

Cancer Registry and Register-Based Cancer Research



Eero Pukkala
Finnish Cancer Registry

Outline

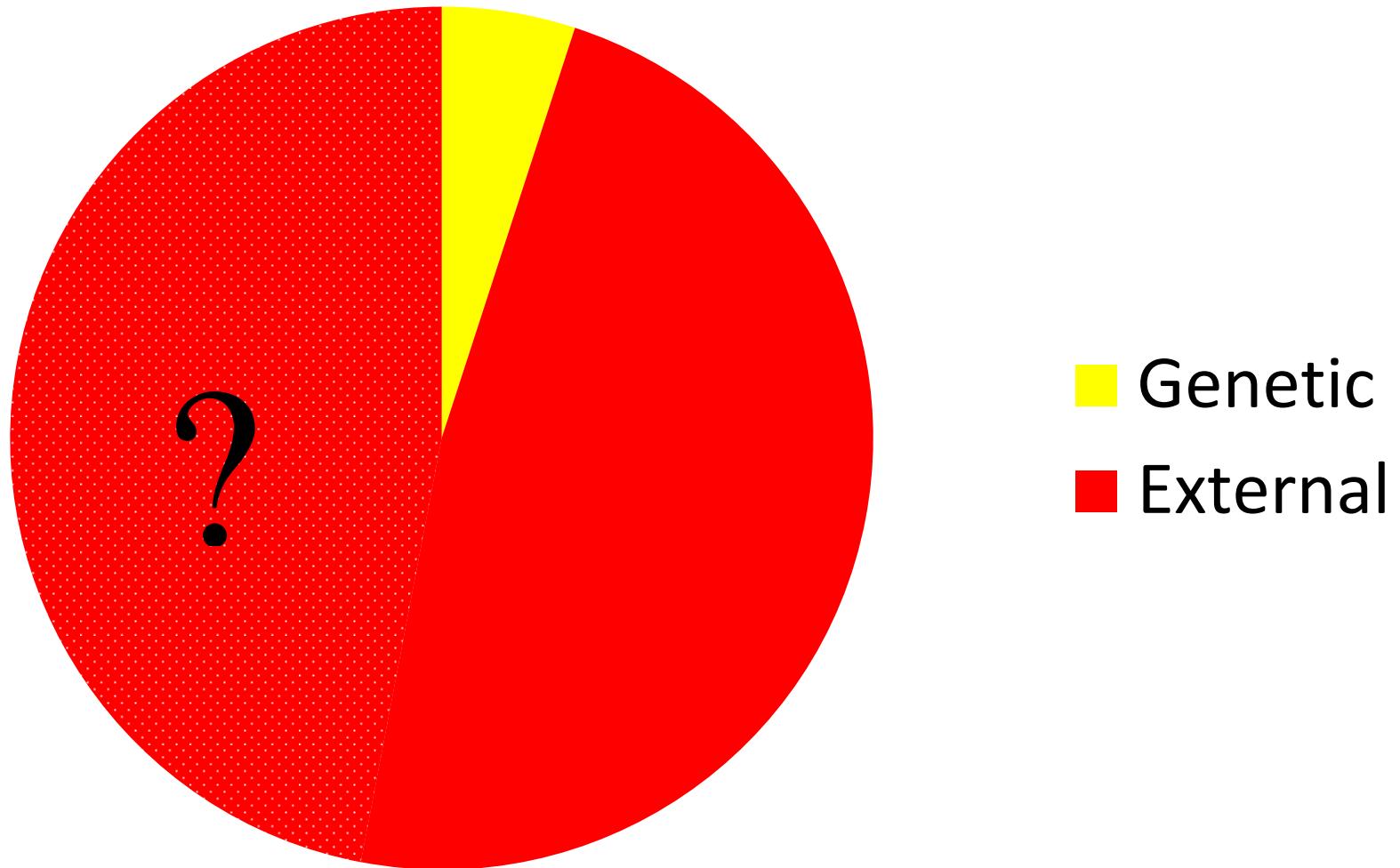
- A bit about the Finnish Cancer Registry
- Record linkages in epidemiological research of cancer
- Quality of register-based record linkage studies in comparison with studies based on tailorer data collection schemes
- Effect of failures in the linkage process
- Examples of multi-register studies
- More about these issues: see hand-outs
 - Pukkala, E.: **Biobanks and registers in epidemiological research on cancer.** In: Dillner, J. (ed.): Methods in Biobanking. Methods in Molecular Biology. Totowa, Humana Press 2011, pp. 61-112.

◦ Thygesen L (Denmark)

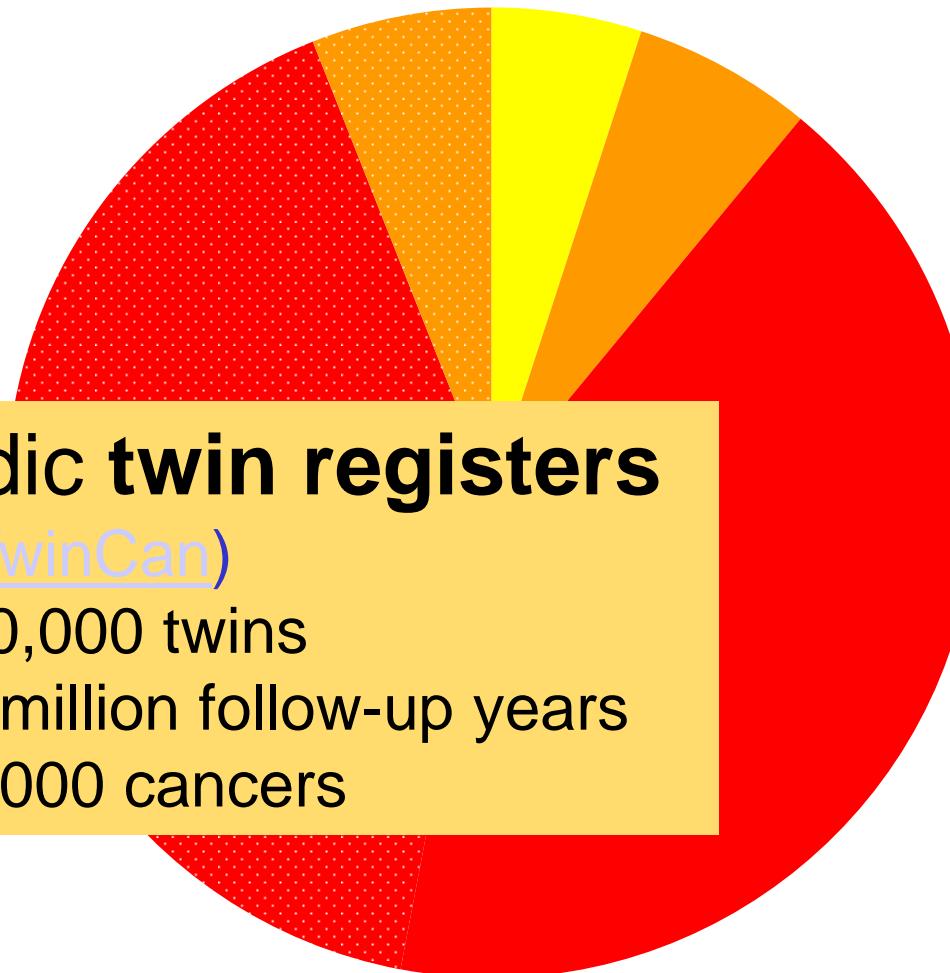
Causes of cancer



Causes of cancer



Causes of cancer



- Genetic
- External
- Interaction

"Paradise of epidemiology"

- *Good historical files of exposed persons*
- *Much registered data on confounding factors*
- *Complete population registration systems (follow-up for death and emigration); no losses to follow-up*
- *Virtually complete nationwide, population-based outcome registries (e.g., Cancer Registry)*
- *Unique personal identity codes; no linking errors*
- *Legislation that allows record linkages*

=> Results are true

... if we have made the study correctly

... and interpreted the findings correctly

Main data sources (computerised and linkable)

Whole population
Population sample

Usually not true:
"This cannot be done."

Statistics Finland

- * Longitudinal data 1950–1985
- occupational history
- SES, parental SES
- * cause of death

Social Insurance Institute

- * reimbursable diseases
- * reimbursed treatments
- * hospital discharges

Population Register Center (VRK) 1967+

- * complete ID
- * place of birth
- * residential history
- * living coordinates
- * living conditions
- * parent-child links
- * PIDs of children
- * immigration/emigration date
- * date of death

Cancer Registry

- * **cancer incidence 1953+**
- * cancer screenings 1963+

National Research and Development Centre for Welfare and Health (Stakes)

- * hospital discharges
- * birth parameters
- * malformations
- * Finnish Information Centre for Register Research (RETKI)

2009: THL

Public Health Institute (KTL)

- * Survey data (Mini Finland 1967, FinRisk 1972+, Adult Population Health Survey 1978+): life habits (smoking, alcohol, diet, BMI, physical exercise etc)
- * Blood sera (maternity cohort etc.)

Finnish Cancer Registry

Guarantee of quality:
own research activity

- Incident cancer cases and causes
- Statistical
- Epidemiological
- Cancer Research
 - about 2 peer-reviewed articles every week (own staff about 10 researchers)



