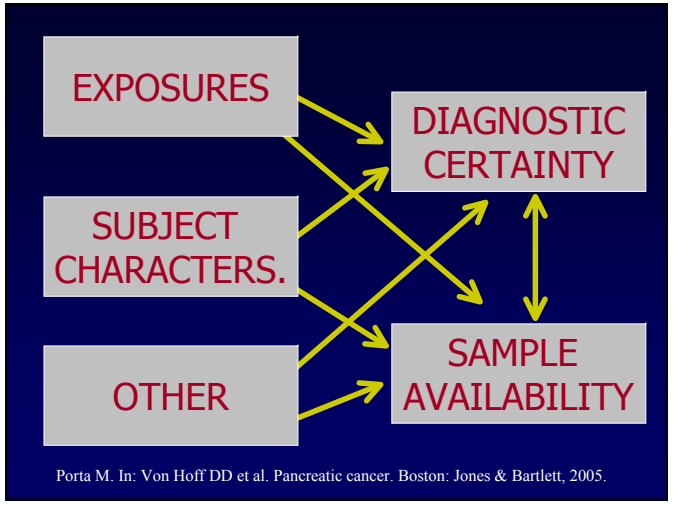


Porta M. In: Von Hoff DD et al. Pancreatic cancer. Boston: Jones & Bartlett, 2005.

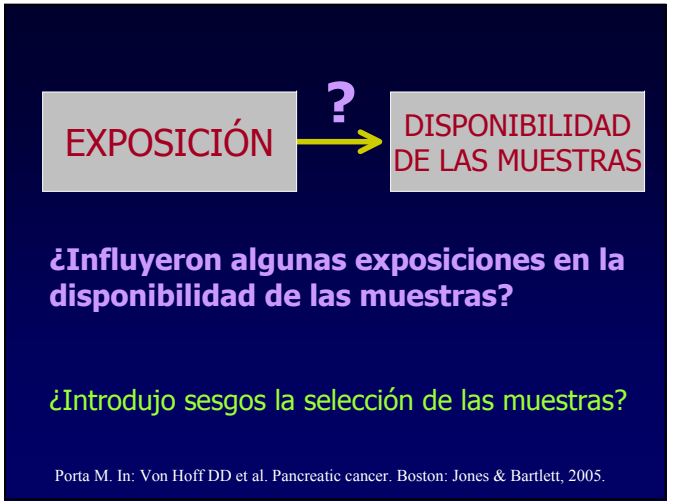
Porta M. In: Von Hoff DD et al. Pancreatic cancer. Boston: Jones & Bartlett, 2005.

DDT and related compounds and risk of pancreatic cancer

1.- Garabrant DH et al. *JNCI 1992; 84: 764-71.*
2.- Malats N, Real FX, Porta M.
+ Garabrant DH et al. *JNCI* 1993; 85: 328-9.

	DDT family	DDT	Ethylan	DDD
All subjects	3.3*	4.8*	5.0*	4.3*
Cytologically confirmed	21.0*	∞*	∞*	15.4*
Death certificate	0.8	1.0	2.6	1.4

*$P \leq 0.02$



Porta M. In: Von Hoff DD et al. Pancreatic cancer. Boston: Jones & Bartlett, 2005.

EXPOSICIÓN → ? CERTEZA DIAGNÓSTICA

¿Influyó alguna exposición en la validez de los diagnósticos (clínicos, anatomopatológicos, moleculares)?

¿Introdujo sesgos la selección de las muestras?

Porta M. In: Von Hoff DD et al. Pancreatic cancer. Boston: Jones & Bartlett, 2005.

EXPOSICIÓN → ? CERTEZA DIAGNÓSTICA

La 'MALACLASIFICACIÓN' DE LA ENFERMEDAD depende de alguna EXPOSICIÓN ?

(i.e., 'MALACLASIFICACIÓN DIFERENCIAL')

Porta M. In: Von Hoff DD et al. Pancreatic cancer. Boston: Jones & Bartlett, 2005.

SAMPLE AVAILABILITY → ? B I A S

Did biological sample procurement influence the characteristics of the patients under study?

Did sample selection introduce biases?

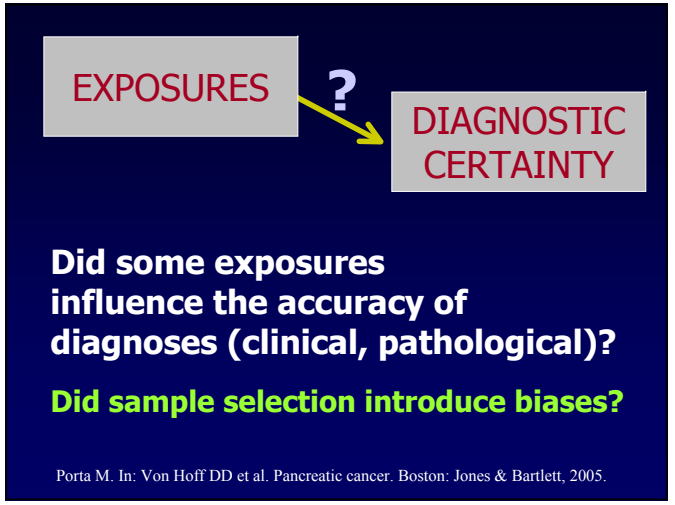
Porta M. In: Von Hoff DD et al. Pancreatic cancer. Boston: Jones & Bartlett, 2005.

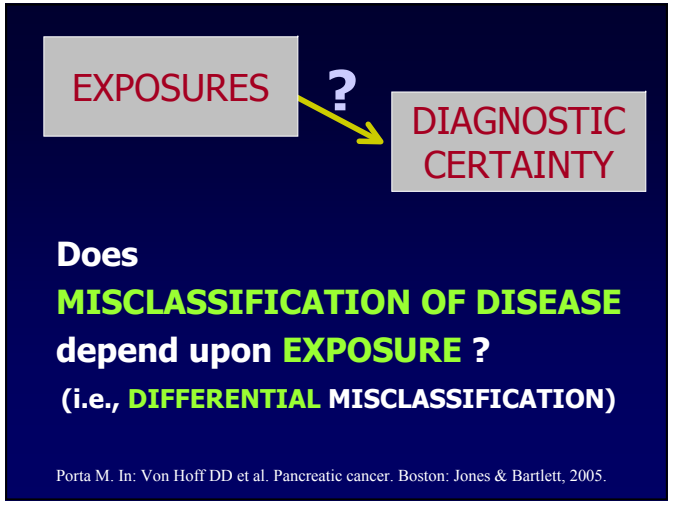
EXPOSURES → ? SAMPLE AVAILABILITY

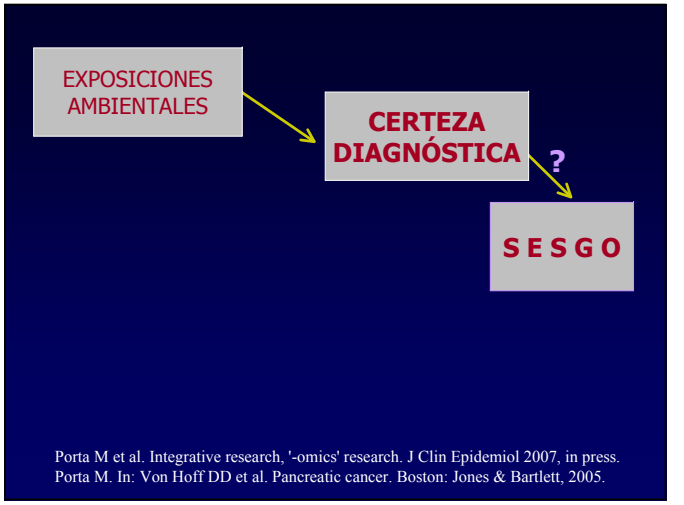
Did some exposures influence the availability of samples for the study?

