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www.imim.es/URECMC/eng

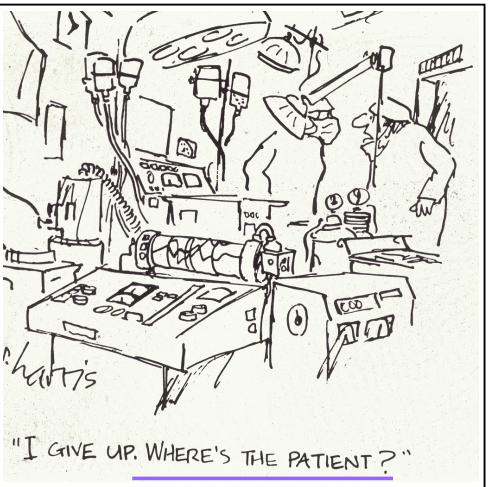
Early Training Session
Friday, September 7
07:30 am – 08:30 am

between

the environment...

and

the molecules...



Between molecules and the environment: keeping patients in the picture.

Miquel Porta

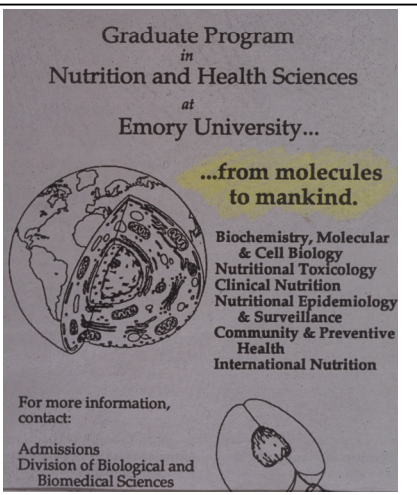
Early Session

between

the environment... mankind...

and

the molecules...

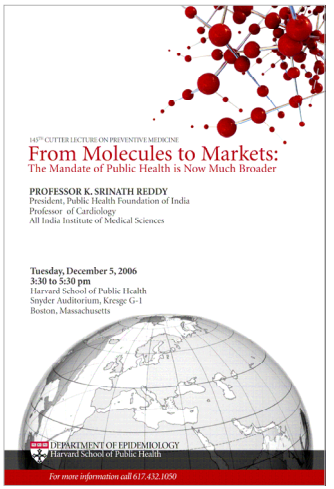


between

the environment...
mankind...
markets...

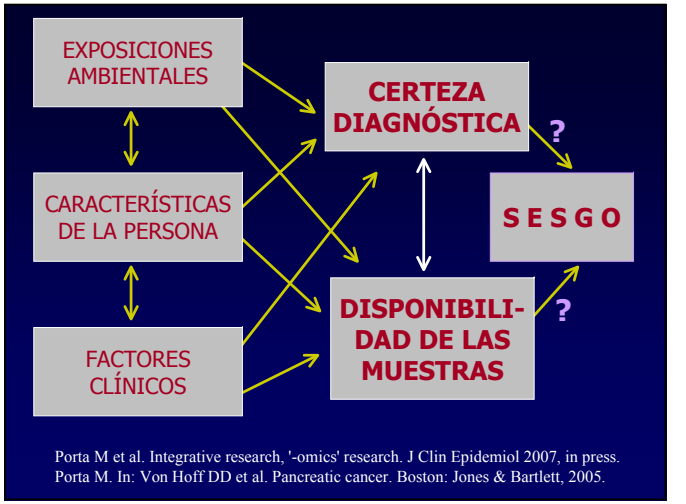
and

the molecules...



Objective: to discuss how disease characteristics and other clinical factors (e.g., signs and symptoms, diagnostic and therapeutic procedures), as well as study conduct (e.g., patient selection, timing of blood extraction) may affect measurement of exposure biomarkers and influence the internal validity of research studies.

We will use real data from studies on the etiological significance of blood concentrations of organochlorine compounds in pancreatic and other cancers. We will analyze what might be relevant clinical factors --in this and other chronic diseases-- that may need to be taken into account during the design, conduct, analysis and interpretation of studies. We will discuss the advantages and limitations of different design options (e.g., retrospective case-control studies and case-control studies nested within cohorts).