QUALITY CONTROL IN THE CANCER REGISTRY

COMPARABILITY

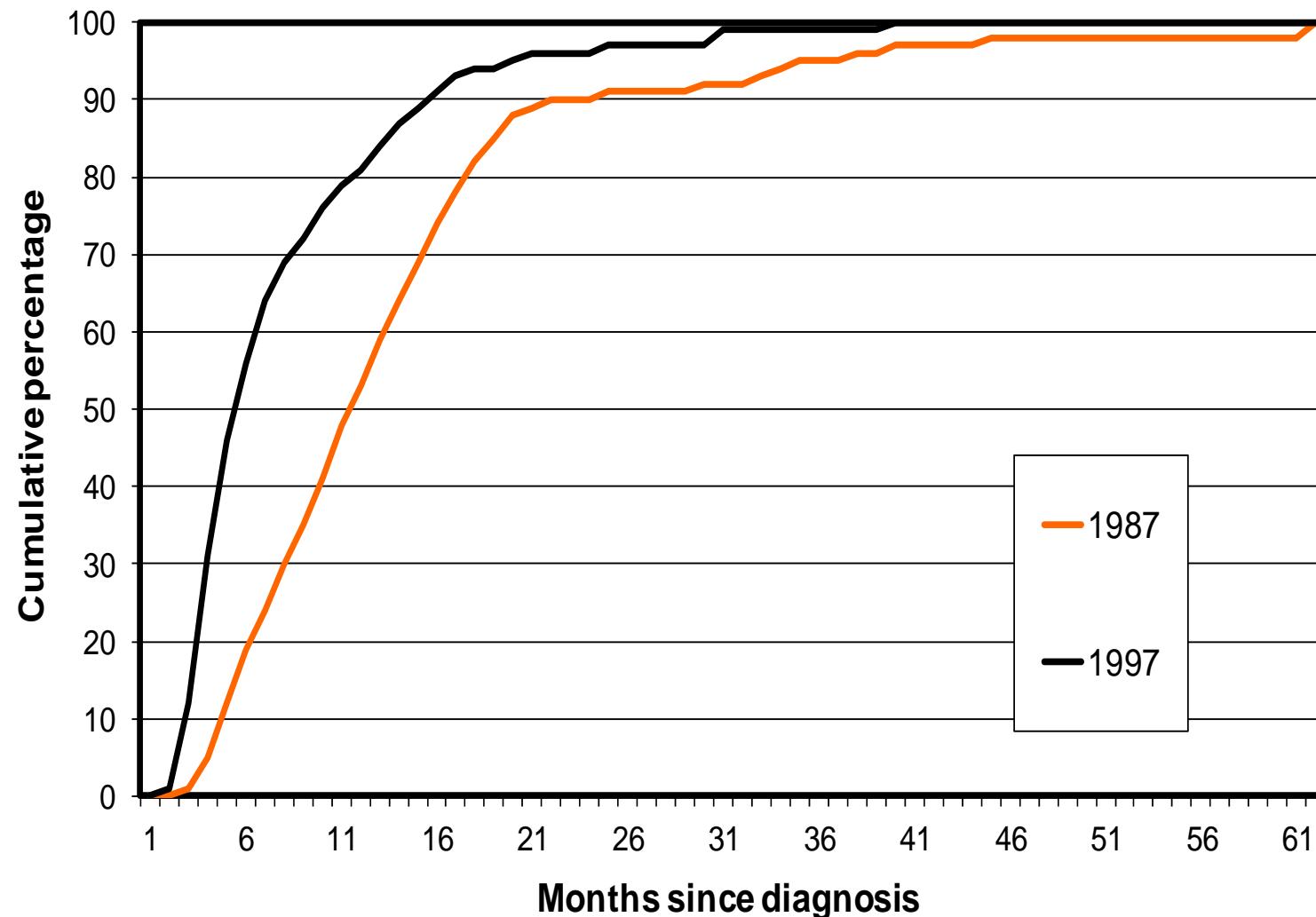
COMPLETENESS

VALIDITY

TIMELINESS

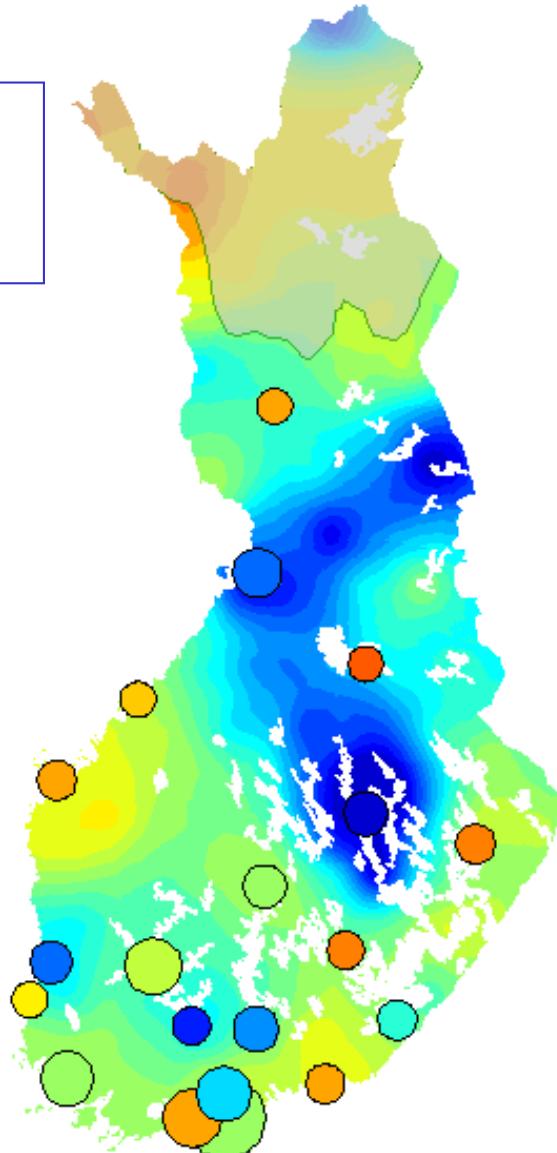
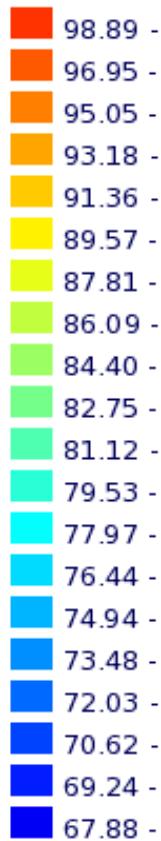
Delay of registration

All sites



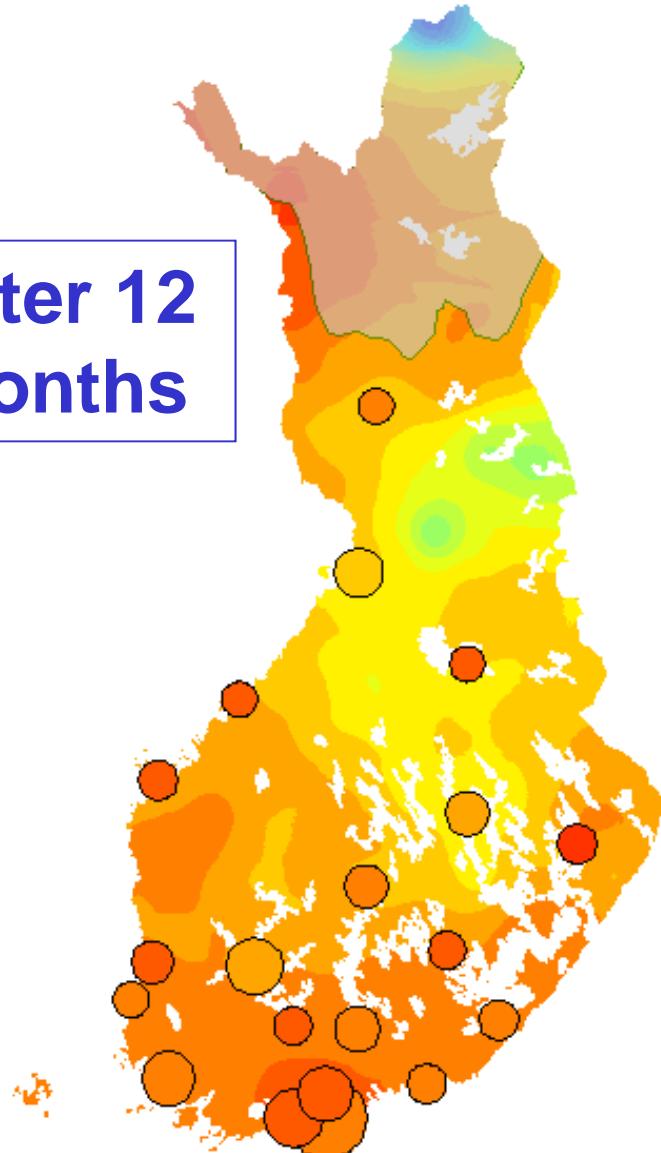
Percentage of cancers registered to Finnish Cancer Registry (2001)

After 3 months



After 12 months

Finnish Cancer Registry 29.08.2006



Finnish Cancer Registry 29.08.2006

Finnish
Cancer
Registry

Hospitals

Death certificates

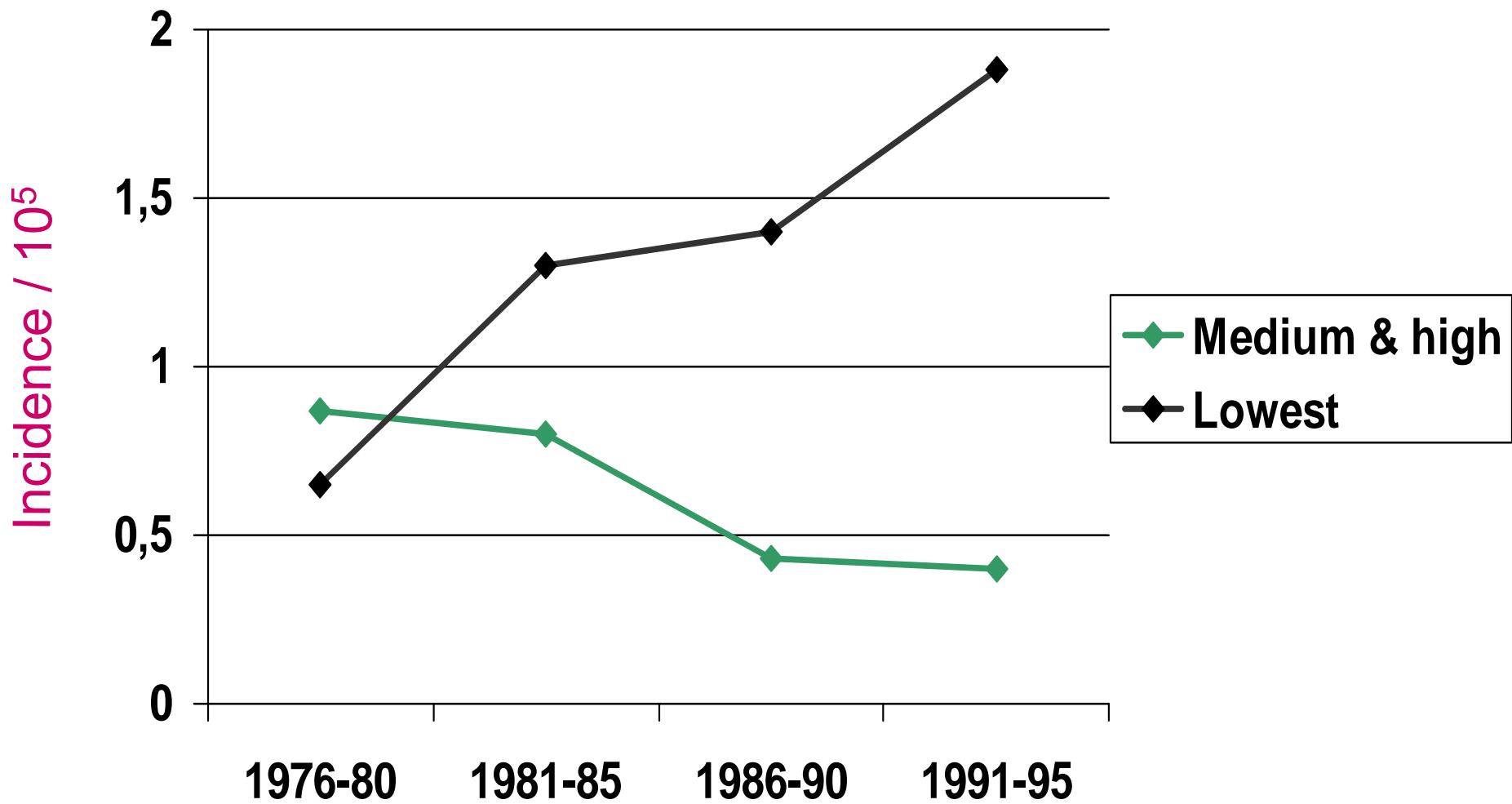
Population Register

Confirmation of the IDs:
Does the person exist?
Residential history
Emigrations
Vital status

Statistics Finland

Education
Occupation

Laryngeal cancer by social class, females



Highest and lowest overall cancer risk, WOMEN



NORDCAN

Association of the
Nordic Cancer
Registries



www.ancre.nu

NORDCAN * ONLINE ANALYSES

Incidence, Mortality, Prevalence, Survival

- Line charts

[Age-specific curves](#)

[Cumulative risk by age](#)

[Time trends](#)

[Time trends by age](#)

[Trends by birth cohort](#)

- Bar charts by

[Countries](#)

[Cancers](#)