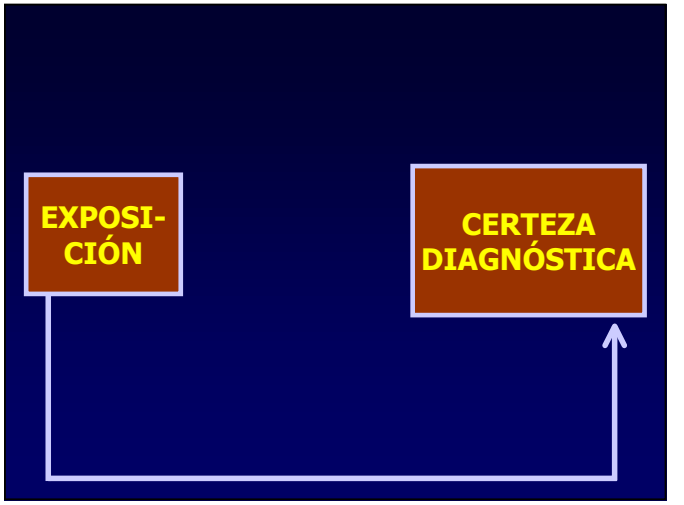
Did sample selection introduce biases?

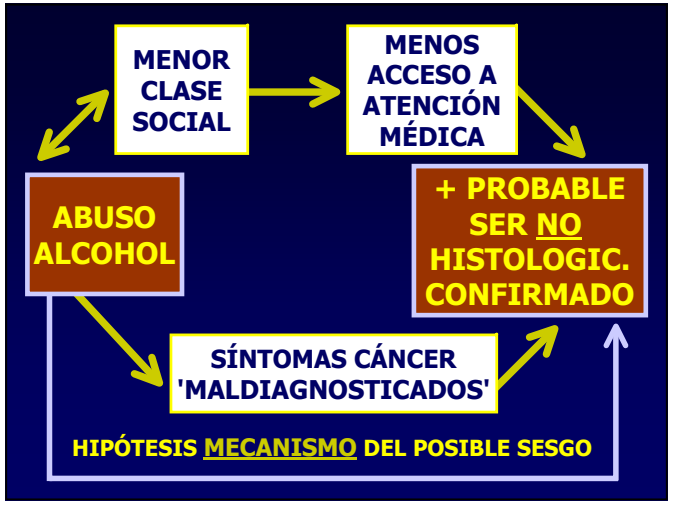
Porta M. In: Von Hoff DD et al. Pancreatic cancer. Boston: Jones & Bartlett, 2005.

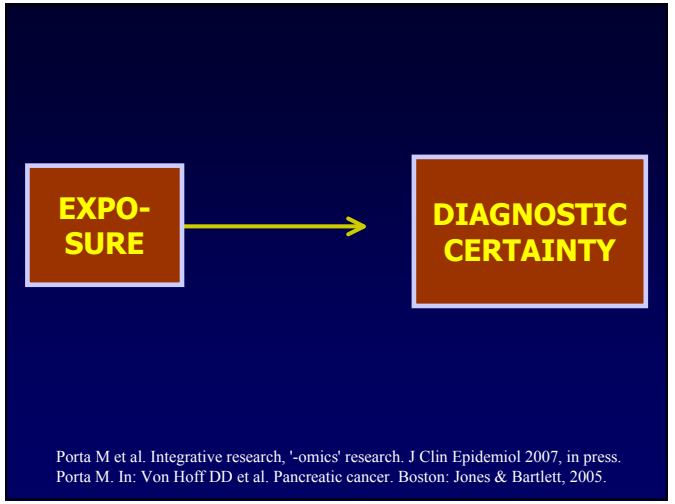

EXPOSURES
?
DIAGNOSTIC CERTAINTY
Did some exposures influence the accuracy of diagnoses (clinical, pathological)?
Did sample selection introduce biases?
Porta M. In: Von Hoff DD et al. Pancreatic cancer. Boston: Jones & Bartlett, 2005.

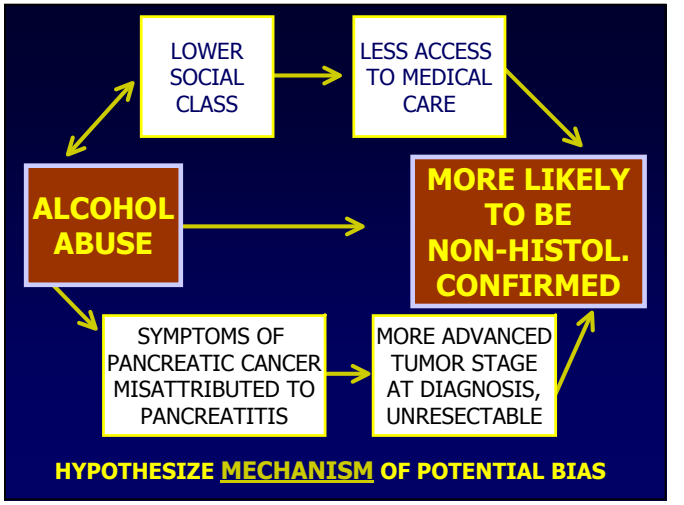

EXPOSURES
?
DIAGNOSTIC CERTAINTY
Does
MISCLASSIFICATION OF DISEASE
depend upon EXPOSURE ?
(i.e., DIFFERENTIAL MISCLASSIFICATION)
Porta M. In: Von Hoff DD et al. Pancreatic cancer. Boston: Jones & Bartlett, 2005.


EXPOSICIONES AMBIENTALES
CERTEZA DIAGNÓSTICA
?
S E S G O
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.


EXPOSI-CIÓN
CERTEZA DIAGNÓSTICA







Silverman DT et al. *Cancer Research* 1995

Case-control studies based exclusively on histologically confirmed cases may preferentially select cases with lower exposure to alcohol. Alcoholics may be more likely to be nonhistologically confirmed than nonalcoholics resulting from less access to medical care or cancer-related symptoms that are misdiagnosed as alcohol related.

Because we included all likely cases, regardless of histological confirmation, our study was less prone to this type of selection bias.

EXCLUDE PATIENTS
>70-80 years, without HV ?

PROBLEM:
Patients without HV ≈ 20 - 60% of all cases
Patients >70 years ≈ 30 - 40% of all cases

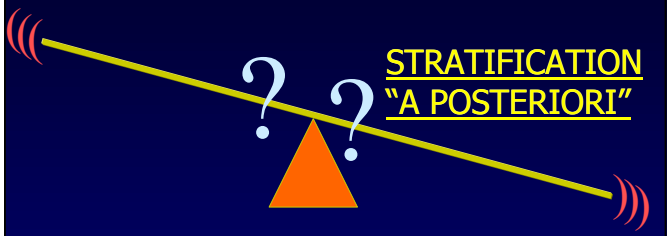
PROBLEM: ↓ EXTERNAL VALIDITY.

PROBLEM: ↓ SCIENTIFIC RELEVANCE.

PROBLEM: MISCLASSIFICATION may persist even with WITH HV.

RESTRICTION
"A PRIORI"

STRATIFICATION
"A POSTERIORI"



Porta M et al. J Clin Epidemiol 1994 & 1996
Silverman DT et al. Cancer Res 1995
Skinner HG et al. CEBP 2003
Michaud DS et al. Am J Epi 2003

IF classification of D was related to E (e.g., through age and sex)

THEN → risk of DIFFERENTIAL MISCLASSIFICATION

→ ↓ INTERNAL VALIDITY

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.

Ann Epidemiol 2002;12:7–14.

ELSEVIER

Attention to selection biases !

Generalizing Molecular Results Arising from Incomplete Biological Samples:

Expected Bias and Unexpected Findings

MIQUEL PORTA, MD, MPH, PHD, NÚRIA MALATS, MD, PHD, JOSEP M. COROMINAS, JULI RIFÀ, MD, PHD, JOSEP L. PIÑOL, MD, PHD, AND FRANCISCO X. REAL, MD, PHD, FOR THE PANKRAS I PROJECT INVESTIGATORS*

PURPOSE: In molecular epidemiology, obtaining biological samples for all subjects targeted for study is frequently hampered by ethical, clinical, and logistic factors. The extent to which the incompleteness of biological samples could cause bias is rarely analyzed in depth. Here we report some expected bias and some unexpected findings during a study on mutations in the K-*ras* gene in exocrine pancreatic cancer

METHODS: In this case–case study, all patients registered with EPC between 1980 and 1990 at two general hospitals were retrospectively identified from the hospital tumor registries. Their clinical records were abstracted and paraffin-embedded samples retrieved from pathology records. DNA was amplified, and mutations in codon 12 of the K-*ras* gene were detected using the artificial RFLP technique.

Ann Epidemiol 2002;12:7–14.

Attention to selection biases !

