Pancreatic Cancer: How to identify high-risk population

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The Facts
Looking into the future: hoping to be wrong
Death rates from *pancreatic cancer* are rising while rates for all other cancers continue to fall in Europe.

PERSONALIZED PREVENTION OF PANCREATIC CANCER

Malvezzi M, Ann Oncol 2014

Pancreatic Cancer Aetiology: Complex

64% attributed to environmental factors
(Lichtenstein P et al. NEJM 2000)

Klein et al. Mol Carcinog 2012
Anticipating **Pancreatic Cancer**: Complex ???

**General Population**
Lifetime PC risk = 0.7%

**High-risk**
Lifetime PC risk >16%

- 90% sporadic
- 8% FPC
- 2% HPC
**PANCREATIC CANCER**: A chronic inflammation-related disease

- **Obesity** PAF=3-16%
- **Tobacco** PAF=11-32%
- **A/B Blood group** PAF=13-19%
- **Alcohol** PAF<9%
- **Allergy/Asthma** PAF=3-7%
- **Metals** (Cd, As, Pb)
- **Helicobacter pylori**
- **Chronic pancreatitis** PAF<3%
- **Family history** PAF=3-10%
- **Selenium**
- **Vitamin D**
- **Statins Metformin**
- **ASA NSAIDs**

PAF: Population Attributable Fraction
Lowenfels et al. Int J Epidemiol 2015
Enriching pancreatic cancer high-risk population: 2-step filter
European Study of Chronic Pancreas Diseases and Genetic

PanGenEU Study

• Hospital-based case-control and cohort study

• Consensus pathology review

• Samples (uniform SOPs)
  • Blood
  • Saliva
  • Urine
  • Toenails
  • Tissue
  • Stool

• Information (EPIQUEST)
  • Epidemiologic
  • Clinical-pathological
  • Prospective follow-up

From 2009 to 2013 28 centres

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Controls</th>
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</thead>
<tbody>
<tr>
<td>Informed consent</td>
<td>2299</td>
<td>1450</td>
</tr>
<tr>
<td>Epi questionnaire</td>
<td>2246</td>
<td>1304</td>
</tr>
<tr>
<td>Clinical &amp;FU data</td>
<td>1175</td>
<td>-</td>
</tr>
<tr>
<td>Blood</td>
<td>2036</td>
<td>1350</td>
</tr>
<tr>
<td>Saliva</td>
<td>1319</td>
<td>1008</td>
</tr>
<tr>
<td>Urine</td>
<td>1608</td>
<td>950</td>
</tr>
<tr>
<td>Toenails</td>
<td>636</td>
<td>669</td>
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</table>

External Scientific Advisors:
D Silverman (NCI, USA)
D Easton (Cambridge U, UK)
PANCREATIC CANCER EXPOSOME

- Periodontitis
- Diabetes
- Helicobacter pylori
- Chronic pancreatitis
- Family history
- Tobacco
- Metals (Cd, As, Pb)
- Selenium
- Vitamin D
- Obesity
- Metals (Cd, As, Pb)
- Allergy/Asthma
- Vitamin D
- Helicobacter pylori
- Chronic pancreatitis
- Family history
- Tobacco
- Selenium
- Obesity

First author, year | Odds Ratio [95%CI]
--- | ---
Mack et al., 1986 | 0.20 [0.05, 0.80]
Farrow et al., 1990 | 1.10 [0.38, 3.20]
Jain et al., 1991 | 0.52 [0.16, 1.70]
Kalapothaki et al., 1993 | 0.37 [0.06, 2.30]
Dai et al., 1995 | 1.00 [0.31, 3.20]
Silverman et al., 1999 | 1.00 [0.67, 1.50]
Eppel et al., 2007 | 0.60 [0.31, 1.16]
Maisonneuve et al., 2010 | 0.57 [0.33, 0.97]
Cotterchio et al., 2014 | 0.89 [0.61, 1.30]
PanGenEU | 0.64 [0.47, 0.88]

RE Model | 0.73 [0.59, 0.89]
Multimorbidity patterns and *pancreatic cancer* risk

**Time-dependence**

<table>
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<tr>
<th>Cases</th>
<th>Controls</th>
<th>OR*</th>
<th>95%CI</th>
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<tbody>
<tr>
<td>N=1705</td>
<td>N=1084</td>
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</table>