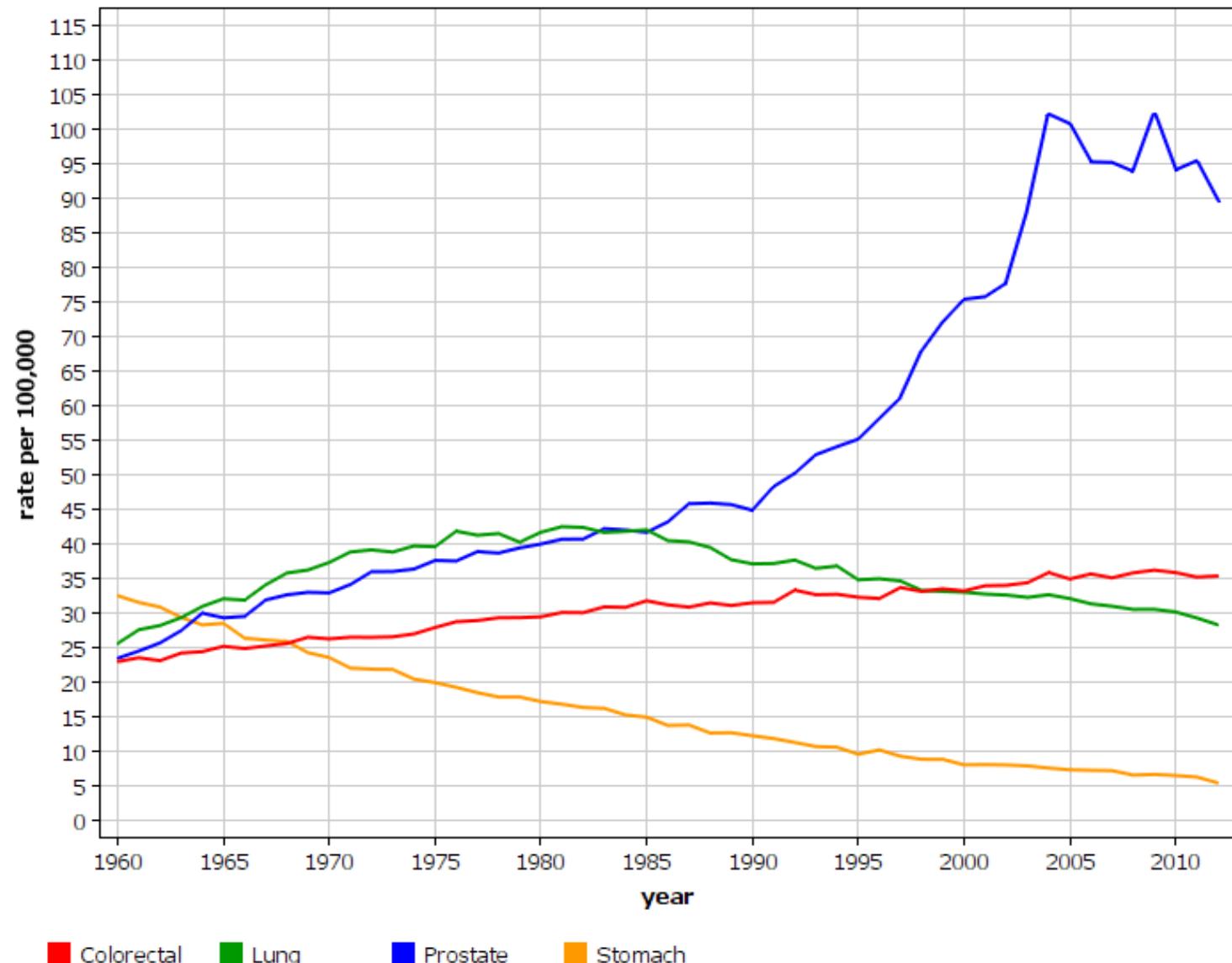
- Cancer maps

- **Advanced options:**

- Short or long term [predictions](#)

- [Breakpoint](#) analysis

Nordic countries
Incidence: ASR (World), Male age 0-85+

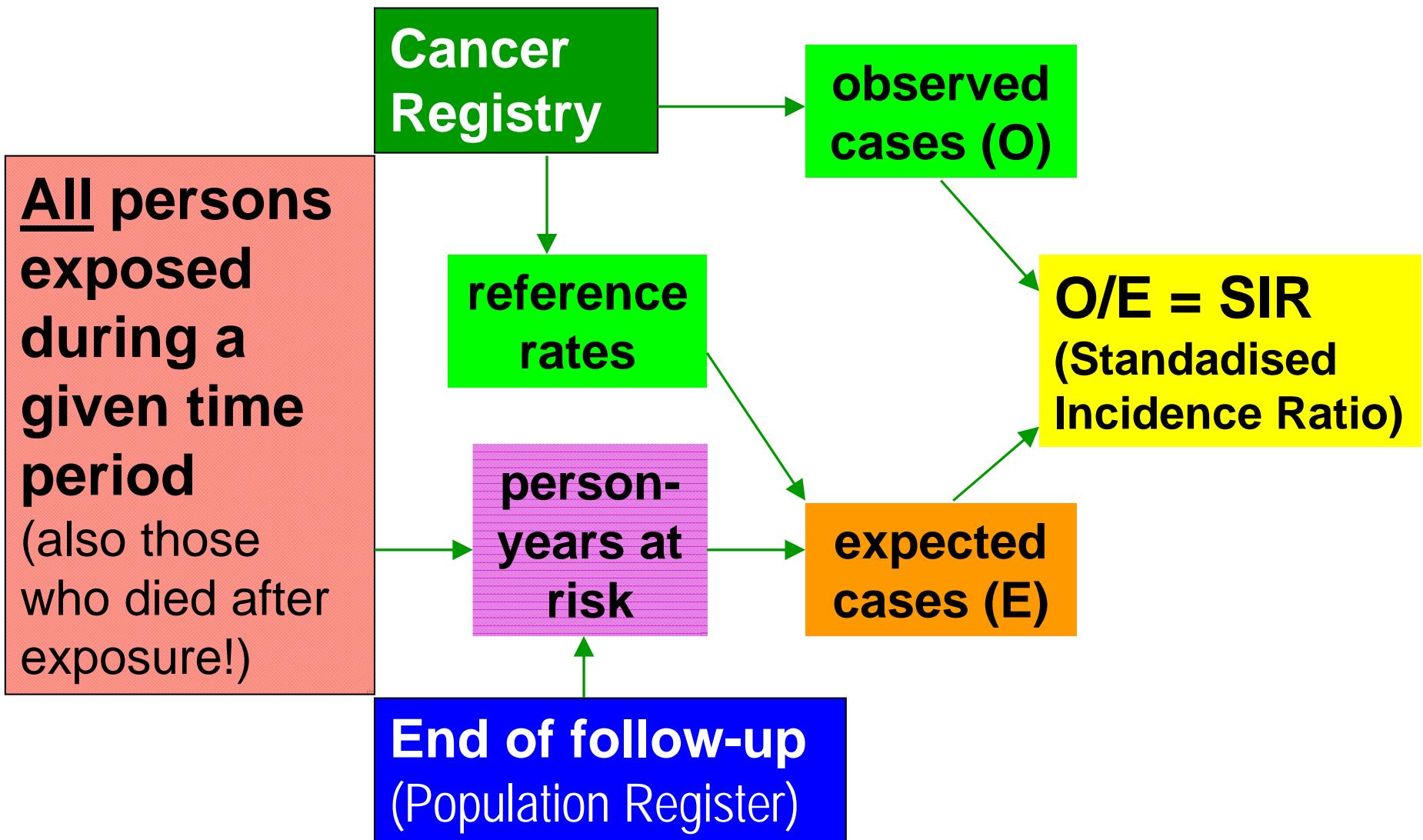


Effect of primary prevention:

Anti-Smoking Policy (1990s +)

Male lung cancer

Cohort study on cancer risk in Nordic countries



Does postmenopausal hormonal therapy increase risk of cancer?

Hormonal therapy & cancer

- Cohort of 1.1 million FinnishHT users identified from the **National Prescription Register** (Social Insurance Institution) 1994...
 - About 1 million reimbursements per year
- Dates of death from **Population Register**
- follow up for cancer incidence through the **Finnish Cancer Registry**
- **data collection: 3 work days, 5000 €**

Incidence of breast cancer among HRT users 1994-2002

women >50 years; estrogen use >180 days: n = 223 464

	Obs	Exp	SIR	95% CI
Estrogen only	1530	1129	1.4	1.3-1.4
+ separate progestin	316	220	1.4	1.3-1.6
+ long cycle progestin	253	167	1.5	1.3-1.7
+ sequential progestin	1021	614	1.7	1.6-1.8
+ continuous progestin	261	132	2.0	1.8-2.2

WARNING

Multiple comparisons

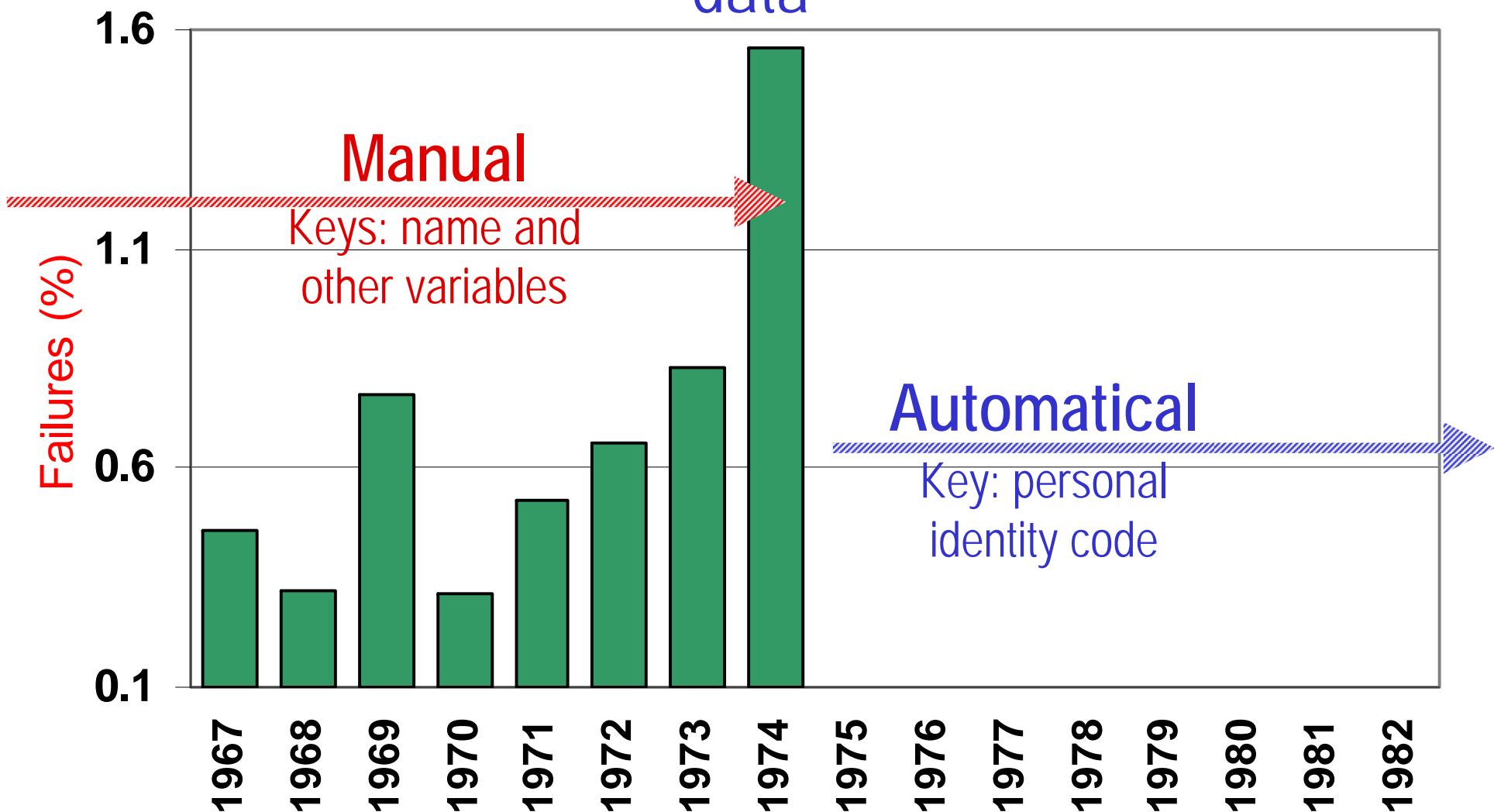
	E X P O S U R E S																			
D	1.0	1.0	1.0	1.0	1.0	0.9	0.9	1.1	1.2	0.8	1.0	1.0	0.9	0.8	1.1	1.2	0.9	0.9	1.0 1	1
I	1.0	1.0	1.0	0.9	0.9	1.1	1.2	0.8	1.0	1.0	0.9	0.8	1.1	1.2	0.9	0.9	1.0 1	1.0	1.1 0	
S	0.9	1.0	1.0	1.0	0.9	0.9	1.1	1.2	0.8	1.0	1.0	0.9	0.8	1.1	1.2	0.9	0.9	1.0 1	1.0	1 1
E	1.1	0.9	0.9	1.0	1.0	1.0	0.9	0.9	1.1	1.2	0.8	1.0	1.0	0.9	0.8	1.1	1.2	0.9	0.9	1 1
A	1.0	1.0	1.0	0.9	0.9	1.1	1.2	0.8	1.0	1.0	0.9	3.8	1.1	1.2	0.9	0.9	1.0 1	1.0	1.1 0	
S	0.8	1.3	1.0	1.0	1.0	0.9	0.9	1.1	1.2	0.8	1.0	1.0	0.9	0.8	1.1	1.2	0.9	0.9	1.0 1	1
E	1.0	0.9	0.9	1.1	1.2	0.8	1.0	1.0	0.9	0.8	1.1	1.2	0.9	0.9	1.0 1	1.0	1.1	0.9	1.0	1
S	1.0	1.0	0.9	0.9	1.1	1.2	0.8	1.0	1.0	0.9	0.8	1.1	1.2	0.9	0.9	1.0	1.0	1.1	0.9	1
	0.9	1.0	1.0	1.0	0.9	0.9	1.1	1.2	0.8	1.0	1.0	0.9	0.8	1.1	1.2	0.9	0.9	1.0 1	1.0	1