RESULTS: Results on the mutations (RM) were obtained for 51 of the 149 cases of EPC (34.2%). There were no significant differences on the availability of RM by age, gender, and tumor stage at diagnosis, but RM were over five times more likely to be available from one of the hospitals. Subjects with RM were more likely to have received a treatment with curative intent (OR = 11.56, 95% CL: 2.88–46.36). The existence of RM was positively associated with the availability of information on alcohol use and family history of cancer. Subjects with RM tended to belong to higher occupational groups and to smoke less than subjects without RM.

Unexpectedly—given that in EPC K-*ras* mutations have consistently been found unrelated to age, gender, tumor stage, and other clinical factors—, cases with a K-*ras* mutation were more likely than wild-type cases to have information on tobacco and alcohol use (OR = 3.29, p = .21), medical history (OR = 4.46, p = .41), and family history of cancer (OR = 4.80, p = .01). The relationship between completeness of clinical records and K-*ras* mutations among cases with RM could not be accounted by age, gender, and occupational group.

CONCLUSIONS: Simple tests of age and gender distributions among subjects with and without available clinical information and molecular results may not rule out selection and information bias. Studies using biologic specimens are even more in need than classic studies to explain clearly the process followed to include and exclude subjects. Additional caution is needed when generalizing molecular results arising from incomplete biological specimens.

J Epidemiol Community Health 2002;**56**:734–738

Attention to selection biases !

DEBATE

Incomplete overlapping of biological, clinical, and environmental information in molecular epidemiological studies: a variety of causes and a cascade of consequences

M Porta, N Malats, J Vioque, A Carrato, M Soler,

Out of >600 cases: 7 wt vs. 17 mutated

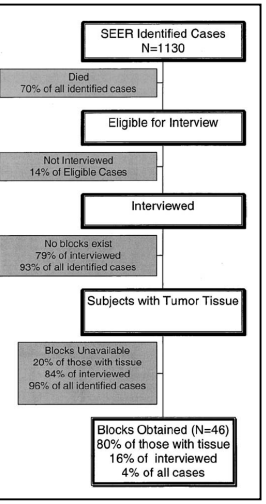
Cancer Epidemiology, Biomarkers & Prevention
Vol. 9, 1223–1232, November 2000

K-*ras* and p53 in Pancreatic Cancer: Association with Medical History, Histopathology, and Environmental Exposures in a Population-based Study[1]

Potential for Selection Bias with
in Molecular Epidemiology Studi

JANE A. HOPPIN, SCD, PAIGE E. TOLBI
JANE C. SCHROEDER, DVM, PHD, AND

Ann Epidemiol 2002;12:1–6.



Ann Epidemiol 2002;12:1–6.

Tumor characteristic	Potential biopsy tissue[a] Yes N = 142		No N = 988		*P*-value[b]
	Mean	sd	Mean	sd	
Tumor size[c] (mm)	179	343	570	474	<0.0001
	n	%	n	%	
Histologic grade[d]					
G1 (lowest grade)	16	11	49	5	0.001
G2	59	42	107	11	
G3	41	29	186	19	
G4 (highest grade)	0	0	17	2	
Unknown	26	18	629	64	
Summary stage					0.001
In situ	2	1	0	0	
Localized	22	15	59	6	
Regional, extension only	49	35	222	23	
Regional, nodes only	7	5	12	1	
Regional, extension and nodes	45	32	58	6	
Remote	13	9	498	51	
Unstaged	4	3	131	13	

Reporting Participation in Case-Control Studies

Sara H. Olson,[1] Lynda F. Voigt,[2] Colin B. Begg,[1] and Noel S. Weiss[2,3]

EPIDEMIOLOGY 2002;13:123–126

TABLE 2. Reporting Outcomes of Recruiting Respondents in Case-Control Studies; Example 1: Controls Contacted by Telephone Using Random-Digit Dialing

Units Selected from Sampling Frame	No.
Total	6,741
Ineligible sampling unit	
Total	3,589
Business, fax, government	1,937
Nonworking numbers	1,436
Institution, group quarters, dataline	216
Unable to determine eligibility	
Total	431
Unknown if residential	274
Residential, unknown if individual eligible	157
Answering machine on all attempts	56
Refusal to answer questions on eligibility	76
Other (language barrier)	25
Respondent not eligible	
Total	1,983
Age	1,749
County	216
Language	18
Respondent screened and eligible, total	738

Data from Rossing *et al.*[8]

Reporting Participation in Case-Control Studies

Sara H. Olson,[1] Lynda F. Voigt,[2] Colin B. Begg,[1] and Noel S. Weiss[2,3]

EPIDEMIOLOGY 2002;13:123–126

TABLE 4. Reporting Outcomes of Recruiting Respondents in Case-Control Studies; Example 3: Controls Contacted by Telephone from List Obtained from the Health Care Financing Administration

Units Selected from Sampling Frame	No.
Total	128
Unable to determine eligibility, total	8
Respondent not eligible	
Total	63
Prior hysterectomy	63
Respondent screened and eligible	
Total	57
Not interviewed (refused)	8
Interviewed	49

Data from Hill *et al.*[10]

ISEE 19th. International Conference - Early Training Sessions
www.imim.es/URECMC/eng Miquel Porta - Mexico City, 7 Sept. 2007
PART 2 – 14

European Journal of Epidemiology **16**: 533–541, 2000.

Validity of the hospital discharge diagnosis in epidemiologic studies of biliopancreatic pathology

M. Porta[1], S. Costafreda[1], N. Malats[1], L. Guarner[2], M. Soler[1], J.M. Gubern[3], E. García-Olivares[4], M. Andreu[3], A. Salas[4], J.M. Corominas[3], J. Alguacil[1], A. Carrato[5], J. Rifà[6] & F.X. Real[1] for the PANKRAS II Study Group*

[1]*Institut Municipal d'Investigació Mèdica, Universitat Autònoma de Barcelona and Universitat Pompeu Fabra, Barcelona;* [2]*Hospital Vall d'Hebron, Barcelona;* [3]*Hospital del Mar, Barcelona;* [4]*Hospital de la Mútua de Terrassa, Terrassa, Barcelona;* [5]*Hospital General de Elche, Alicante;* [6]*Hospital Son Dureta, Mallorca, Spain*

Table 2. Changes between the initial hospital discharge diagnosis and the main clinicopathological diagnosis

Initial hospital discharge diagnosis	Main clinicopathological diagnosis (post-review)								
	Exocrine pancreatic cancer	Extrahepatic biliary cancer	Acute pancreatitis	Chronic pancreatitis	Syndromic diagnoses	Digestive neoplasm of ill-defined sites	Malignant neoplasm, site unspecified	Other benign diseases	Total
Exocrine pancreatic cancer	176 (86.3)	8 (3.9)	3 (1.5)	1 (0.5)	4 (2.0)	7 (3.4)	5 (2.5)		204
Extrahepatic biliary cancer	4 (3.1)	114 (88.4)			3 (2.3)	5 (3.9)		3 (2.3)	129
Acute pancreatitis			20 (54.1)	13 (35.1)	1 (2.7)			3 (8.1)	37
Chronic pancreatitis	4 (4.4)	1 (1.1)	2 (2.2)	79 (86.8)	2 (2.2)			1 (1.1)	89
Pancreatic cyst and pseudocyst			13 (34.2)	19 (50.0)			1 (2.6)	5 (13.2)	38
Other specified diseases of pancreas			1 (33.3)	2 (66.7)					3
Syndromic diagnoses					4 (44.4)		1 (11.1)	4 (44.4)	9
Digestive neoplasm of ill-defined sites						1 (50.0)		1 (50.0)	2
Malignant neoplasm, site unspecificied		3 (9.7)					26 (83.9)	2 (6.5)	31
Other benign diseases	1 (1.7)	2 (3.4)	1 (1.7)	3 (5.2)	2 (3.4)		1 (1.7)	48 (82.8)	58
Total	185	128	40	117	16	13	34	67	600

Figures are number of patients; figures within brackets are the row percent (i.e. the positive predictive value of the hospital discharge diagnosis), taking the main clinicopathological diagnosis as the gold standard. Cells with no patients are left blank.