**Gastric + Diabetes**

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<tr>
<td>0</td>
<td>730</td>
<td>610</td>
<td>1</td>
</tr>
<tr>
<td>1</td>
<td>482</td>
<td>256</td>
<td>1.97</td>
</tr>
<tr>
<td>2</td>
<td>322</td>
<td>150</td>
<td>2.48</td>
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<tr>
<td>&gt;=3</td>
<td>171</td>
<td>68</td>
<td>3.5</td>
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</tbody>
</table>

P. of trend 4.39E-14

^ Heartburn, Acid regurgitation, H. pylori, Ulcer, and T2D

* Adjusted for age, sex, country, pack/years, and number of morbidities

† Last two categories combined into one (>=2 conditions). Subjects with >=3 con.
Autoimmune disease and *pancreatic cancer* risk

PanGenEU Study
1705 cases & 1084 controls

http://www.disgenet.org/web/DisGeNET
PANCREATIC CANCER and GENOME

- Metals (Cd, As, Pb)
- Obesity
- Tobacco
- A/B Blood group
- Statins
- Metformin
- Alcohol
- ASA NSAIDs
- Allergy/Asthma
- Helicobacter pylori
- Diabetes
- Chronic pancreatitis
- Periodontitis
- Family history
- Selenium
- Vitamin D
- Family history

GENOME
PANCREATIC CANCER and GENOME


https://www.ebi.ac.uk/gwas/
PANCREATIC CANCER and GENOME

- Periodontitis
- Diabetes
- Helicobacter pylori
- Chronic pancreatitis
- Metabolism (Cd, As, Pb)
- Tobacco
- Obesity
- A/B Blood group
- Statins
- Pancreatitis Metformin
- Alcohol
- ASA
- NSAIDs
- Allergy/Asthma
- Selenium
- Vitamin D
- Family history

GENOME Blood
(SNP, CNV, Rare variants)
GWAS (PanGenEU)
WES/WGS (ICGC)

López de Maturana E, et al. *Work in progress*
**PANCREATIC CANCER** and METHYLATION

- Metals (Cd, As, Pb)
- Helicobacter pylori
- Chronic pancreatitis
- Periodontitis
- Diabetes
- Obesity
- Tobacco
- A/B Blood group
- Statins
- Metformin
- Alcohol
- ASA
- NSAIDs
- Allergy/Asthma
- Family history
- Selenium
- Vitamin D

**GENOME**
- Blood
  - SNP, CNV, Rare variants
- GWAS (PanGenEU)
- WES/WGS (ICGC)

**EPIGENOME**
- Blood
  - mCpG
- 850K Illumina
- Col. M Fraga, UNIOVI

Alonso L, et al. *Work in progress*
PANCREATIC CANCER and MICROBIOME

- Periodontitis
- Diabetes
- Helicobacter pylori
- Chronic pancreatitis
- Tobacco
- Obesity
- A/B Blood group
- A/B Blood group
- Statins
- Metformin
- Alcohol
- ASA NSAIDs
- Allergy/Asthma
- Selenium
- Vitamin D
- Metals (Cd, As, Pb)
- Family history

**GENOME**
- Blood
  - SNP, CNV, Rare variants
  - GWAS (PanGenEU)
  - WES/WGS (ICGC)

**EPIGENOME**
- Blood
  - (mCpG)
  - 850K Illumina
  - Col. M Fraga, UNIOVI

**MICROBIOME**
- Oral – Gut
  - (pathogens)
  - MetaG, 16S
  - Col. P Bork, EMBL

Molina E & Gómez P. Work in progress
Multifactorial PANCREATIC CANCER aetiology

- Periodontitis
- Diabetes
- Chronic pancreatitis
- Helicobacter pylori
- Obesity
- Tobacco
- Blood group A/B
- Statins
- Metformin
- Vitamin D
- Alcohol
- ASA
- NSAIDs
- Allergy/Asthma
- Selenium
- Metals (Cd, As, Pb)
- Family history
- Periodontitis

**GENOME**
- Blood
- SNP, CNV, Rare variants
- GWAS (PanGenEU)
- WES/WGS (ICGC)

**EPIGENOME**
- Blood
- mCpG
- 850K Illumina
- Col. M Fraga, UNIOVI

**MICROBIOME**
- Oral – Gut
- Pathogens
- MetaG, 16S
- Col. P Bork, EMBL

Molina E & Gómez P. Work in progress
Take-home Messages

1. Pancreatic cancer aetiology is complex with highly-correlated genomic and non-genomic factors involved

2. Definition of high-risk populations should mirror such complexity by building multifactorial algorithms

3. Multimorbidity patterns associate with pancreatic cancer, highlighting the importance of the systems concept (diseasome)