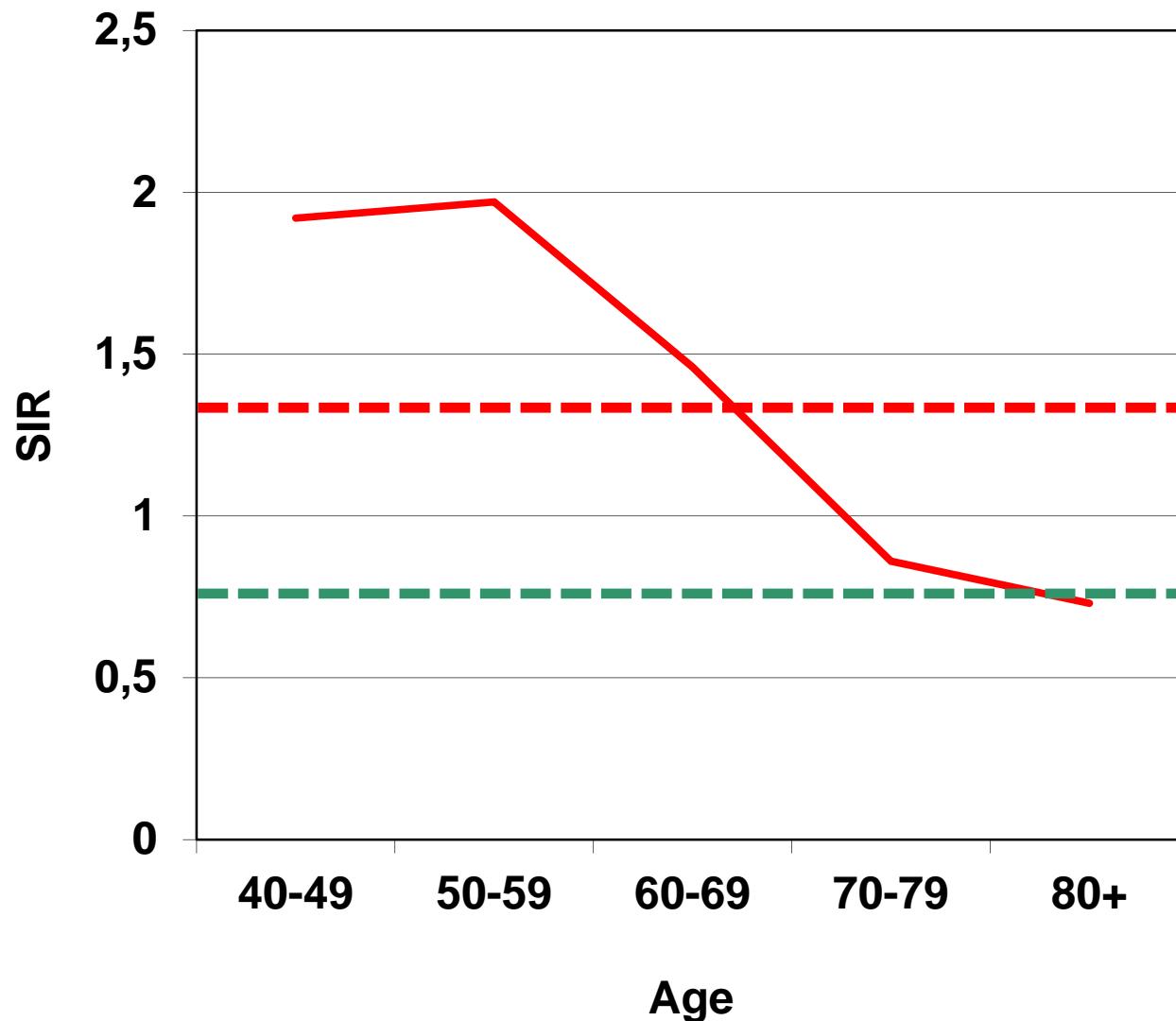
FISHING STRICTLY FORBIDDEN!
(in epidemiology)

**KEY ISSUE:
REGISTER DATA
QUALITY**

Failures in record linkage between Finnish Cancer Registry and death certificate data

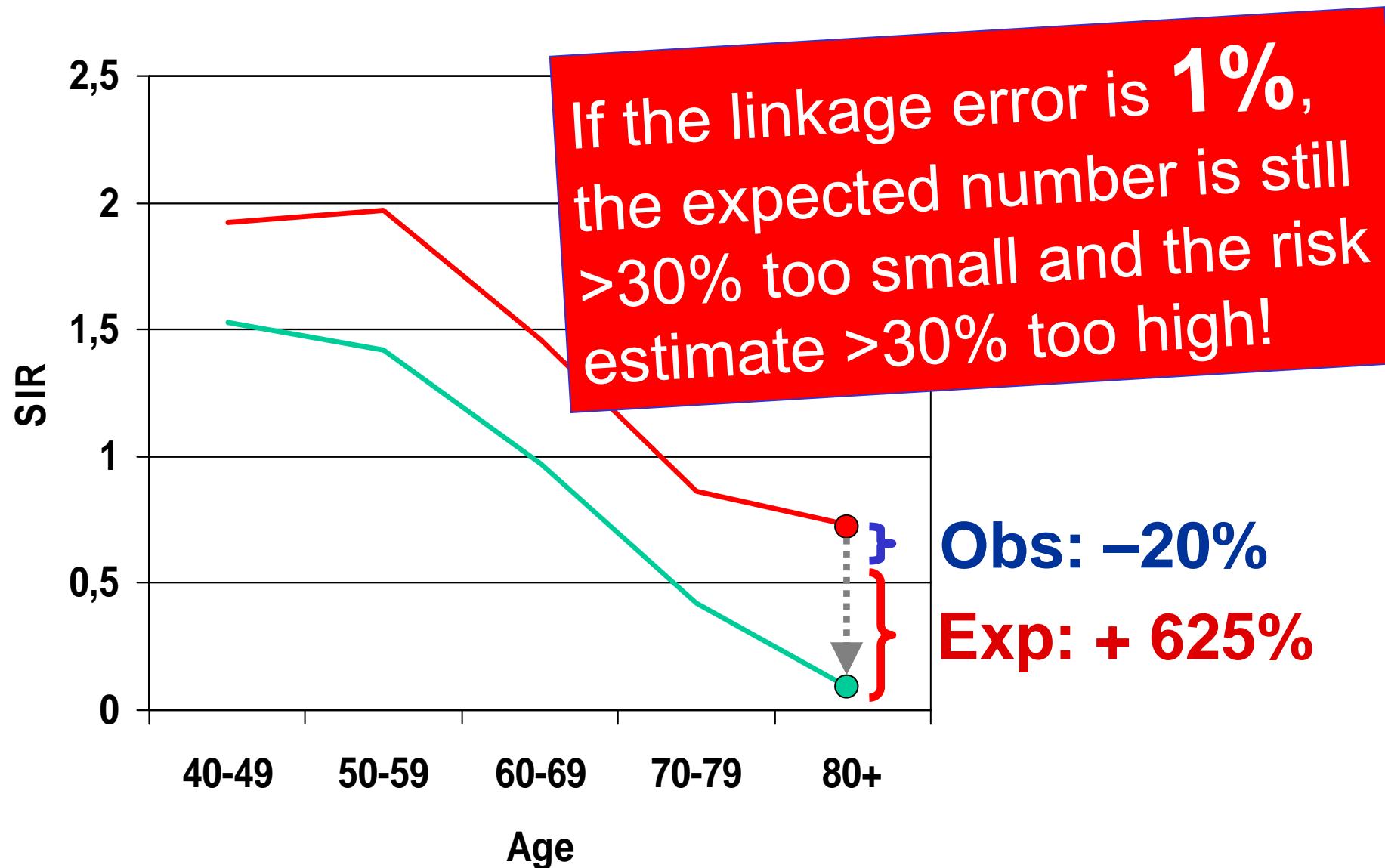


Effect of errors in linkage key: Cancer risk among asbestos mine workers (old cohort)



EXCESS risk
(SIR 1.35; 1.17-1.55)
turns to a
**significantly
DECREASED
risk** if there are
15% or more
linkage failures

Effect of errors in linkage key: Cancer risk among asbestos mine workers (old cohort)



**Can we trust on results
based on linked routine
registers?**

OR from a case-referent study [1] vs. SIR of census-based calculation [2]:
Pancreatic cancer in Finland

Occupational branch	Case-referent			Census		
	N	OR ¹	95% CI	N	SIR ²	95% CI
Agriculture, forestry, fishing	169	0.8	0.7-1.0	555	0.9	0.8-0.9
Mining and quarrying	6	1.5	0.6-4.2	14	1.5	0.8-2.6
Transport and communication	54	1.0	0.7-1.5	204	1.2	1.0-1.3
Textiles and clothes	12	0.7	0.4-1.4	42	0.8	0.6-1.1
Sawmilling	10	1.3	0.6-2.9	17	1.0	0.6-1.6
Paper and board	17	1.4	0.8-2.5	15	1.6	0.9-2.6
Restaurants, cafés, snack bars	7	1.8	0.3-1.9	21	1.3	0.8-2.1
Hairdressing, manicure	4	1.8	0.5-6.4	14	2.1	1.2-2.3

¹ Odds ratios adjusted for age, gender, smoking, alcohol consumption and diabetes.

² Adjusted for social class.

[1] Partanen T, & al. Pancreatic cancer in industrial branches and occupations in Finland. Am J Ind Med 1994;36:616-622

[2] Pukkala E. Cancer risk by social class and occupation. A survey of 109,000 cancer cases among Finns of working age. Contributions to Epidemiology and Biostatistics, vol 7. Karger, Basel 1995 (288 pages)

STUDY EXAMPLES

Does living close to asbestos quarry cause cancer?