Porta M et al. Integrative research, '-omics' research. J Clin Epidemiol 2007, in press.
Porta M. In: Von Hoff DD et al. Pancreatic cancer. Boston: Jones & Bartlett, 2005.

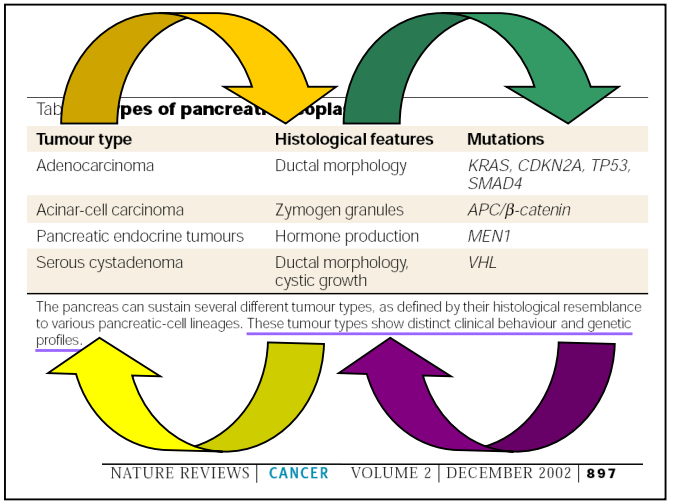
→ integrate...

Integrative research

Yes.

- **Clinical investigation in the XX century: the major change was the rise of quantitative reasoning –medical statistics and clinical applications of epidemiology.**
- **Scientific explanations in medicine are an *integration* of numerical (statistical and epidemiological, i.e., probabilistic and empirical) and mechanistic (deterministic and explanatory) reasoning.**

Vandenbroucke JP.
***Lancet* 1998; 352 (Supl. 2): S212-S216.**



Tab pes of pancreat opla

Tumour type	Histological features	Mutations
Adenocarcinoma	Ductal morphology	*KRAS, CDKN2A, TP53, SMAD4*
Acinar-cell carcinoma	Zymogen granules	*APC/β-catenin*
Pancreatic endocrine tumours	Hormone production	*MEN1*
Serous cystadenoma	Ductal morphology, cystic growth	*VHL*

The pancreas can sustain several different tumour types, as defined by their histological resemblance to various pancreatic-cell lineages. These tumour types show distinct clinical behaviour and genetic profiles.

MOLECULAR CARCINOGENESIS 36:45–52 (2003)

WORKING HYPOTHESIS

Exploring Environmental Causes of Altered *ras* Effects: Fragmentation Plus Integration?

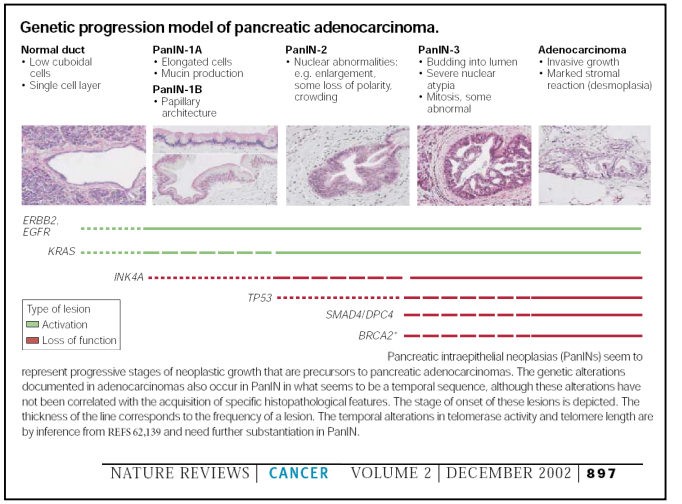
Miquel Porta,[1,2]* Daniel Ayude,[1,2] Juan Alguacil,[1,3] and Manuel Jariod[1]
[1]*Institut Municipal d'Investigació Médica, Barcelona, Spain*
[2]*Universitat Autónoma de Barcelona, Catalonia, Spain*
[3]*Occupational Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland*

Human cancer, carcinogenic exposures and mutation spectra

Paolo Vineis [a,*], Nùria Malats [b], Miquel Porta [b], Francisco X. Real [c]

Causal Thinking, Biomarkers, and Mechanisms of Carcinogenesis*

Paolo Vineis[1] and Miquel Porta[2]
[1]UNIT OF CANCER EPIDEMIOLOGY, 10126 TORINO, ITALY AND [2]INSTITUT MUNICIPAL D'INVESTIGACIÓ MÈDICA, UNIVERSITAT AUTÒNOMA DE BARCELONA, BARCELONA, SPAIN E-08003



Genetic progression model of pancreatic adenocarcinoma.