Table 3. Potential predictors of diagnostic change

	Exocrine pancreatic cancer			
	N	n	(%)	*p*
Global	204	28	(13.7)	
Gender				
Men	122	18	(14.8)	
Women	82	10	(12.2)	0.603[a]
Age (tertiles)				
1st	68	5	(7.4)	
2nd	68	11	(16.2)	
3rd	68	12	(17.6)	0.082[b]
Tumour stage				
Local	43	7	(16.3)	
Regional	55	6	(10.9)	
Distant metastases	97	7	(7.2)	0.103[b]
Missing[d]	9	8	(88.9)	

N, number of subjects with original discharge diagnosis; n, number whose original diagnosis changed; % = (n/N) * 100

Table 3. Potential predictors of diagnostic change

	Exocrine pancreatic cancer			
	N	n	(%)	*p*
Diagnostic basis				
Clinical investigation[e]	24	9	(37.5)	
Laparotomy	15	5	(33.3)	
Tumour markers	18	3	(16.7)	
Cytology	66	5	(7.6)	
Histology (primary)	57	5	(8.8)	0.001[c]
Histology (metastasis)	24	1	(4.2)	
Cyto-histological confirmation				
No	57	17	(29.8)	
Yes	147	11	(7.5)	< 0.001[a]
Histology[f]	81	6	(7.4)	1.000[c]
Cytology	66	5	(7.6)	
Missing[d]	9	8	(88.9)	

N, number of subjects with original discharge diagnosis; n, number whose original diagnosis changed; % = (n/N) * 100
[f] Histology obtained from a primary lesion, a metastasis or in the necropsy.

Table 4. Diagnostic procedures and diagnostic change stratified by presence or absence of cyto-histological confirmation

	Exocrine pancreatic cancer				Exocrine pancreatic cancer			
	N	n	(%)	*p*	N	n	(%)	*p*
Cyto-histologically confirmed[a]					Non cyto-histologically confirmed			
CT					CT			
Yes	114	8	(7.0)		Yes	39	9	(23.1)	
No	33	3	(9.1)	0.711[b]	No	18	8	(44.4)	0.101[b]
ERCP					ERCP			
Yes	53	6	(11.3)		Yes	33	12	(36.4)	
No	94	5	(5.3)	0.205[b]	No	24	5	(20.8)	0.206[c]
Laparotomy					Laparotomy			
Yes	87	3	(3.4)		Yes	22	6	(27.3)	
No	60	8	(13.3)	0.051[b]	No	35	11	(31.4)	0.738[c]

Attention to selection biases !

The characteristics of the disease and the state of knowledge / ignorance justify (and give meaning to) innovative research approaches.

simple but tough things... difficult to achieve, e.g., collaboration + involvement of clinical colleagues.

Estudio PANKRAS II

Diseñado en 1990-91, 5 centros, prospectivo, unos de sus objetivos primarios es valorar interacciones entre alteraciones genéticas (K-*ras* y otras) y factores ambientales.

- J Clinical Epidemiology 1998, 2008
- The Lancet 1999
- Digestive Diseases & Sciences 1999, 2007
- Annals of Occupational Hygiene 2000
- International J of Epidemiology 2000
- Occupational & Environmental Med 2000
- European J of Epidemiology 2000, 2006-07
- Gut 2001, 2002
- J Epi Comm Health 1999, 2000, 2002, 2007
- Epidemiology 2001

- Carcinogenesis 2002
- Organohalogen Compounds 2002
- Molecular Carcinogenesis 2003
- International Journal of Cancer 2003
- Clinical & Translational Oncology 2005
- Pancreas 2007
- Environment International 2007
- Gaceta Sanitaria 2002, 2005-2008.
- Int J Occupational & Environ Health 2003

Table 2

K-ras mutations and regular coffee consumption among cases of cancer of the pancreas

Regular coffee drinker	Yes	No	Total
K-ras mutated	73	10	83
K-ras wild type	16	8	24
Total	89	18	107

Source: Porta et al. (1999).

Paul R. Rosenbaum
The Case-Only Odds Ratio as a Causal Parameter
BIOMETRICS 60, 233–240
March 2004

"In a case-only design (...) the odds ratio in this table is taken as a measure of gene-environment interaction"

Indicators

- Time symptom onset → sample extraction
- Site of sample extraction
- Symptoms and clinical status at sample extr.
- Lipid levels
- Tumor stage
- Treatment
- Survival
- Other laboratory findings
- Diagnostic procedures
- Clinical complications
- Other factors

- **Elucidating the etiologic significance of each OC requires an understanding of its relationships with other OCs, with lipids and with prediagnostic signs & symptoms.**

TABLE 1. Operational Elements of a Framework to Assess the Etiologic Significance of Associations Between Internal Concentrations of Organochlorine Compounds and Cancer Risk (or Related Biologic Events)

1. Consider which potential indicators may be relevant within the context of knowledge (see 4 below) relevant for your study:
   Time between symptom onset and sample extraction
   Site of sample extraction
   Symptoms and clinical status at sample extraction
   Lipid levels
   Other laboratory findings
   Tumor stage
   Diagnostic procedures
   Treatment
   Clinical complications
   Survival
   Other factors

2. Based on your study hypotheses and design, select indicators and collect information.
3. Conduct quantitative analyses:
   Do the indicators vary among the groups of subjects under comparison?
   Do associations exist between the indicators and the concentrations of the organochlorine compounds?
   Do the indicators induce effect modification or confounding of the causal estimators of the relation between organochlorine concentrations and your clinical or biological end-point?
4. Assess to what extent results are coherent with and contribute to the existing knowledge on issues such as:
   Half-life and physico-chemical characteristics of the compound.
   Influence of the specific cancer on the metabolism of the compound.
   Biodegradation, bioaccumulation, and interactions.
   Timing and dose required to influence the biological or clinical end-point.
5. Develop and test quantitative standards for the relevant indicators.

Timing of blood extraction in epidemiologic and proteomic studies: results and proposals from the PANKRAS II Study

Miquel Porta · José Pumarega · Olga Ferrer

European Journal of Epidemiology 2007

There are no consensus guidelines or standards for epidemiologic and '-omics' studies using blood biomarkers on how to report the timing of extraction of blood samples. However, disease-induced changes in blood concentrations of exogenous and endogenous compounds may bias studies.

Results suggest ways to report intervals involving blood biomarkers and may contribute to develop consensus guidelines and standards on the collection of blood samples in epidemiologic and '-omics' research.

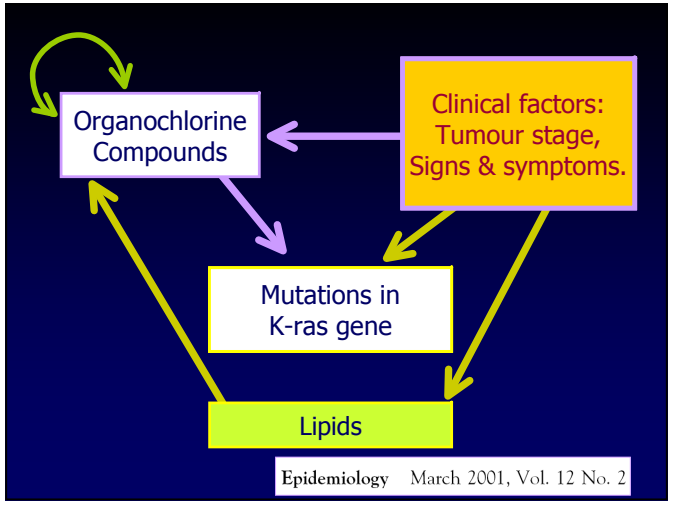
Journal of Clinical Epidemiology 61 (2008)

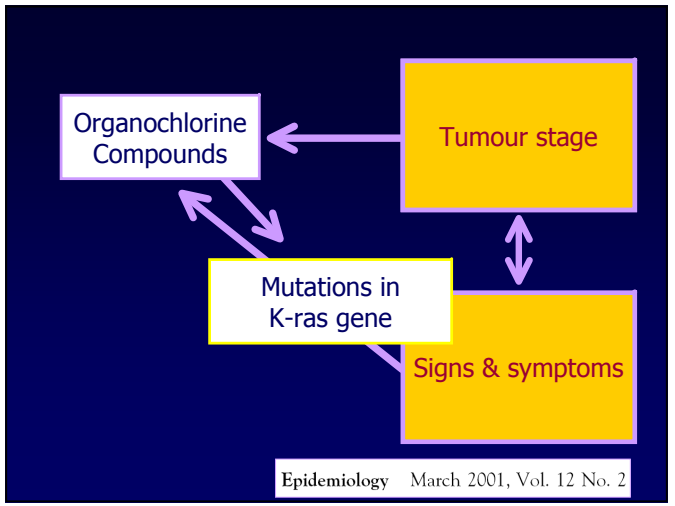
In exocrine pancreatic cancer clinical factors