External living environment

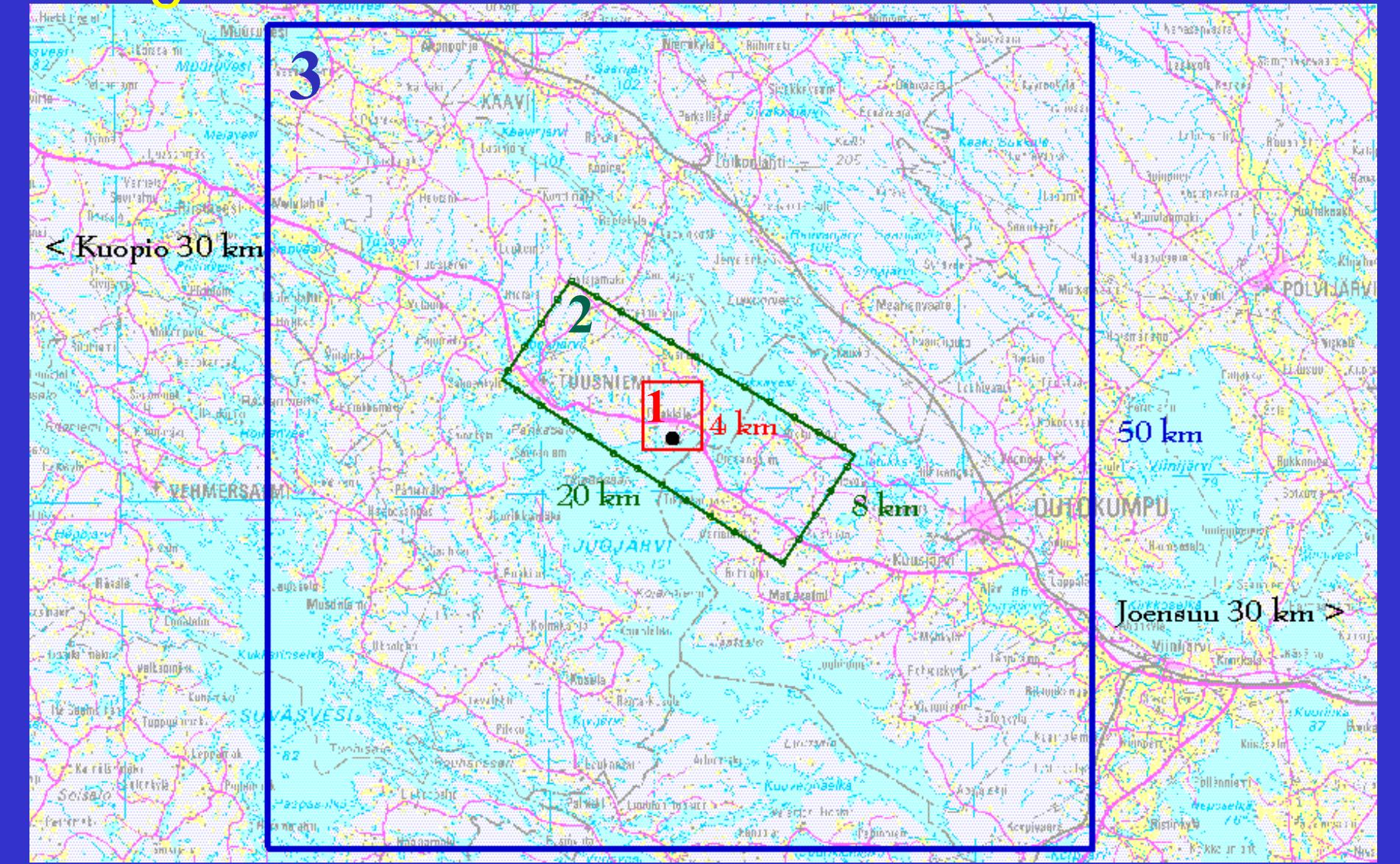


- usually small hazards
- often BIG worry
- risk communication



Response to the client in one day

Example: Lung cancer around former asbestos mine



Example:

Lung cancer around former asbestos mine

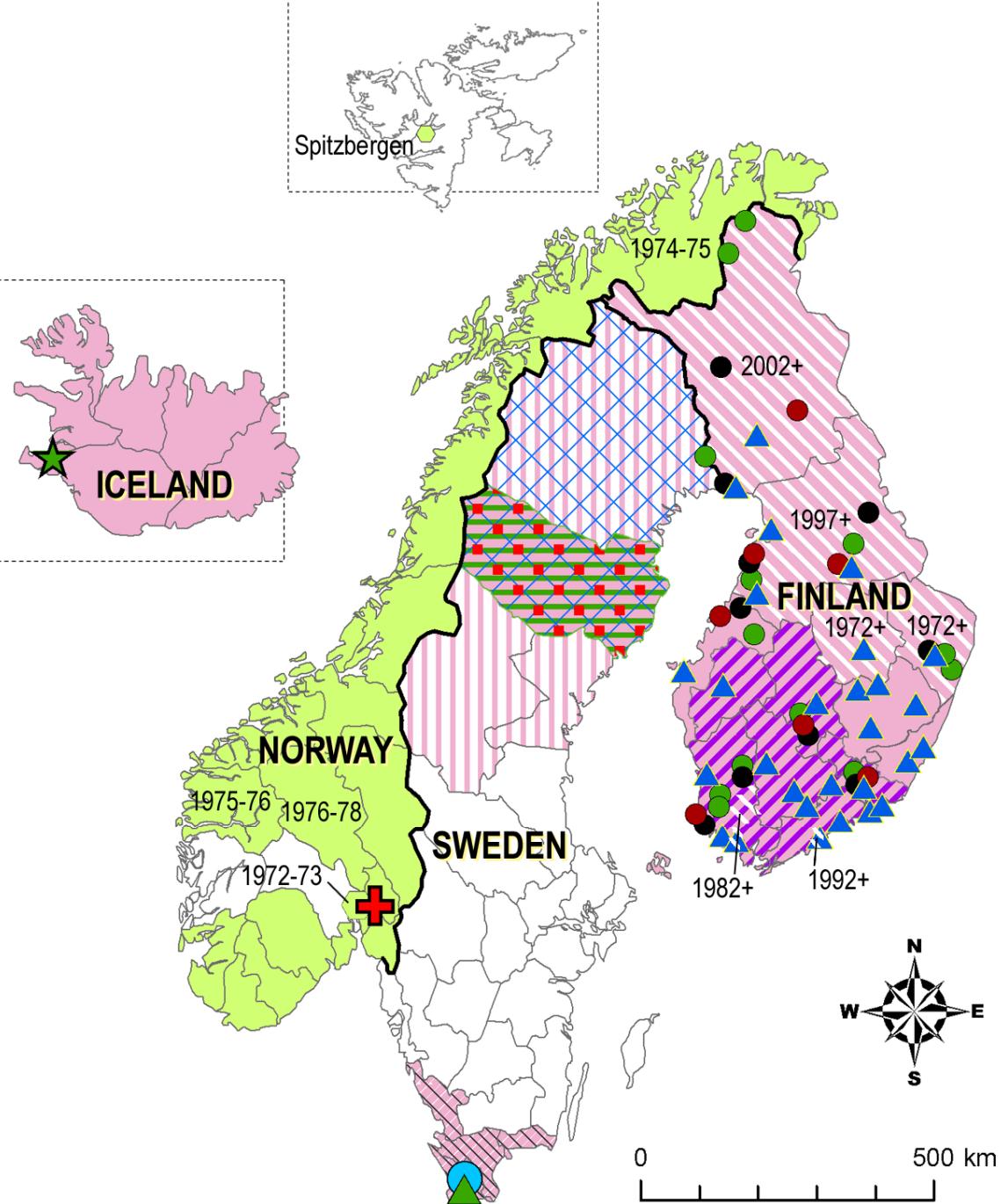
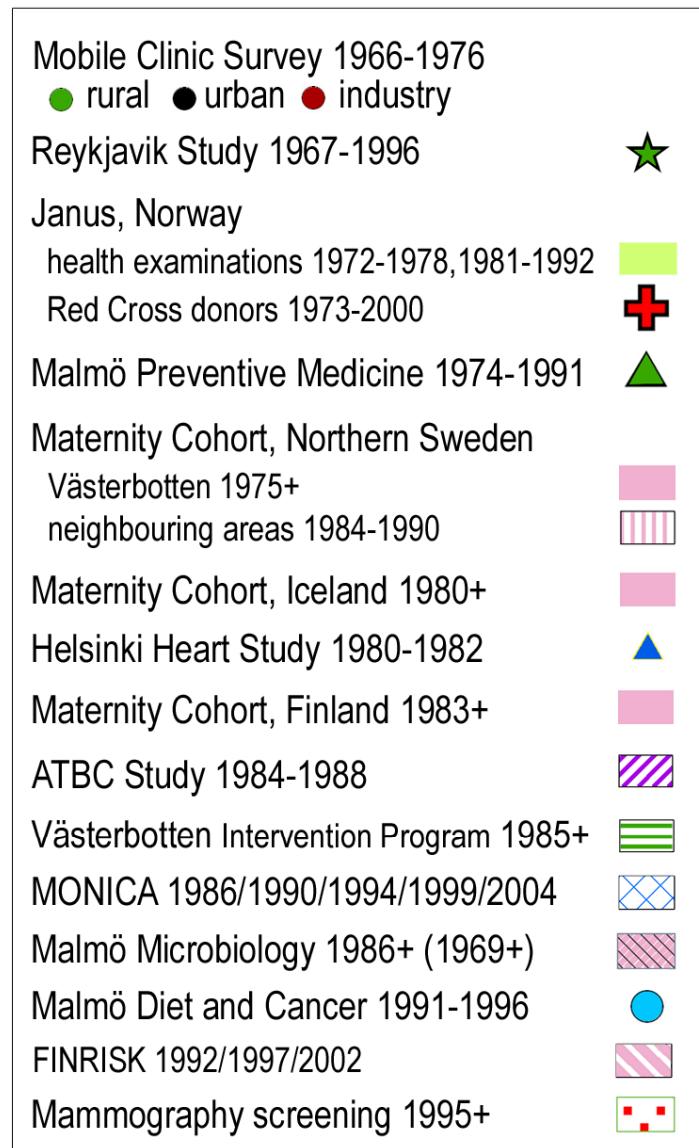
Area	Population	N of cancers	SIR (95% CI)
1	194	6	3.80 (1.39 - 8.28)
2	2 124	24	1.44 (0.92 - 2.13)
3	17 507	154	1.20 (1.02 - 1.41)

There is no excess risk in any of the regions, if we exclude persons who were working in the asbestos mine.

