
<td>Wang, 2011 (23)</td>
<td>399</td>
<td>411</td>
<td>1.28 (1.02, 1.59)</td>
</tr>
<tr>
<td>Mikhailichenko, 1976 (31)</td>
<td>445</td>
<td>1,816</td>
<td>1.80 (1.46, 2.22)</td>
</tr>
<tr>
<td>Risch (this analysis)</td>
<td>625</td>
<td>663</td>
<td>1.31 (1.07, 1.61)</td>
</tr>
<tr>
<td>Zhou, 2005 (25)</td>
<td>476</td>
<td>845</td>
<td>0.93 (0.76, 1.14)</td>
</tr>
<tr>
<td>Rahbari, 2012 (38)</td>
<td>431</td>
<td>8,072</td>
<td>1.35 (1.14, 1.61)</td>
</tr>
<tr>
<td>Ben, 2011 (26)</td>
<td>1,022</td>
<td>970</td>
<td>1.23 (1.05, 1.45)</td>
</tr>
<tr>
<td>Aird, 1960 (28)</td>
<td>348</td>
<td>32,893</td>
<td>1.16 (0.99, 1.36)</td>
</tr>
<tr>
<td>Low, 2010 (36)</td>
<td>725</td>
<td>3,635</td>
<td>1.18 (1.01, 1.37)</td>
</tr>
<tr>
<td>Wolpin, 2010 (27)</td>
<td>1,023</td>
<td>926</td>
<td>1.43 (1.27, 1.61)</td>
</tr>
<tr>
<td>Total Pooled (CE studies)</td>
<td>4,087</td>
<td>27,675</td>
<td>1.20 (1.11, 1.30)</td>
</tr>
<tr>
<td>Total Pooled (CNE studies)</td>
<td>3,065</td>
<td>460,988</td>
<td>1.41 (1.26, 1.57)</td>
</tr>
<tr>
<td>Total Pooled (All studies)</td>
<td>7,152</td>
<td>488,663</td>
<td>1.31 (1.21, 1.41)</td>
</tr>
</tbody>
</table>
## Risk of pancreatic cancer in US Jews according to birthplace

<table>
<thead>
<tr>
<th>First Author, Year</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>European Born</strong></td>
<td></td>
</tr>
<tr>
<td>MacMahon, 1960</td>
<td>1.38 (1.19-1.61)</td>
</tr>
<tr>
<td>Newill, 1981</td>
<td>1.23 (1.14-1.32)</td>
</tr>
<tr>
<td>Haenszel, 1961</td>
<td>1.51 (1.25-1.82)</td>
</tr>
<tr>
<td>Moldow, 1968</td>
<td>1.47 (0.84-2.57)</td>
</tr>
<tr>
<td>Seidman, 1970</td>
<td>1.21 (1.06-1.39)</td>
</tr>
<tr>
<td>Greenwald, 1975</td>
<td>1.15 (0.83-1.59)</td>
</tr>
<tr>
<td>Eldridge, 2011</td>
<td>1.03 (0.73-1.44)</td>
</tr>
<tr>
<td>Wynder, 1973</td>
<td>1.36 (0.99-1.87)</td>
</tr>
<tr>
<td><strong>Pooled, European Born</strong></td>
<td><strong>1.27 (1.19-1.36)</strong></td>
</tr>
</tbody>
</table>

| **Mixed European/North American Born** |
| Mack, 1985       | 1.39 (1.20-1.62) |
| Coogan, 2000     | 1.60 (1.11-2.32) |
| **Pooled, Mixed Born** | **1.42 (1.23-1.63)** |

| **North American Born** |
| Eldridge, 2011    | 1.47 (1.33-1.63) |
| Risch, unpublished | 1.87 (1.19-2.94) |
| **Pooled, No. American Born** | **1.49 (1.33-1.68)** |
| **Total Pooled (All studies)** | **1.34 (1.26-1.43)** |
Pancreatic Cancer and *Helicobacter pylori* Seropositivity

Likely a gastric acidity mechanism involved.

Risch, JNCI 2003; Mol Carcinog 2012.
Why should Jews be at Higher Risk?

Overall, Jews should be at *lower* risk of pancreatic cancer compared to non-Jews.

Fewer Jews are current smokers (7%↓).

Ex-smokers average quit 30 years in past.

Non-O ABO accounts for ~2.5%↑ in Jews.

BRCA1/2 mutations ~7↑% in Jews.

Positive family history infrequent.

Differences in BMI and diabetes are small.

Education: adj OR=0.85/category (p=10⁻⁴.¹).

For Jews, OR=1.87 adj for education but 2.30 unadjusted, thus education ~20%↓.

Likely a genetic contribution to increased risk for Jews.
Education is Strongly Inversely Associated with Colonization by *Helicobacter pylori*

Over the last 2-3 generations, *H. pylori* colonization in the US and other developed countries has been declining substantially, particularly of CagA+ strains.

This decline closely follows increases in socioeconomic status and education, which differ strongly between Jews and non-Jews, but are seen in both.