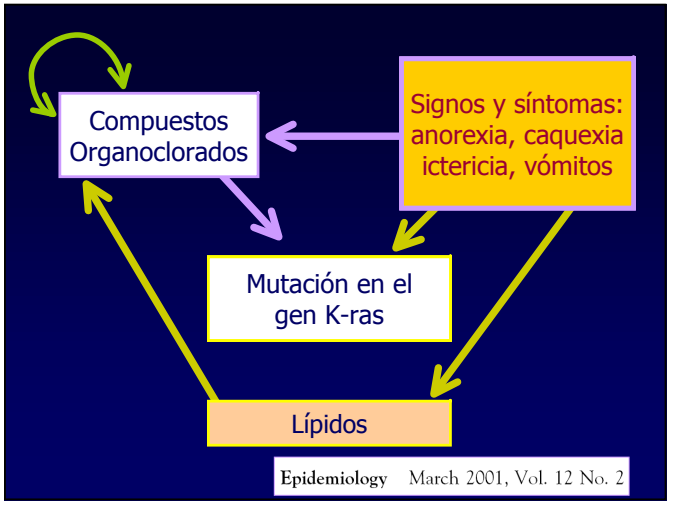
were related to timing of blood extraction

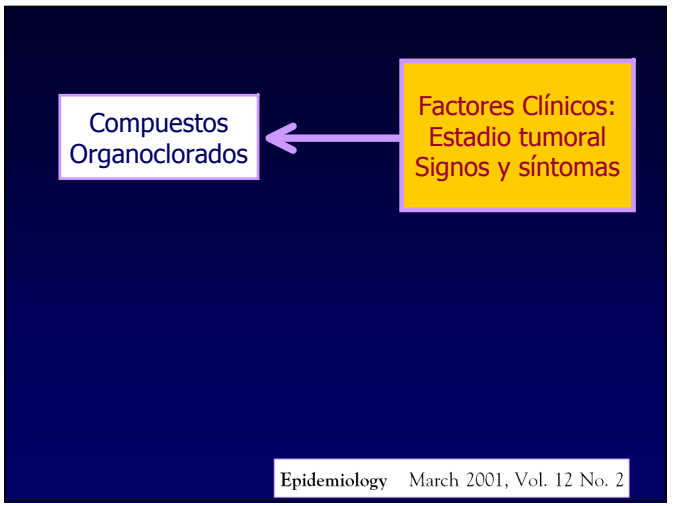
and influenced serum concentrations of lipids

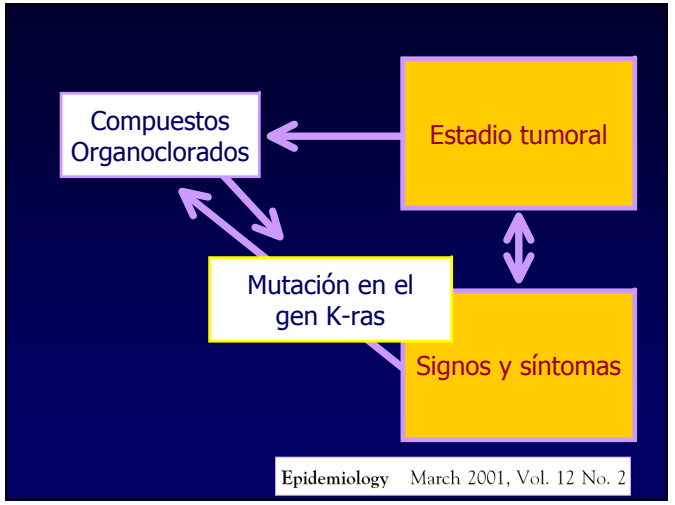
Miquel Porta[a-c]*, Olga Ferrer-Armengou[a], José Pumarega[a], Tomàs López[a]

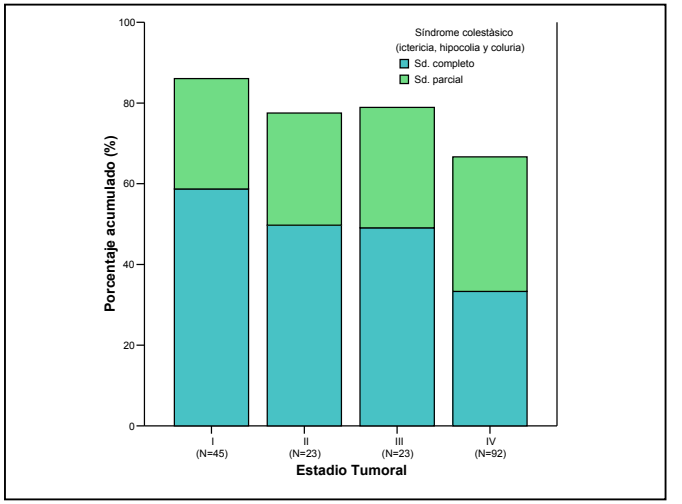

Organochlorine Compounds
Clinical factors: Tumour stage, Signs & symptoms.
Mutations in K-ras gene
Lipids
Epidemiology March 2001, Vol. 12 No. 2


Organochlorine Compounds
Tumour stage
Mutations in K-ras gene
Signs & symptoms
Epidemiology March 2001, Vol. 12 No. 2


Compuestos Organoclorados
Signos y síntomas: anorexia, caquexia ictericia, vómitos
Mutación en el gen K-ras
Lípidos
Epidemiology March 2001, Vol. 12 No. 2


Compuestos Organoclorados
Factores Clínicos: Estadio tumoral Signos y síntomas
Epidemiology March 2001, Vol. 12 No. 2





clinical epidemiology ↔ proteomics

Clin Transl Oncol. 2005;7(5):195-204

Exocrine pancreatic cancer: symptoms at presentation and their relation to tumour site and stage

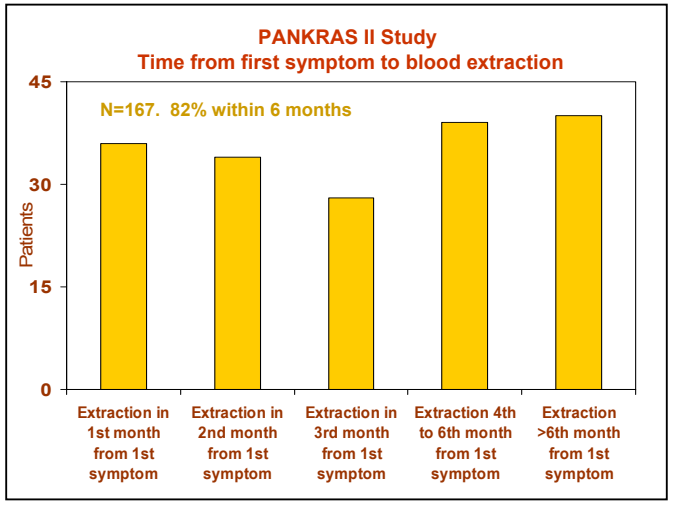
Miquel Porta[a,b], Xavier Fabregat[b,c], Núria Malats[a], Luisa Guarner[d], Alfredo Carrato[e], Ana de Miguel[e],

There was a clear trend towards more localized tumours with increasing numbers of cholestatic signs ($p<0.001$).

Indicators

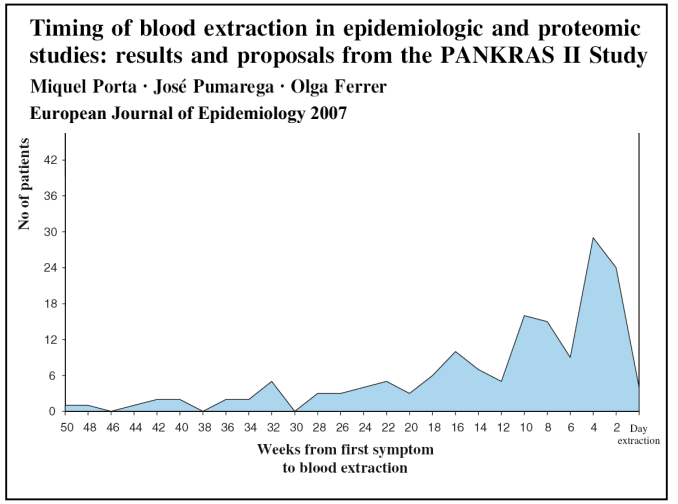
- **Time from symptom onset to sample extraction (TSOSE)**
  – The lower, the better...