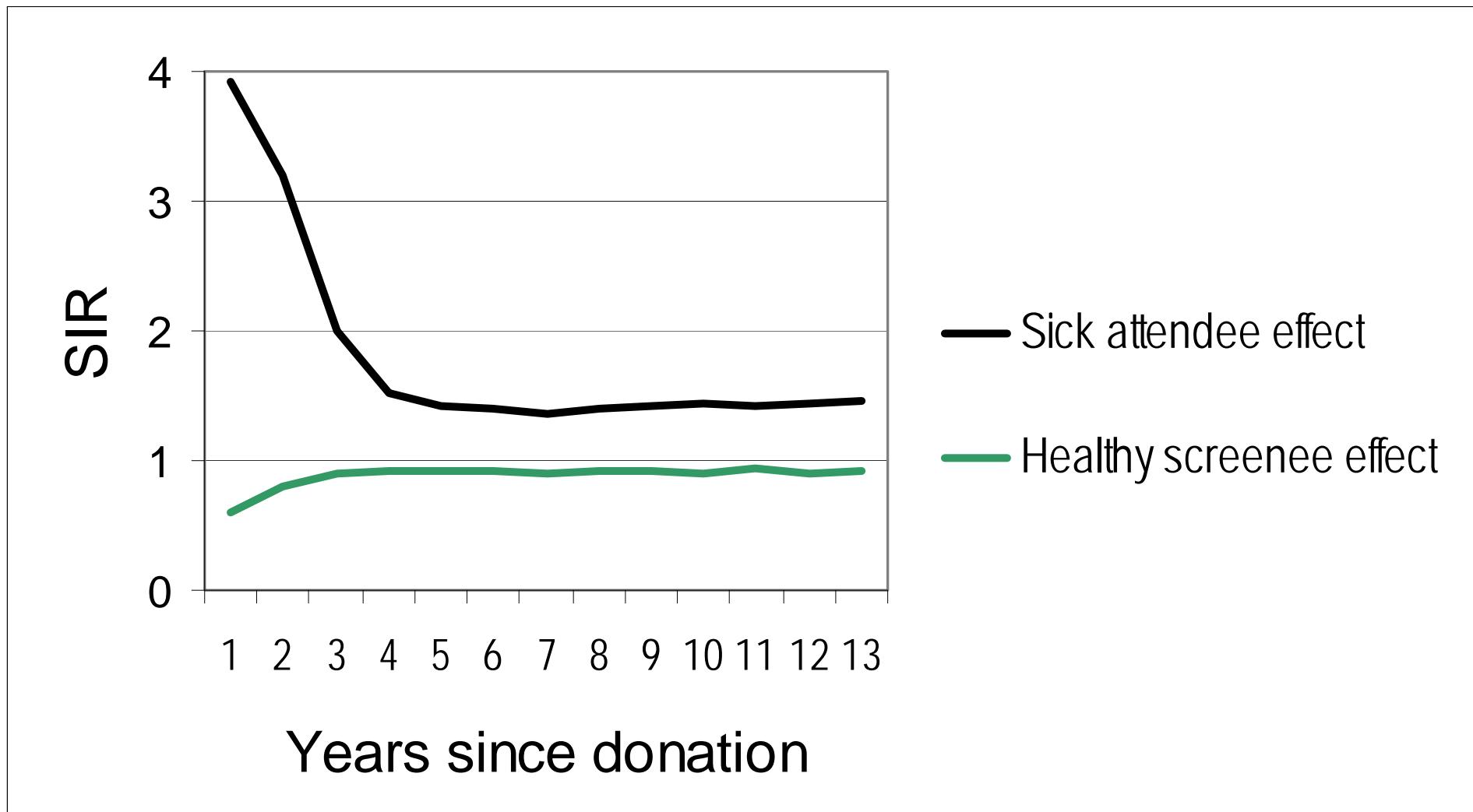
Pukkala, E., Andersen, A., Berglund, G., Gislefoss, R., Guðnason, V.,
Hallmans, G., Jellum, E., Jousilahti, P., Knekt, P., Koskela, P., Kyrrönen, P.,
Lenner, P., Luostarinen, T., Löve, A., Ögmundsdóttir, H., Stattin, P.,
Tenkanen, L., Tryggvadóttir, L., Virtamo, J., Wadell, G., Widell, A.,
Lehtinen, M., Dillner, J.

**Nordic biological specimen banks as basis
for studies of cancer causes and control –
more than 2 million sample donors, 25 million
person-years and 100,000 prospective cancers**

Acta Oncol. 2007; 46: 286-307



Biases related to the indication of serum donation





Johannes Clemmesen (1908-2010)

- Established the Danish Cancer Registry (1943)
- Observed large spatio-temporal differences in testis cancer incidence ([maps](#))
- "If the cancer epidemiologists are not able to find the reason behind the large increase in testicular cancer, with its striking epidemiologic features, they'd better find another job"

Does maternal smoking cause testicular cancer in the sons?

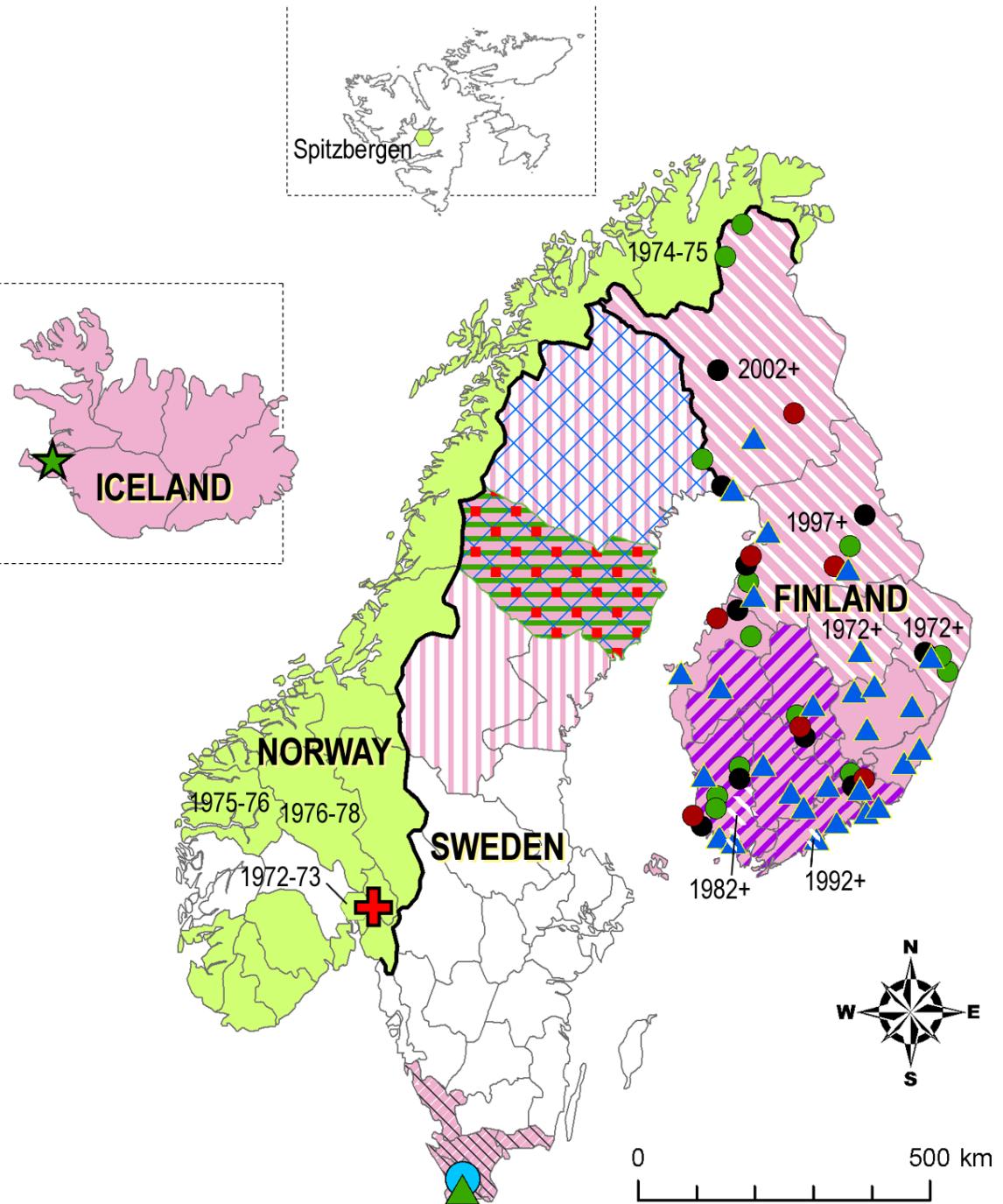
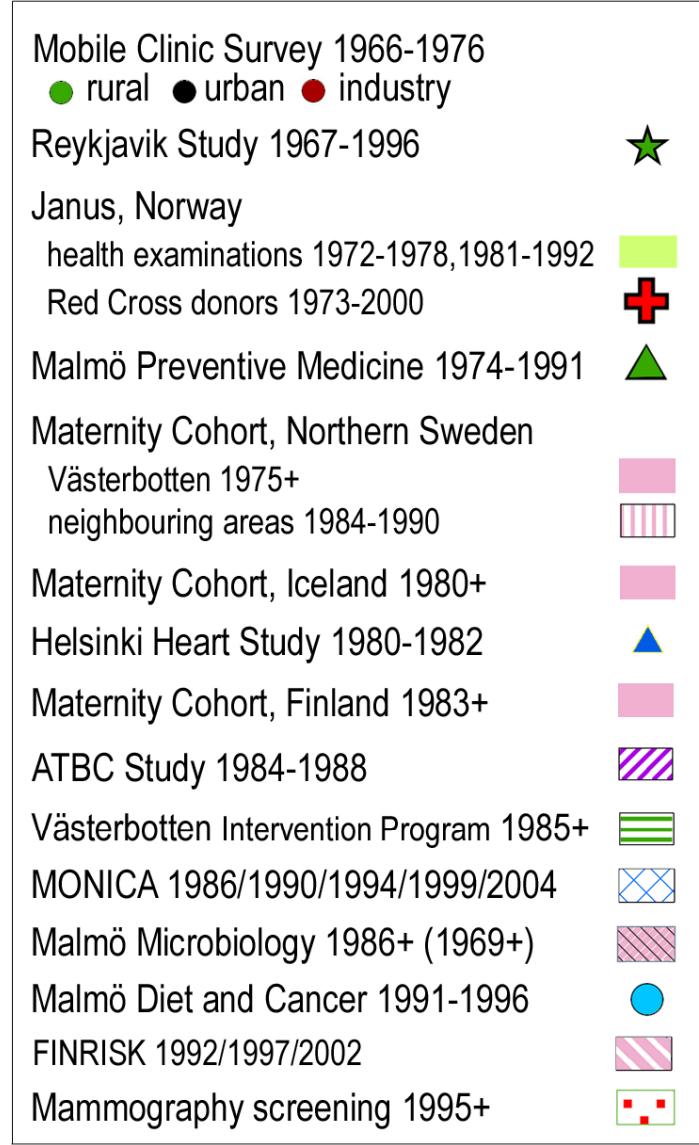
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**Nordic biological specimen banks as basis
for studies of cancer causes and control –
more than 2 million sample donors, 25 million
person-years and 100,000 prospective cancers**