4. Hyper-reactivity of the immune system (asthma, allergies, and autoimmune diseases) reduces the risk of pancreatic cancer

5. Medical conditions included in the multimorbidity patterns have a common genetic background partly shared with pancreatic cancer

6. Genomics, methylomics, and microbiomics patterns associated with pancreatic cancer risk
Anticipating Pancreatic Cancer: Complex ???

High-risk population:
- Precursor Conditions (NODM, Chronic pancreatitis)
- Precursor Lesions (IPMN)
- Risk/Protective Factors

General Population
Lifetime PC risk = 0.7%

High-risk
Lifetime PC risk >16 %
Larger investment in primary & secondary prevention

Present/Future challenges in *pancreatic cancer* aetiology research

- Need to apply a “**systems thinking**”
- Large & international **standardized** studies
- **Longitudinal** data and sample collection
  - e-*medical records*
  - novel “smart” technologies: **e-exposures**
  - associated **biobanks** using same SOPs
- **Omics** data generation: adequate **platforms**
- Next-generation database platforms and Quantum-computing
- Algorithms allowing *Omics* and non-*omics** data integration
- **Multidisciplinary** approaches involving health professionals
Acknowledgments

PanGenEU Study

CNIO, Madrid (Genetic and Molecular Epidemiology, Epithelial Carcinogenesis (FX Real), Structural Computational Biology, Bioinformatics Unit, Human Genotyping Unit-CEGEN)

Institut Municipal d’Investigació Mèdica, Barcelona
Hospital del Mar, Barcelona (I Poves, L llzarbe)
Hospital de Sant Pau, Barcelona (A Farré)
Hospital Vall d’Hebron, Barcelona (X Molero, L Guarner)
Hospital Universitari d’Oviedo (A Tardón)
Hospital CLínic de Salamanca (L Muñoz-Bellvis)
Hospital Universitario de Santiago de Compostela (E Dominguez-Muñoz)
Hospital Universitari de Elche (V Barberá)
Hospital 12 de Octubre, Madrid (P Peláez)
Hospital Ramón y Cajal, Madrid (A Carrato)
Centro Oncológico Integral “Clara Campal”, Madrid (M Hidalgo)

Philipps-Universität Marburg (T Gress, M Buchholz)
Technische Universität Munchen (C Michalski)
University of Liverpool (B Greenhalf)
Queen Mary University of London (T Crnogorac-Jurcevic)
Univsersità di Verona (A Scarpa, R Lawlor)
Karolinska Institute, Stockholm (M Löhrl)
PanCAM, Ireland (L Sharp, L Murray)

External Scientific Advisors: D Silverman (NCI, US), D Easton (Sanger, UK)

Patients, monitors, technicians, doctors, and researchers

Multimorbidity studies Investigators

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Chronic Pancreatitis Team: D Whitcomb, L Amundadottir, M Lehr, W Greenhalf, A Ferré, X Molero

Pancreas cancer studies collaborators

Microbiome: P Bork (EMBL, Germany)
Methylome: M Fraga (UniOvi, Spain)
ICGC: A Biankin (Glasgow U, UK), S Gallinger (OICR, Canada)
PanGenFAM: A Carrato (HRyC, Spain)
Pancreatic Cancer Europe // PancreOS Registry

EUPancreas COST Action

Vice-Chair: C La Vecchia (U. Milan, Italy)

WG Coordinators: I Esposito (U. Düsseldorf, Germany), K Van Steen (U. Liège, Belgium), S Hahn (U. Bohum), A Brand (U Maastricht)

Action coordination: E Molina (CNIO, Spain)
PANCREATIC CANCER and MICROBIOME

Periodontitis

Diabetes

Chronic pancreatitis

Obesity

Allergy/Asthma

Helicobacter pylori

Neisseria elongata

Streptococcus mitis

Porphyromona gingivalis

Aggregatibacter actinomycetemcomitans

Phylum Fusobacteria

Leptotrichia

NIH Public Access


Variations of oral microbiota are associated with pancreatic diseases including pancreatic cancer

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