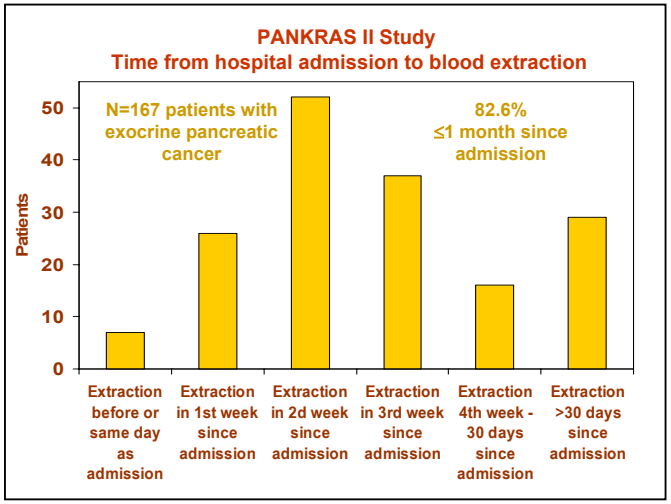
  but TSOSE depends on patient, referral system, hospital admission, diagnosis, study inclusion...

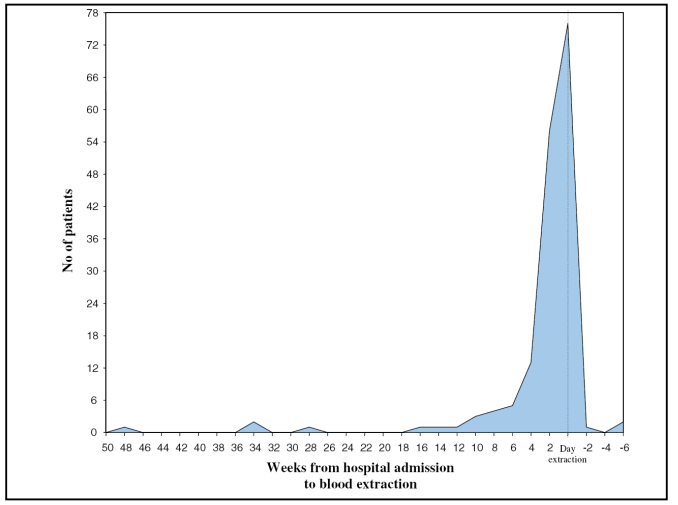


Indicators

- Time from
- symptom onset
- hospital admission
- diagnosis
- study inclusion
- treatment onset...
- to sample extraction.



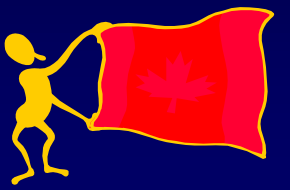




Indicators

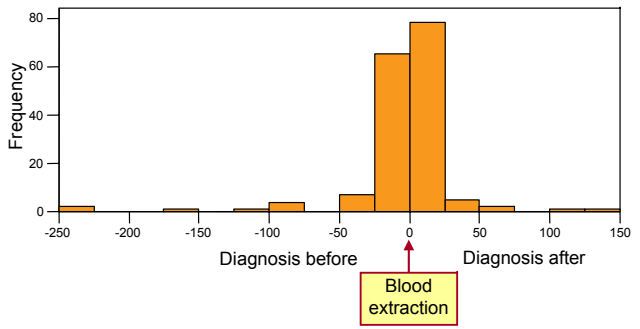
- Time from symptom onset to sample extraction (TSOSE)

  – Is TSOSE + related to OCs levels? if so...
  – Is TSOSE related to the outcome? if so...



Timing of diagnosis and blood extraction

N=167 patients with exocrine pancreatic cancer



PANKRAS II Study
N=121 patients with exocrine pancreatic cancer

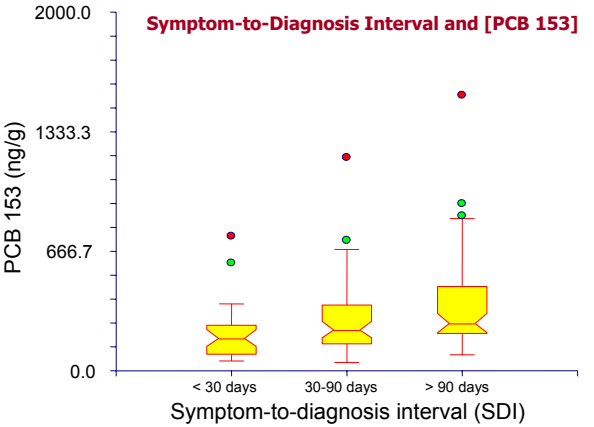
Characteristics	K-ras gene: Mutated (N=94)	K-ras gene: Wild-type (N=27)	P
First sypmtom to extraction ≤31 days (%)	76 19.8	69 17.4	0.733[1] 1.000[2]

Values are medians [1]Mann-Whitney's U test [2]Fisher's exact test

PANKRAS II Study
N=121 patients with exocrine pancreatic cancer

Characteristics	K-ras gene: Mutated (N=94)	K-ras gene: Wild-type (N=27)	P
Hospital admission to blood extraction	15	18	0.732[1]
≤31 days (%)	79.1	73.9	0.581[2]
Hospital admission to interview	16	19	0.725[1]
≤31 days (%)	77.1	70.8	0.591[2]
First sypmtom to extraction	76	69	0.733[1]
≤31 days (%)	19.8	17.4	1.000[2]

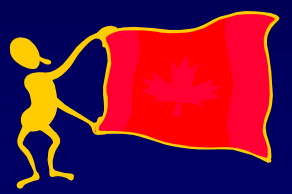
Values are medians [1]Mann-Whitney's U test [2]Fisher's exact test



Indicators

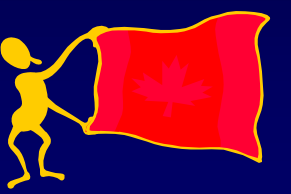
- Time from symptom onset to diagnosis (SDI) (duration of symptoms, 'delay')

  – Is SDI + related to OCs levels? if so...



Indicators

- Symptoms and clinical status at time of sample extraction.
  – Malnourishment, weight loss / changes in BMI, anorexia-cachexia, jaundice...
  – Are symptoms associated with biological outcome...? if so...

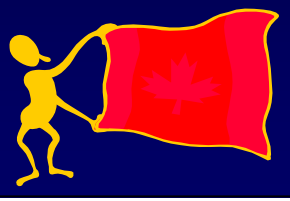


Signs & symptoms	K-ras gene Mutated (N=94)	Wild-type (N=27)	P[1]
Constitutional syndrome	70.2	59.3	0.469
Asthenia	86.0	85.2	1.000
Anorexia	81.7	77.8	0.781
Weight loss	86.0	81.5	0.550
Cachexia	12.9	7.4	0.734
Cholestatic syndrome	38.3	40.7	0.751
Jaundice	51.6	44.4	0.662
Choluria	52.7	55.6	0.830
Hypocholia	50.5	44.4	0.664
Vomiting	31.2	37.0	0.642

[1]Fisher's exact test

Indicators

- Symptoms and clinical status at time of sample extraction.
  – Malnourishment, weight loss / changes in BMI, anorexia-cachexia, jaundice...
  – Are symptoms associated with OCs levels...? if so...



Relationship between cholestasic syndrome and serum concentrations of p,p'-DDE

	Cholestatic syndrome			
	Absent (N=56)	Partial (N=27)	Complete (N=61)	P
p,p'-DDE (median)	4.067,70	3.479,24	2.405,69	0,037[a] 0,018[b]

OCs levels lipid adjusted (ng/g).
N: Number of patients.
P: Statistical significance.
[a] : Kruskal-Wallis' test.
[b] : Spearman's correlation between OC levels and number of cholestatic symptoms.

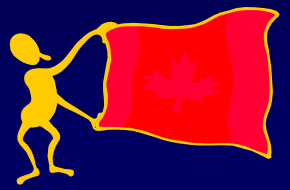
Relationship between complete cholestatic syndrome and serum concentration of 4 organochlorine compounds

	B	95% CI	P
p,p'-DDE	-0,533	-0,948 -0,118	0,012
PCB 153	-0,372	-0,634 -0,110	0,006
PCB 180	-0,377	-0,653 -0,102	0,009[a]
β-HCH	-0,340	-0,631 -0,049	0,024[a]

Linear regression adjusted by age, sex and tumour stage.
OCs lipid-corrected and log transformed.
Reference category: total absence of syndrome.
B: Regression coefficient (Beta).
95% CI : Beta coefficient 95% CI.
P: Statistical significance Beta coefficient.
[a] : Statistical significance conservative F.