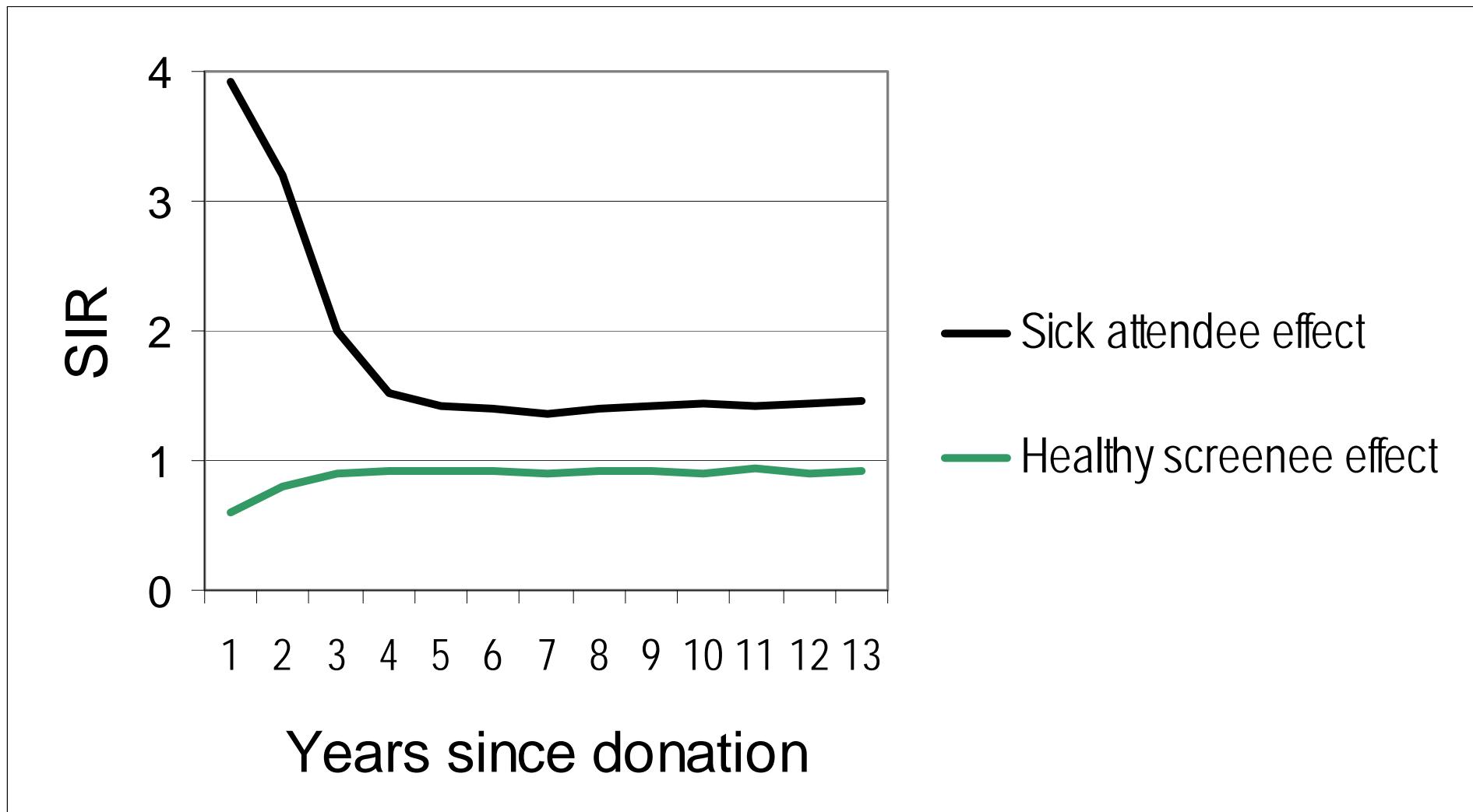
Acta Oncol. 2007; 46: 286-307

Nordic Biological Specimen Banks for Cancer Causes and Control

- **blood sera collected long time ago and stored at $-20^{\circ}\dots -135^{\circ}\text{C}$**
- **2 million persons, 30 million p-years**
- **170,000 cancers; increase 10,000/year**
- **case control studies**
 - **tens of papers published so far (NEJM etc)**



Biases related to the indication of serum donation



Does maternal smoking cause
testicular cancer in their sons?

NO

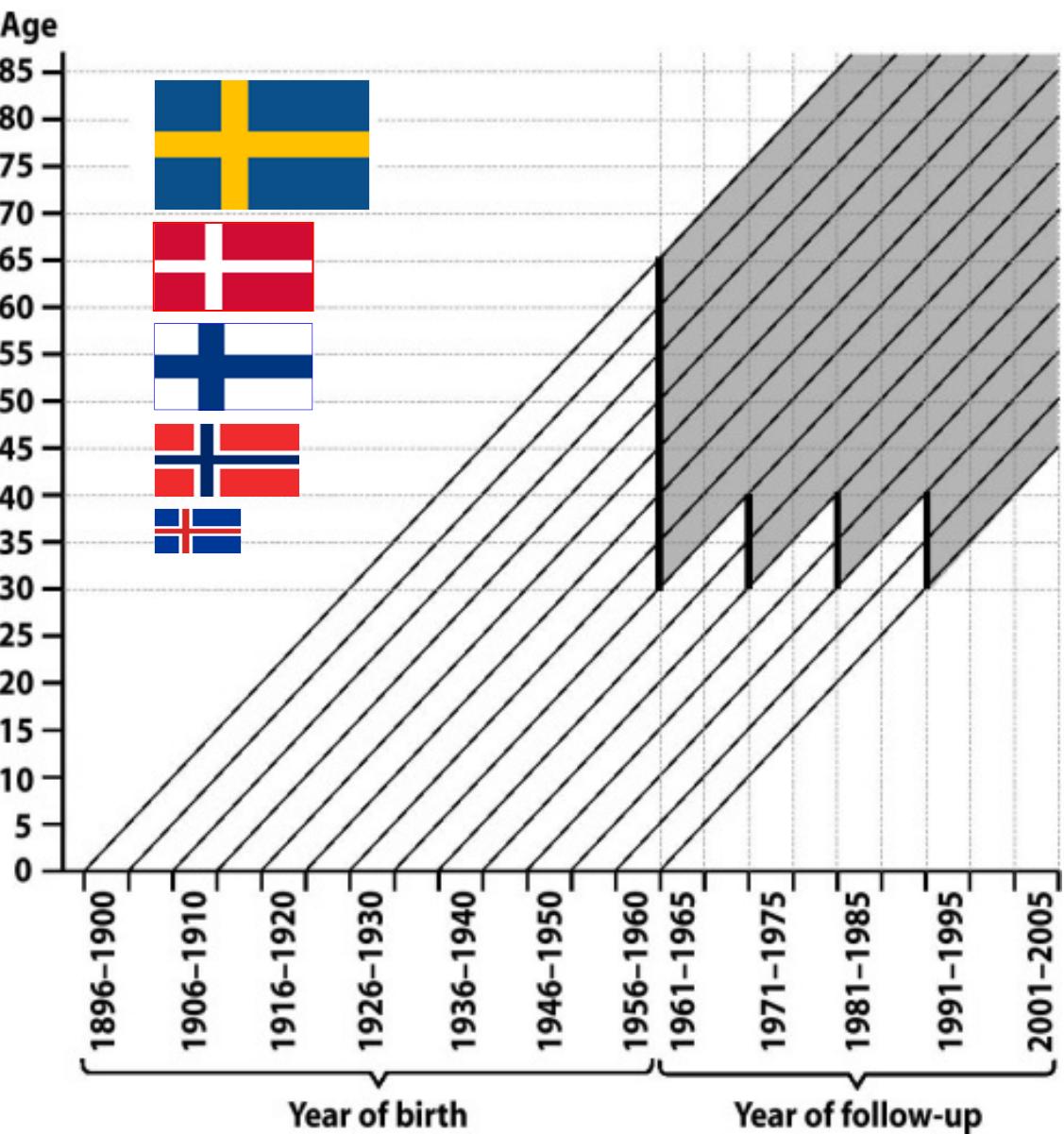
Tuomisto, J., Holl, K., Rantakokko, P., Koskela, P. Hallmans, G., Wadell, G.,
Stattin, P., Dillner, J., Ögmundsdottir, H.M., Vartiainen, T., Lehtinen, M.,
Pukkala, E.:

Maternal smoking during pregnancy and testicular cancer in the
offspring: a nested case-control study.

Eur. J. Cancer 2009; 45: 1640-1648.

Study population, follow-up

3 million
invasive
cancer cases



ORIGINAL ARTICLE

Occupation and cancer – follow-up of 15 million people in five Nordic countries

EERO PUKKALA^{1,2}, JAN IVAR MARTINSEN³, ELSEBETH LYNGE⁴, HOLMFRIDUR KOLBRUN GUNNARSDOTTIR⁵, PÄR SPARÉN⁶, LAUFEO TRYGGVADOTTIR⁷, ELISABETE WEIDERPASS^{3,6,8,9} & KRISTINA KJAERHEIM³

¹Finnish Cancer Registry, National Institute for Health and Welfare, Helsinki, Finland; ²Helsinki University Central Hospital, Helsinki, Finland; ³Norwegian Institute of Public Health, Oslo, Norway; ⁴Icelandic Cancer Registry, Reykjavik, Iceland; ⁵Hospital University of Iceland, Reykjavik, Iceland; ⁶Karolinska Institutet, Stockholm, Sweden; ⁷Landspítali National University Hospital, Reykjavik, Iceland; ⁸University of Southern Denmark, Odense, Denmark; ⁹American University of Beirut, Beirut, Lebanon

Cancer risk estimates for any cancer and any occupation:

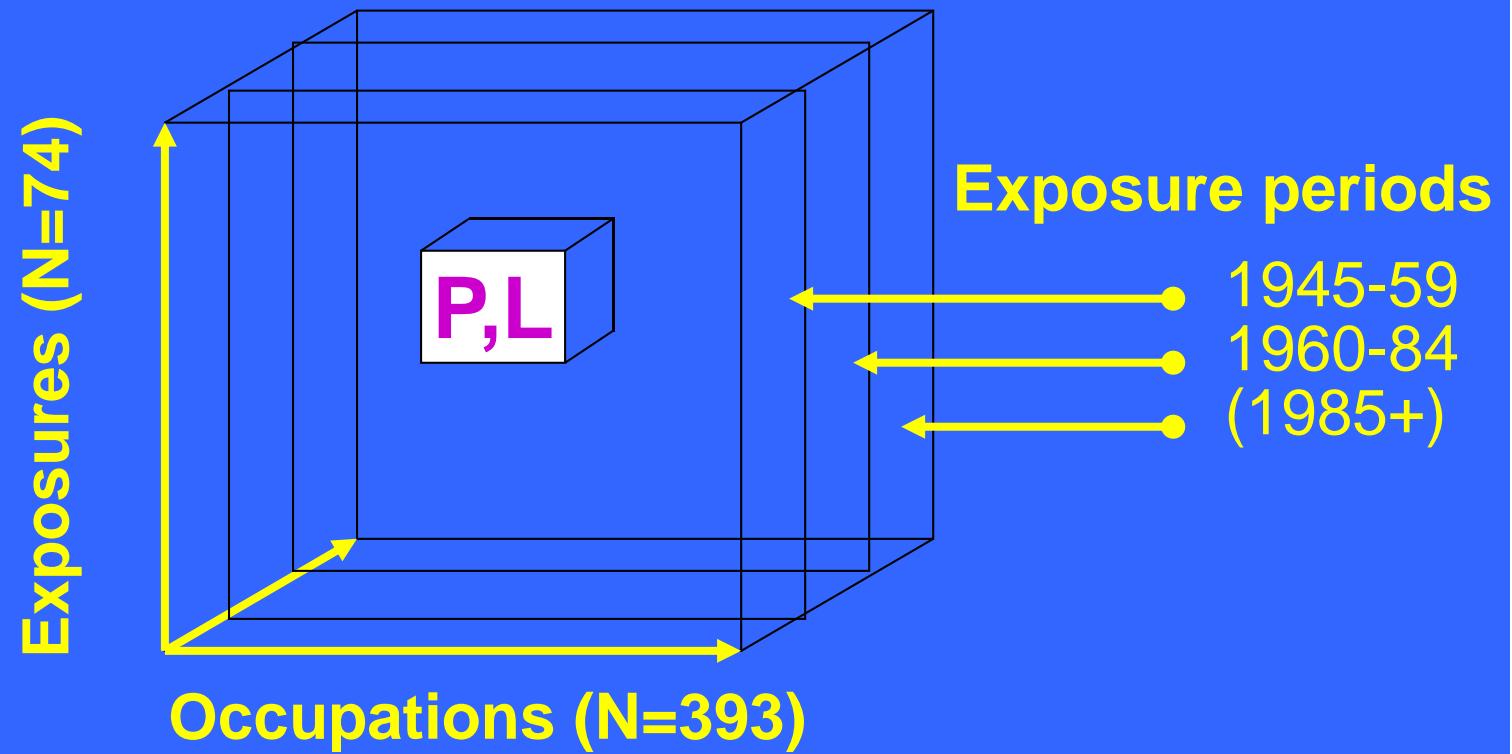
<http://astra.cancer.fi/NOCCA/>

Can we estimate amount of
occupational exposures for
every Nordic person at any
point of time?