Thus, the protective effect of CagA-positive colonization for pancreatic cancer has been waning and average US risks slowly continue to increase.
Reducing Mortality of Pancreatic Cancer

**Primary Prevention**

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Pancreas

Chemoprevention factors:
Pancreas

Chemoprevention factors:

True, little established to-date. Candidates:

- Capsaicin
- Sulforaphane
- Saffron
- Green tea
- Aspirin
- Curcumin
- Flavonoids
- Citrus or Vitamin C
- Fruits and vegetables in general
- NSAIDs in general

Little consistent human evidence for any of these, except for Vitamin C and Aspirin.
Vitamin C and Risk of Pancreatic Cancer

Significant association for case-control studies ($p = 10^{-13.1}$) but not for cohort studies ($p = .61$).

Reverse causality?

Diet changes before diagnosis?

Lack of recent diet information?
Aspirin and Risk of Pancreatic Cancer

Time trend with mid-year of study:

\[ \text{OR} = \exp(0.29 - 0.019 \times (\text{year} - 1976)) \]

Trend \( p = 0.00012 \)

Fitted 2011 OR = 0.69 (0.62–0.78)
Low-dose Aspirin and Risk of Pancreatic Cancer

Time trend with mid-year of study:

\[ OR = \exp(0.14 - 0.027 \times (\text{year} - 1991)) \]

Trend \( p = 0.0059 \)

Fitted 2011 OR = 0.68 (0.55-0.82)

Risch et al, Cancer Epidemiol Biomarkers Prev, 2017
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**Early detection:** There is currently no reliable method for the early detection of pancreatic cancer.

**LABORATORY TESTING**

Molecular markers of pancreatic malignancy do not have a significant role in screening for pancreatic cancer. Both the carcinoembryonic antigen and the CA 19-9 lack specificity and sensitivity. In this case, the CA 19-9 level was found to be within the normal range, despite the presence of malignancy.

Odds Ratios Needed in Models for Rare Diseases

Prior Probability = 0.1%

Wentzensen and Wacholder, Cancer Discovery, 2013.
MUC5AC Expression in Normal and Cancer Tissue

Figure 3. MUC5AC expression in normal tissues (left) and cancer tissues (right). No other organ sites of normal tissue showed expression (omitted for brevity).
Figure 4. ROC curves for serum 1-13M1 epitope MUC5AC (Kaur et al., 2017). EPC = early stage pancreatic cancer; PC = pancreatic cancer; HC = healthy controls; CP = chronic pancreatitis; BC = breast cancer.

**Figure 2.** ROC curves in Shanghai and Connecticut studies. All curves have >60% sensitivity at 90% specificity (red box).
Odds Ratios Needed in Models for Rare Diseases

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Wentzensen and Wacholder, Cancer Discovery, 2013.
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**Signs and symptoms:** Cancer of the pancreas usually develops without early symptoms. Symptoms may include weight loss, mild abdominal discomfort that may radiate to the back, and occasionally the development of diabetes. Tumors that develop near the common bile duct may cause a blockage that leads to jaundice (yellowing of the skin and eyes), which can sometimes allow the tumor to be diagnosed at an early stage. Signs of advanced stage disease may include severe abdominal pain, nausea, and vomiting.
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Also: anorexia, dysgeusia, heartburn, acute pancreatitis.
Risk of Pancreatic Cancer by Years in the Past of Diabetes Diagnosis

Connecticut Pancreas Cancer Study

Risch et al., Am J Epidemiol 2015
Risk of Pancreatic Cancer by Years in the Past of Quitting Cigarette Smoking

Connecticut Pancreas Cancer Study

Risch et al., Am J Epidemiol 2015
Risk of Pancreatic Cancer by Years in the Past of Pancreatitis Diagnosis

Connecticut Pancreas Cancer Study

Risch et al., Am J Epidemiol 2015
Risk of Pancreatic Cancer by Years in the Past of Starting Use of PPIs

Connecticut Pancreas Cancer Study
Conclusions and Next Steps

Modifiable Risk Factors:

Cigarette smoking accounts for about 20% and successful cessation by age 40 decreases most of the elevated risk by age 60. Long-term obesity and diabetes contribute to risk.

Chemoprevention:

Aspirin use, including low-dose aspirin, likely cuts risk by one-third. Perhaps half or more of the general population has indications for use of aspirin (cardioprophylaxis, familial risk of colon cancer, etc.). What about PPI use? May counteract the secular trend of declining CagA+ *H. pylori* colonization. If not initiated for GERD symptoms, PPIs may lower risk—odds ratio for starting use 10+ years in past = 0.88. Needs further study. Have to determine whether Vitamin C association is real or artifactual.
Conclusions and Next Steps

Early Detection:

Combinations of quitting smoking, symptomatic starting of PPI use, diagnoses of diabetes and pancreatitis that are temporally related, especially at older ages, can be self-recognized without lab tests. These prodrome factors may yield 2-3 years earlier diagnosis and more access to surgical resection as treatment. Whether the improved survival would exceed the lead time must be determined empirically.

Molecular markers may contribute to prodrome-factor models but are just beginning to achieve sufficient specificity and sensitivity to be useful as stand-alone early-detection or diagnostic markers. Nevertheless, marker exploration is still potentially important and needs clinical validation.
Conclusions and Next Steps

Lung cancer is a largely man-made disease. Pancreatic cancer is not, but we still have opportunities to achieve reductions in its horrible mortality. It should not be considered a “rare” disease, just because other less fatal types of cancer are more common.