Indicators

- Stage at diagnosis
  - Is stage + related to the biological outcome / end-point? if so...

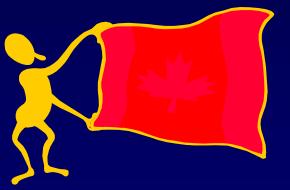


Characteristics	K-ras gene: Mutated (N=94)	K-ras gene: Wild-type (N=27)	P
SDI mean	94.6	131.8	0.268[1]
median	70.0	72.0	0.932[2]
≤31 days (%)	20.2	22.2	0.793[3]
Stage			0.256[3]
I	18.5	22.7	
II	21.0	4.5	
III	13.6	9.1	
IV	46.9	63.6	

[1]Student's t-test [2]Mann-Whitney's U test [3]Fisher's exact test

Indicators

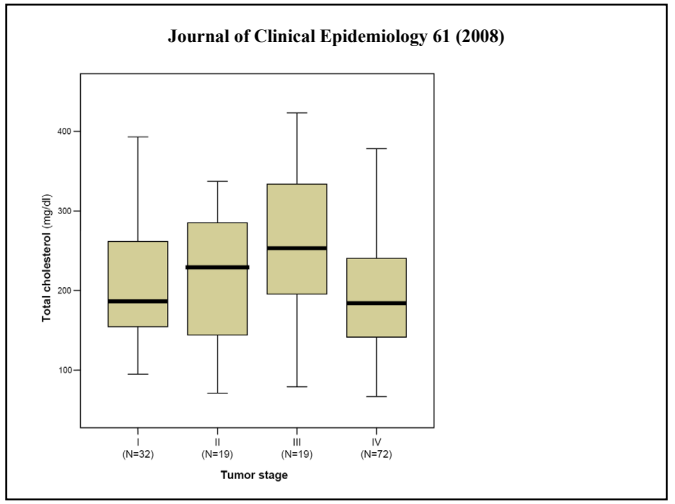
- Stage at diagnosis
  - Is stage + related to OCs levels? if so...

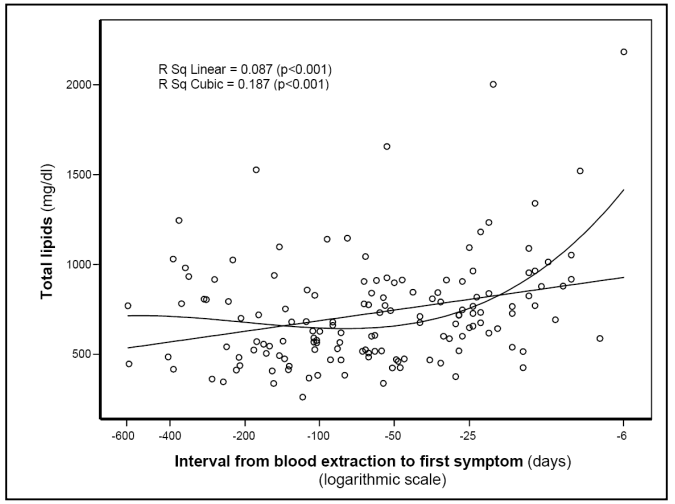


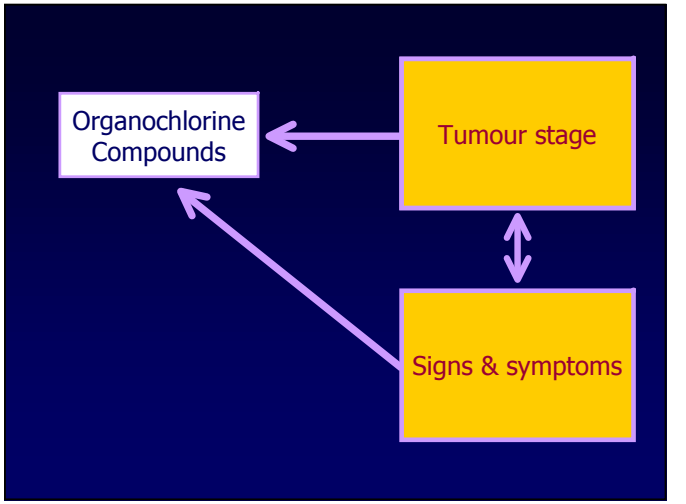
Relationship between age, tumour stage and [organochlorine compounds]

	B	95%CI of B		P	Model parametres
p,p'-DDT					
Age	0,025	0,006	0,043	0,009	R^2: 0,074
Tumour stage II *vs.* I	0,065	-0,729	0,859	0,872	F: 2,723
Tumour stage III *vs.* I	-0,661	-1,448	0,126	0,099	P^a: 0,032
Tumour stage IV *vs.* I	-0,016	-0,595	0,563	0,956	Levene: 0,209
HCB					
Age	0,025	0,015	0,034	<0,001	R^2: 0,193
Tumour stage II *vs.* I	-0,048	-0,472	0,376	0,823	F: 8,168
Tumour stage III *vs.* I	-0,537	-0,958	-0,117	0,013	P^a: <0,001
Tumour stage IV *vs.* I	-0,201	-0,510	0,109	0,202	Levene: 0,110
β-HCH					
Age	0,025	0,015	0,034	<0,001	R^2: 0,194
Tumour stage II *vs.* I	-0,024	-0,450	0,403	0,913	F: 8,265
Tumour stage III *vs.* I	-0,566	-0,988	-0,143	0,009	P^a: <0,001
Tumour stage IV *vs.* I	-0,257	-0,568	0,054	0,104	Levene: 0,111

General lineal model.
OCs lipid-corrected and log-transformed.
B: Regression coefficient (Beta)
P: Statistical significance Beta coefficient.
R^2: Determination coefficient of the global model.
F: Fisher-Snedecor's F (degree of freedom v_1=4,v_2=137).
P^a: Statistical significance degree of the model.
Levene: Levene's test statistical significance variance homegeneity.







Symptoms do influence tumour stage

Sign or symptom, or SDI	Tumour stage I N=45 (%)	Tumour stage II–III N=46 (%)	Tumour stage IV N=92 (%)	P
Any pain	71,1	80,4	89,0	0,034
No cholestatic symptoms	13,3	28,3	48,9	<0,001
One or two symptoms	15,6	19,6	23,9	<0,001 [a]
All three symptoms	71,1	52,2	27,2	
Constitutional syndrome	91,1	93,5	95,6	0,558
SDI (*median*, in months)	1,5	2,3	2,6	0,048 [b]

N: Numbers of patients.
P: Fisher's exact test.
[a] Spearman's correlations between stage and numbers of cholestatic symptoms.
[b] Kruskal-Wallis' test.

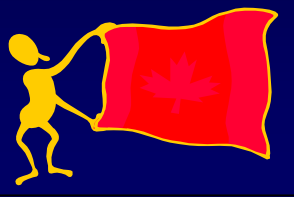
Constitutional syndrome, age, sex, and tumour stage and concentrations of p,p'-DDT

	B	95% CI		P	Model parameters
p,p'-DDT					
Partial syndrome	0,901	-0,033	1,835	0,059	R^2: 0,109
→ Complete syndrome	0,873	0,010	1,735	0,047	F: 2,348
→ Age (each year)	0,021	0,002	0,040	0,034	P^a: 0,027
Sex (male vs. female)	0,231	-0,266	0,728	0,360	Levene: 0,595
Tumour stage II *vs.* I	0,075	-0,719	0,869	0,852	
Tumour stage III *vs.* I	-0,598	-1,382	0,186	0,134	
Tumour stage IV *vs.* I	0,025	-0,555	0,604	0,933	

General lineal model.
OCs lipid-adjusted and log transformed.
B: Regression significance Beta.
P: Statistical significance for each parameter.
R^2: Determination coefficient of the model.
F: Fisher-Snedecor's F with degree of freedom ν_1=7, ν_2=134.
P^a: Statistical significance of the model.
Levene: Levene's test statistical significance variances homogeneity.

Indicators

- Samples drawn before or after some diagnostic tests, surgery, other treatments?
  - Are OCs levels before ≠ after? if so...