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

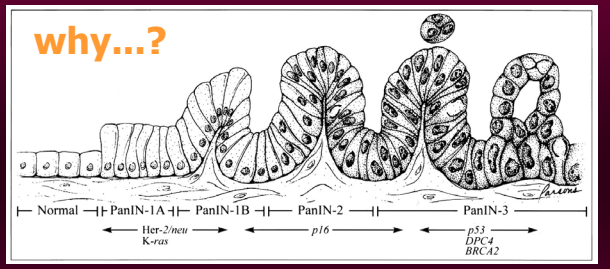
Adenocarcinoma
- Invasive growth
- Marked stromal reaction (desmoplasia)

ERBB2, EGFR
KRAS
INK4A
TP53
SMAD4/DPC4
BRCA2

Type of lesion
Activation
Loss of function

Pancreatic intraepithelial neoplasias (PanINs) seem to represent progressive stages of neoplastic growth that are precursors to pancreatic adenocarcinomas. The genetic alterations documented in adenocarcinomas also occur in PanIN in what seems to be a temporal sequence, although these alterations have not been correlated with the acquisition of specific histopathological features. The stage of onset of these lesions is depicted. The thickness of the line corresponds to the frequency of a lesion. The temporal alterations in telomerase activity and telomere length are by inference from REFS 62,139 and need further substantiation in PanIN.

why...?



**Hruban RH, Goggins M, Parsons J, Kern SE.
Progression model for pancreatic cancer.
Clin Cancer Res 2000; 6: 2969-72.**

why...?

Why is not more research being done
– on 'why'?
– on the causes of genetic alterations that have a well-established role in diseases of complex etiology?

... y sólo una minoría de la investigación trata de:

b) las causas de las alteraciones genéticas adquiridas.
b1) las exposiciones ambtls. como causas de alters. gén. adq.

Although a genetic profile for pancreatic cancer is emerging, many biological aspects of this disease are poorly understood. Indeed, fundamental questions regarding progenitor cell lineages, host stromal milieu, and the role of specific genetic alterations in tumor progression remain unresolved.

Bardeesy N et al.
The genetics of pancreatic adenocarcinoma:
a roadmap for a mouse model
SEMINARS IN CANCER BIOLOGY 2001

+ Bardeesy & DePinho. *Nature Reviews Cancer* 2002.

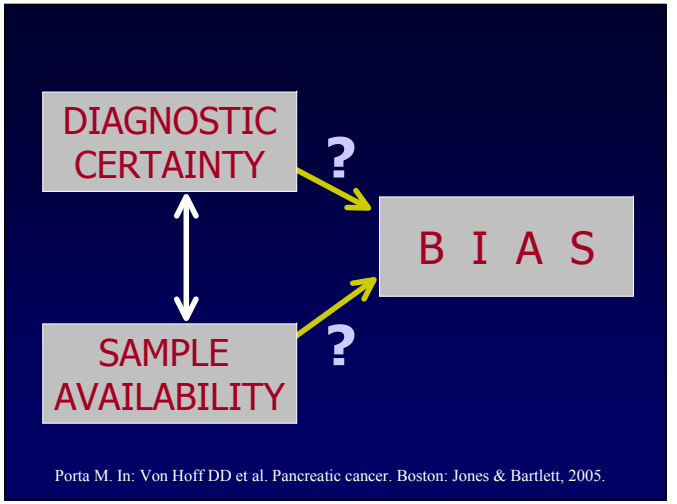
Out of 31,136 cases of primary invasive pancreatic cancer recorded by SEER in 1973 - 1987, 23,107 (74%) were confirmed histologically.