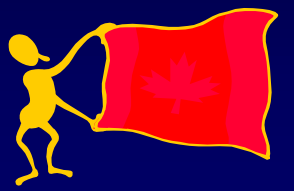


Indicators

- Stage at diagnosis
  - Is stage + related to OCs levels? if so...
  - **Are ORs homogeneous across stage strata?**

Indicators

- Survival (more clinically aggressive tumors may both ↑ OCs levels and ↓ survival).
  - Is survival – related to OCs levels? if so...



Effects of cholestatic symptomatology on [OC]

Sign, symptom or syndrome	p,p'-DDT	p,p'-DDE	PCB 138	PCB 153	PCB 180	HCB	β-HCH
Jaundice (symptom)				↓	↓		
Jaundice (sign)				↓	↓		
Hypocholia		↓		↓	↓		↓
Choluria		↓		↓	↓		↓
Pruritus		↓					
Partial cholestatic syndrome			↓	↓	↓	↓	
Complete cholestatic syndrome		↓		↓	↓		↓

General linear model, adjusted by age, sex and tumour stage.

Effects of constitutional syndrome on [OC]

Sign, symptom or syndrome	p,p'-DDT	p,p'-DDE	PCB 138	PCB 153	PCB 180	HCB	β-HCH
Asthenia							
Anorexia							
Loss of weight				↑	↑		
Cachexia						↑	
Partial toxic syndrome	↑					↑	
Complete toxic syndrome	↑						

General linear model, adjusted by age, sex and tumour stage.

Journal of Clinical Epidemiology 61 (2008)

Factors influencing serum concentrations of total cholesterol.

Model*	β†	95% CI	Partial *p* value‡	R^2	Model *p* value
6. Interval from blood extraction to first symptom (IES), jaundice, weight loss, and number of invasive diagnostic tests performed before blood extraction (IDT)				0.285	<0.001
IES 40-120 days vs. IES<40 days	-47.6	-91.5, -3.7	0.034		
IES>120 days vs. IES<40 days	-57.9	-102.9, -12.8	0.012		
Jaundice (present vs. absent)	67.2	29.4, 105.0	0.001		
Weight loss (present vs. absent)	53.5	6.5, 100.4	0.026		
1 test vs. 0 tests	-61.6	-101.9, -21.2	0.003		
≥2 tests vs. 0 tests	-57.8	-107.5, -8.1	0.023		
Tumor stage II vs. stage I	75.0	16.9, 133.1	0.012		
Tumor stage III vs. stage I	83.9	28.4, 139.4	0.003		
Tumor stage IV vs. stage I	46.3	0.9, 91.8	0.046		

The effect of PCB 153 on the probability of a mutated (vs. wild-type) tumour.

PCB 153	OR1	P-value (OR 95% CI)	OR2	P-value (OR 95% CI)
≤187 (ng/g)	1.0	0.017*	1.0	0.012*
188 – 313	1.7	(0.6-5.0)	1.6	(0.5-4.8)
>313	5.2	(1.3-20.5)	6.0	(1.5-24.8)
≤305 (ng/g)	1.0	0.026	1.0	0.017
>305	4.4	(1.2-16.0)	5.1	(1.3-19.1)

OR1: adjusted by age and sex
OR2: age + sex + cholestatic syndrome
*Mantel's extension test for linear trend.

clinical epidemiology ↔ proteomics

Clin Transl Oncol. 2005;7(5):195-204

Exocrine pancreatic cancer: symptoms at presentation and their relation to tumour site and stage

Miquel Porta[a,b], Xavier Fabregat[b,c], Núria Malats[a], Luisa Guarner[d], Alfredo Carrato[c], Ana de Miguel[c],

There was a clear trend towards more localized tumours with increasing numbers of cholestatic signs ($p<0.001$).

An increased symptom-to-diagnosis interval was associated with more advanced stage ($p=0.048$).

clinical epidemiology ↔ proteomics

Clin Transl Oncol. 2005;7(5):195-204

Conclusions. **Proper attention to signs and symptoms, especially cholestasis, may help identify patients with pancreatic cancer at an earlier stage. Results also provide a current picture of the semiology of pancreatic cancer which could be of use in studies on the potential of proteomic tests in the early detection of this neoplasm.**

clinical epidemiology ↔ proteomics

Clin Transl Oncol. 2005;7(5):195-204

First, the analysis of signs and symptoms is one practical way to assess whether early manifestations of the disease were related to a specific pattern of proteins[43,44].

And second, since test results may vary with the spectrum of disease/patients[43-47], such information would aid to judge the properties of the proteomic test (e.g., its predictive values) in each stage of disease and patient spectrum.

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Although the study of cancer signs and symptoms might appear as just a traditional concern for clinicians, at the moment such analysis is also most relevant to appraise the biological and clinical significance of the emerging proteomic technologies.

In particular, proteomic pattern diagnostics are currently under investigation to improve early detection of different cancers[40,42]. This naturally includes the analysis of such patterns in the different stages of cancer[40,43].

Yet, there is only scant information on the correlation between semiology, cancer stage and the 'protein ion signatures'.

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Such technologies may provide new insights into the biologic changes that occur in the different phases of tumourigenesis[40-44]. However, some aspects remain unclear; for instance, the discriminatory peaks identified by mass spectrometry and bioinformatic systems may represent molecules released into the circulation as a result of the disease, or reflect cancer epiphenomena (malnutrition, inflammation, immunodeficiency)[44].

Proteomic patterns may also be particular to the spectrum of cases under study.

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Because thousands of proteins and protein fragments are analysed at once, bioinformatic analyses often must overlook the identity of the proteins, as well as the mechanisms by which proteins are released into the circulation, their concentration in biologic fluids, their metabolism, and their relationships within the human host[44]. In this context signs and symptoms constitute an important referent; for instance, a combined analysis of semiology and tumour stage may enable to assess in what spectrum of patients the proteomic test may detect disease early (i.e., to select patients for the test), and to judge what pathophysiological processes (weight loss and malnutrition, inflammation, metabolic changes associated with obstructive jaundice), as reflected in signs and symptoms, may be associated with the putatively discriminatory proteomic pattern[43,44].

clinical epidemiology ↔ proteomics

ELSEVIER

Journal of Clinical Epidemiology 56 (2003) 815–819

Journal of Clinical Epidemiology

Semiology, proteomics, and the early detection of symptomatic cancer

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the new wave of genomic and proteomic analyses of early-stage cancers might provide new insights into changes that occur in early phases of tumorigenesis; it is already offering new candidate biomarkers for early-stage disease [37–39].

Studies that profile proteomic patterns in body fluids should adhere to the methodologic standards that are usual in clinical epidemiology but less widely applied in basic science [40–42]. Rigorous pathophysiologic and clinical thinking should guide studies that pretend to correlate molecular abnormalities, symptoms, diagnostic performance, and clinical course—as exemplarily illustrated by *auxometric* measures of tumor growth and other works of Alvan Feinstein [8–17,43]. Whether the degree of correlation between proteomic patterns and classic semiology will be strong or weak remains to be seen ("weak" is our informed guess). Such analysis is of interest in itself. The respective relations of proteomic and semiologic patterns with cancer prognosis should be assessed in properly designed clinicoepidemiologic studies.

BOX 5 **Ethical, legal and social implications (ELSI)**

Today's genomics research and applications rest on more than a decade of valuable investigation into their ethical, legal and social implications. As the application of genomics to health increases along with its social impact, it becomes ever more important to expand on this work. There is an increasing need for focused ELSI research that directly informs policies and practices. One can envisage a flowering of 'translational ELSI research' that builds on the knowledge gained from prior and forthcoming 'basic ELSI research', which would provide knowledge for direct use by researchers, clinicians, policy-makers and the public. Examples include:

- The development of models of genomics research that use attention to these ELSI issues for enhancing the research, rather than viewing such issues as impediments
- The continued development of appropriate and effective genomics research methods and policies that promote the highest levels of science and of protecting human subjects
- The establishment of crosscutting tools, analogous to the publicly accessible genomic maps and sequence databases that have accelerated other genomics research (examples of such tools might include searchable databases of genomic legislation and policies from around the world, or studies of ELSI aspects of introducing clinical genetic tests)
- The evaluation of new genetic and genomic tests and technologies, and effective oversight of their implementation, to ensure that only those with confirmed clinical validity are used for patient care

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MUCHAS GRACIAS POR
VUESTRA ATENCIÓN

THANK YOU VERY MUCH
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