Carriaga & Henson. *Cancer* 1995

Histologic distribution, microscopically confirmed cases (n=23,107) SEER, 1973-87

Histology	%
Carcinoma	98.4
"Epidermoid"carcinoma	0.4
Adenocarcinoma	**81.8**
Adenocarcinoma, NOS	**69.2**
Papillary adenocarcinoma, NOS	0.8
Mucinous adenocarcinoma	2.5
Mucin-producing adenocarcinoma	3.5
Infiltrating duct carcinoma	3.9
Other specific carcinomas	2.6
Islet cell carcinoma	1.7
Unspecified ("Carcinoma, NOS")	13.5
Sarcoma	0.1

Carriaga & Henson. *Cancer* 1995



Histopathological confirmation (%) among incident cases of cancer of the pancreas, males, all ages.

Area	Registry Entries	Mean (%)	Range (%)
Poland	6	21	11-31
Africa	3	29	14-40
United Kingdom	13	38	24-64
Latin America	9	39	13-73
Japan	6	44	28-56
Canada	12	51	33-65
Scandinavia	5	74	55-86
United States	14	77	63-85

From Parkin et al., 1992. In: Schottenfeld & Fraumeni, 1996: 727.

La Vecchia C et al. Eur J Cancer 1992; 28: 132-235.

PANCREAS

Certified mortality from pancreatic cancer over the last 4 decades has been systematically upwards in all European countries. Only in Britain has a favourable trend been observed since the late 1970s, particularly in middle aged men. Starting from appreciably lower levels, mortality rates approached 8–12/100 000 males and 4–6/100 000 females in most countries over most recent years.

Since this is a tobacco-related site [16, 32, 33], some of these generalized upward trends are probably real, and related to increased tobacco consumption over the past decades [33]. These trends should however be considered with caution, since the diagnosis of pancreatic cancer is difficult, and hence the reliability of death certification generally poor. Thus, at least part of the upward trends registered are probably attributable to improved diagnosis and certification.

Not surprisingly, therefore, the upward trends were more moderate in middle aged and even smaller in the younger age groups, when death certification is more accurate and reliable.

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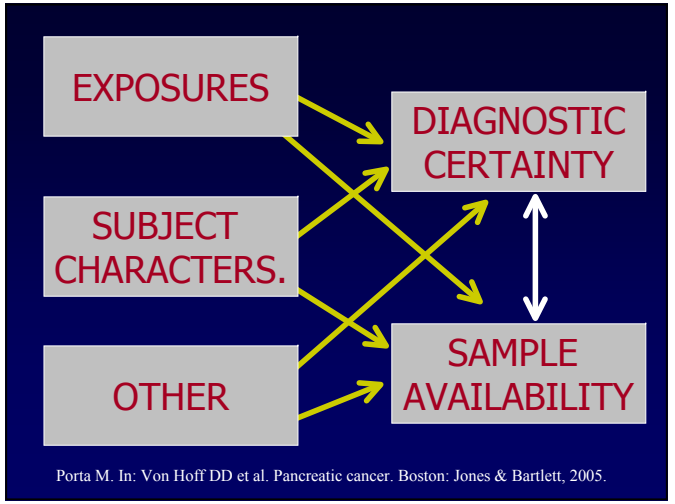
Carriaga & Henson. *Cancer* 1995



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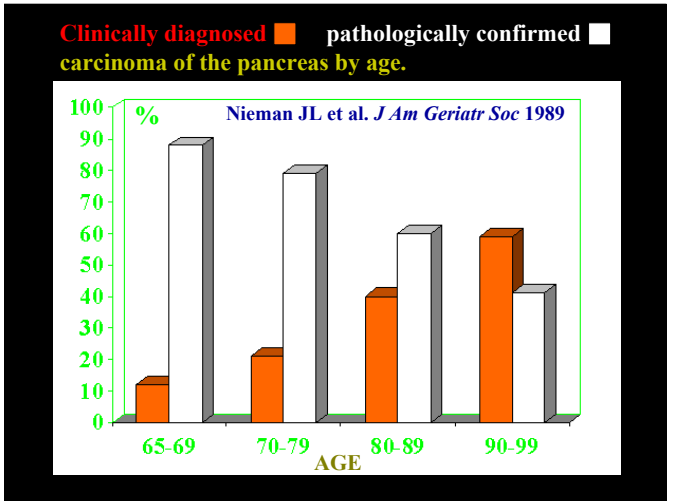


Accuracy of diagnosis of pancreatic cancer decreases with increasing age.

Nieman JL et al. J Am Geriatr Soc 1989

Pancreatic cancer is common in the elderly and often is diagnosed clinically without pathologic confirmation... The percentage of clinical diagnoses increased significantly from 12% in those aged in their 60s to 59% for those in their 90s ($P < .005$). Observed 5-year survival for all of the clinically diagnosed patients was 8.4% compared with 0.6% for those pathologically confirmed. ...These findings suggest that in many elderly patients clinical diagnoses of pancreatic cancer are wrong.

+Carpelan-Holmström et al., *Gut* 2005.
+Gudjonsson B, various years. +Levin DL, *Cancer* 1981.

PANCREAS

Gut 2005;**54**:385–387

Does anyone survive pancreatic ductal adenocarcinoma? nationwide study re-evaluating the data of the Finnish Cancer Registry

M Carpelan-Holmström, S Nordling, E Pukkala, R Sankila, J Lüttges, G Klöppel, C Haglund

Background: Worldwide survival data for ductal adenocarcinoma of the pancreas are the lowest among the 60 most frequent types of organ cancers. Hence published data on long time survivors of this disease are controversial. We performed a nationwide study comprising all Finnish patients diagnosed with pancreatic cancer in the period 1990–1996 who survived for at least five years after diagnosis.

Methods: Data on patients registered as five year survivors of pancreatic cancer were obtained from the Finnish Cancer Registry and Statistics Finland. Slides or paraffin blocks were collected from patients recorded as having histologically proven pancreatic ductal adenocarcinoma (PDAC) and were re-evaluated in a double blind fashion by three pathologists with special expertise in pancreatic pathology.

Results: Between 1990 and 1996, the Finnish Cancer Registry recorded 4922 pancreatic cancer patients, 89 of whom survived for at least five years. Reviewing this series of patients revealed 45 (49%) non-PDACs and 18 cases without histological verification. In 26 patients recorded as having histologically proven PDAC, re-evaluation of histological specimens confirmed PDAC in only 10 patients.

Conclusions: This study indicates that (1) the prognosis of PDAC remains poor and (2) careful histopathological review of all patients with pancreatic cancer is mandatory if survival data are to be meaningful.

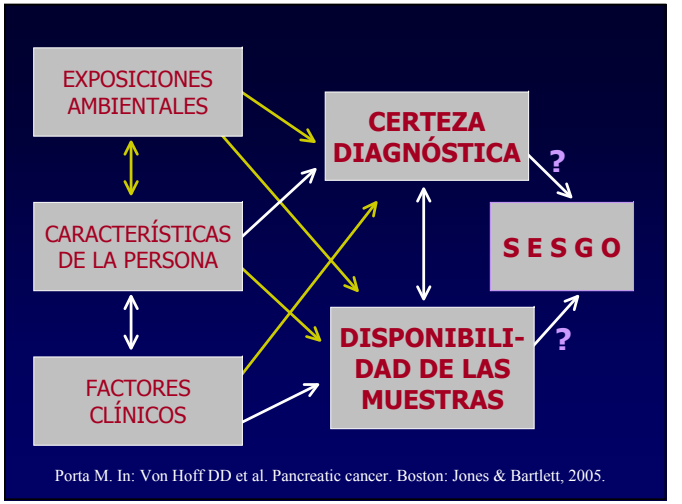
Table 1 Histological data from the Finnish Cancer Registry (1990–1996) for patients with pancreatic malignancies who survived for more than five years

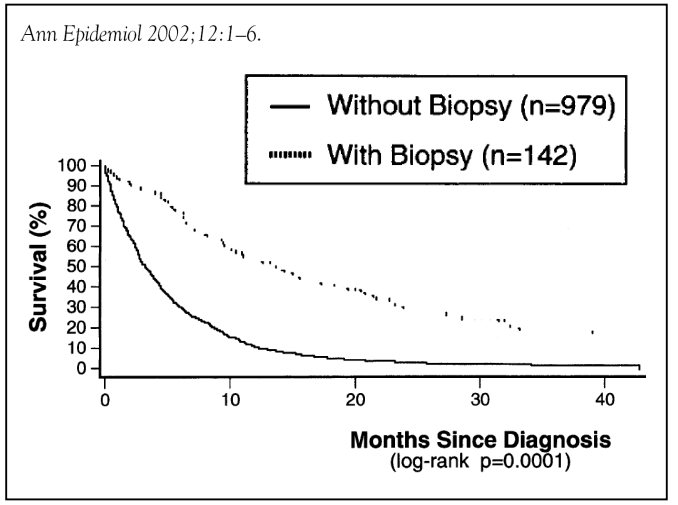
	n	(%)
Ductal pancreatic adenocarcinoma	26	29
Mucinous cystadenocarcinoma	7	8
Ampullary or periampullary carcinoma	12	13
Endocrine tumours	25	28
Benign lesion	1	1
Solid pseudopapillary neoplasm	1	1
Cytology only	7	8
Benign cytology: endocrine tumour	1	1
Malignant cytology: endocrine tumour	2	2
Malignant cytology: adenocarcinoma	4	4
Neither histology nor cytology	11	12
Total	89	100

Table 2 Histological re-evaluation of 26 patients who, according to the Finnish Cancer Registry, were diagnosed with pancreatic ductal adenocarcinoma between 1990 and 1996 and survived for at least 5 years

	n	(%)	Follow up data
Verified ductal adenocarcinoma	10	38	
Stage IA (T1 N0 M0)	1	4	1 DCR (5.48 y)
Stage IB (T2 N0 M0)	5	19	3 DCR (5.10–5.86 y), 1 DOD (5.06 y), 1 AWC (13.4 y)
Stage IIA (T3 N0 M0)	2	8	1 DCR (5.31 y), 1 DOD (6.20 y)
Stage IIB (T2-3N1M0)	2	8	2 DCR (5.12–5.59 y)
Wrong diagnosis	14	54	
Intraductal papillary-mucinous neoplasm	2	8	
Solid pseudopapillary neoplasm	1	4	
Pancreatitis	2	8	
Serous cystadenoma	1	4	
Common bile duct carcinoma	1	4	
Ampullary/periampullary carcinoma	7	27	
Histological material not available	2	8	
Total	26	100	

DCR, dead from cancer recurrence; DOD, dead from other disease; AWC, alive without cancer.





Smoking: Reanalysis by Silverman et al.
[J Clin Epidemiol 1996; 49: 601-3]
of JNCI 1994; 86: 1510-1516

Microscopically confirmed ?	Considered «likely» to have had PC ?	OR (95%CI)* for «ever smokers»
YES	YES	1.8 (1.4 - 2.4)
NO	YES	1.3 (0.6 - 2.8)
---	NO	1.0 (0.4 – 2.4)

* Adjusted for age, race, sex, geographic area, alcohol drinking, gallbladder disease, and income.

Long-term survival after pancreatic adenocarcinoma–often a misdiagnosis?

Alanen KA, Joensuu H. Br J Cancer 1993

Prognosis of adenocarcinoma of the pancreas has remained poor, but a few patients are reported to live 5 years or longer after the diagnosis. Using the data of the Finnish Cancer Registry, we could identify only 78 patients (1.3%) who had survived for longer than 5 years after the diagnosis of pancreatic cancer among 5,837 patients diagnosed in Finland in 1975-1984. However, in 33 of the 78 cases a histological diagnosis of pancreatic cancer had never been made, and the majority of the remaining 45 patients turned out not to have pancreatic adenocarcinoma after a review. The results suggest that the majority of patients with long-term survival following the diagnosis of pancreatic cancer have never had pancreatic adenocarcinoma. Taking a biopsy from a suspected pancreatic neoplasm and careful histological evaluation may prohibit misdiagnosis of this highly lethal disease.