YES WE CAN.

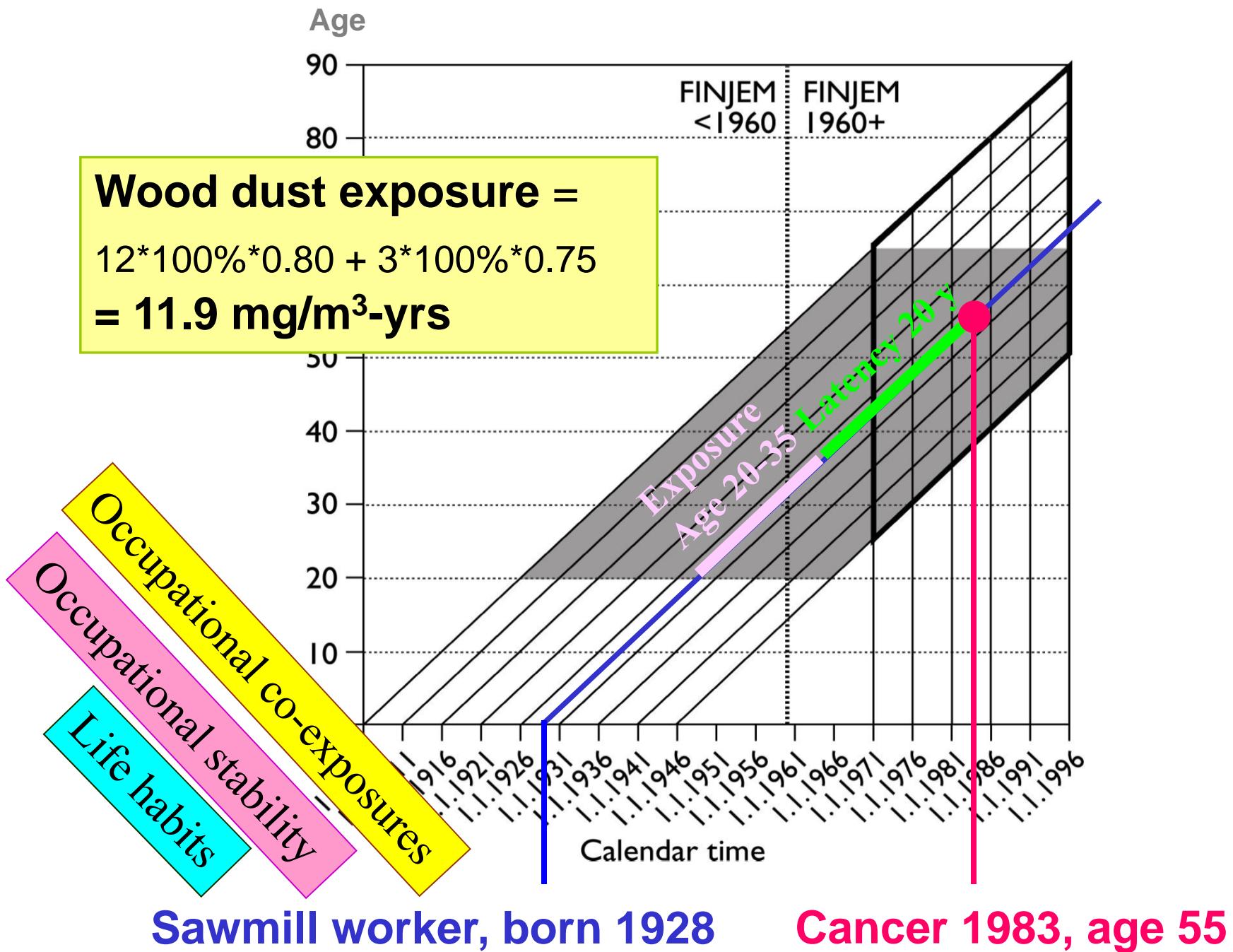
FINJEM

JEM + exposure information system



P = proportion of exposed persons (%)

L = mean level of exposure (ppm, etc.)



Dose-response RRs {CONFIDENTIAL}

Wood dust - Nasal adenocarcinoma

(FI-ICE-NO-SWE, lag 10 years)

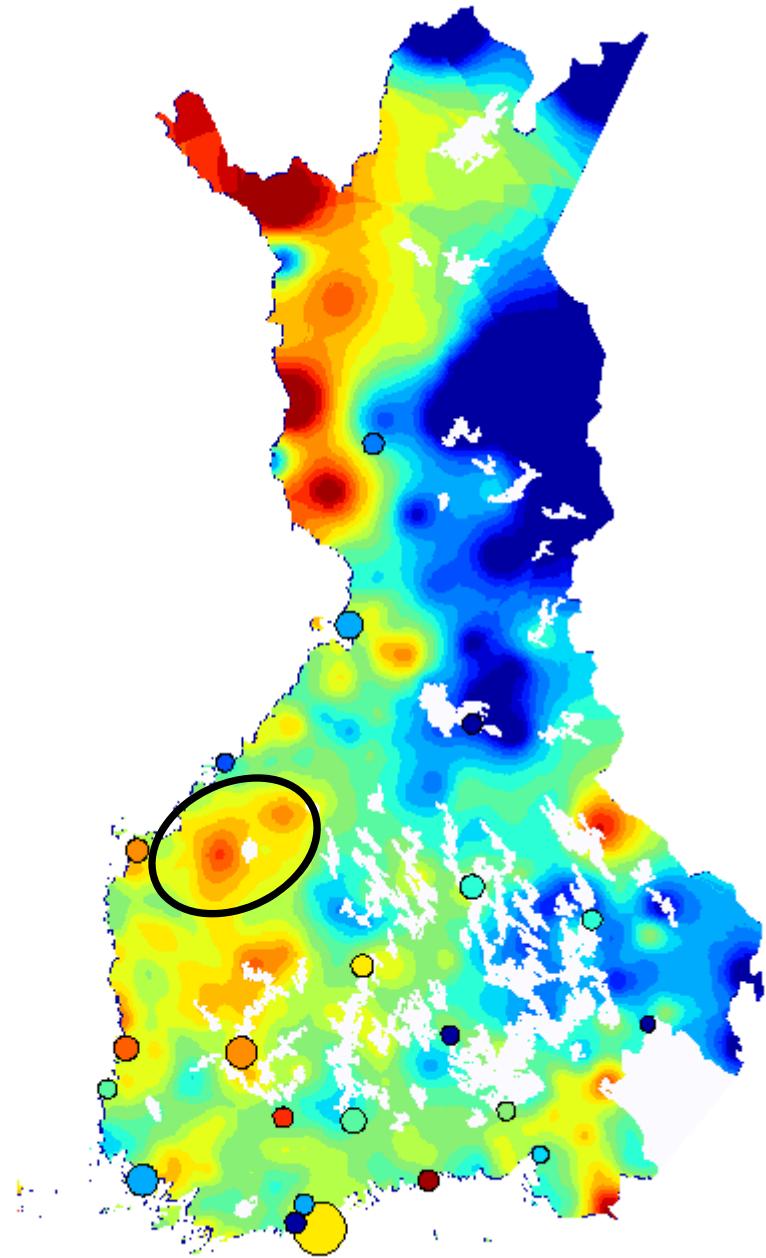
Exposure	n	HR	95% CI
High	24	31	11-91
Moderate	77	11	7.6-17
Low	37	3.0	2.0-4.6
None	255	1.0	reference

How to identify systematically families with increased cancer risk?

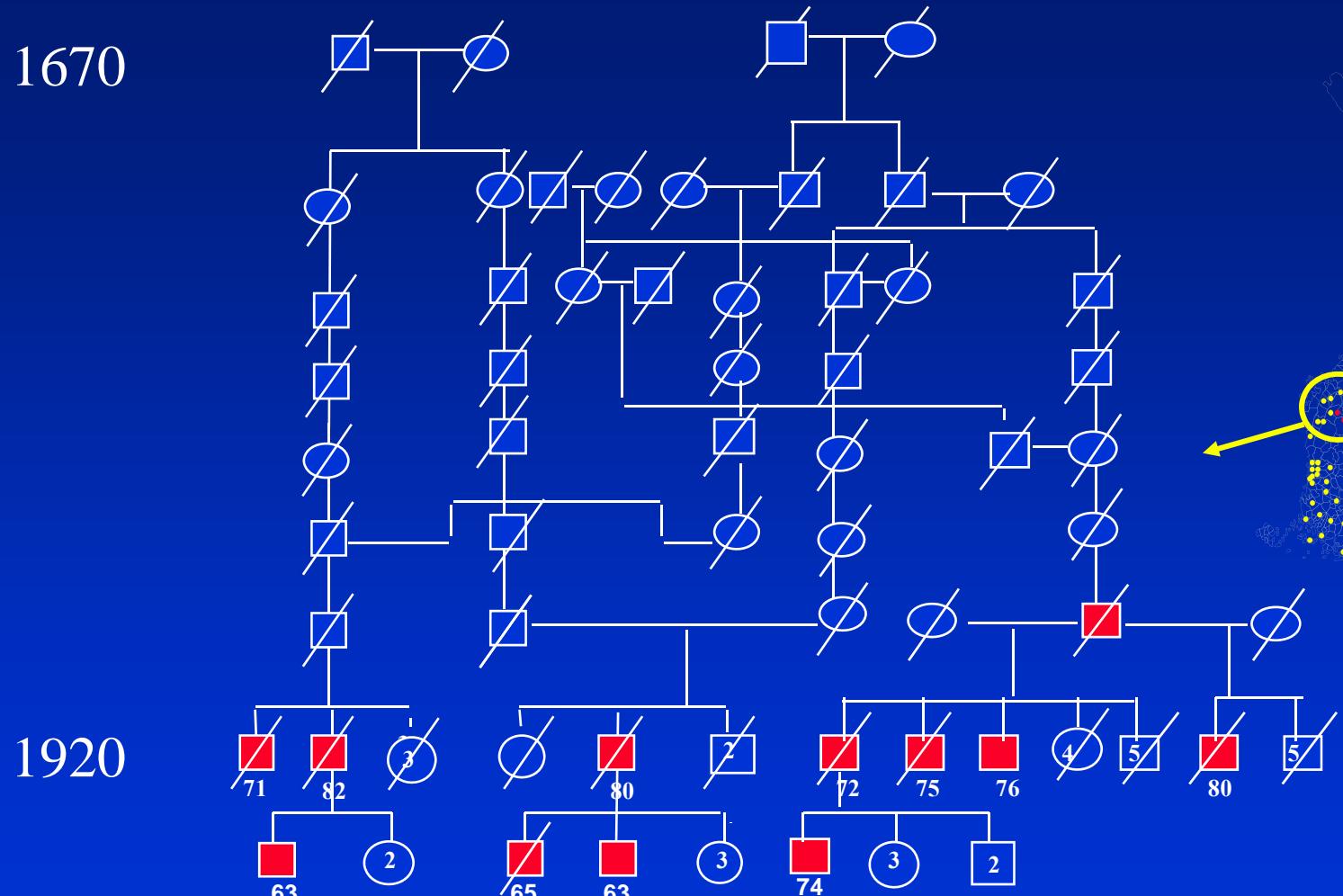
(First step in identification of new cancer genes)

Incidence of prostate cancer (ages < 50 years) according to place of birth

1. Identify highest O/E ratios for **family name** & birth municipality combinations
2. Search common ancestors of current high-risk families
3. Identify riks gene chromosome region
4. Identify founder of the mutation
5. Identify all carriers of the mutation in the present population (**if that increases their life quality**)



Three families with significantly elevated O/E ratios from the same geographical region connected with genealogical links



Family no.

O/E

72

5.88

88

7.04

264

6.28

Matikainen, M.P., Sankila, R., Schleutker, J.,
Kallioniemi, O.-P., Pukkala, E.:

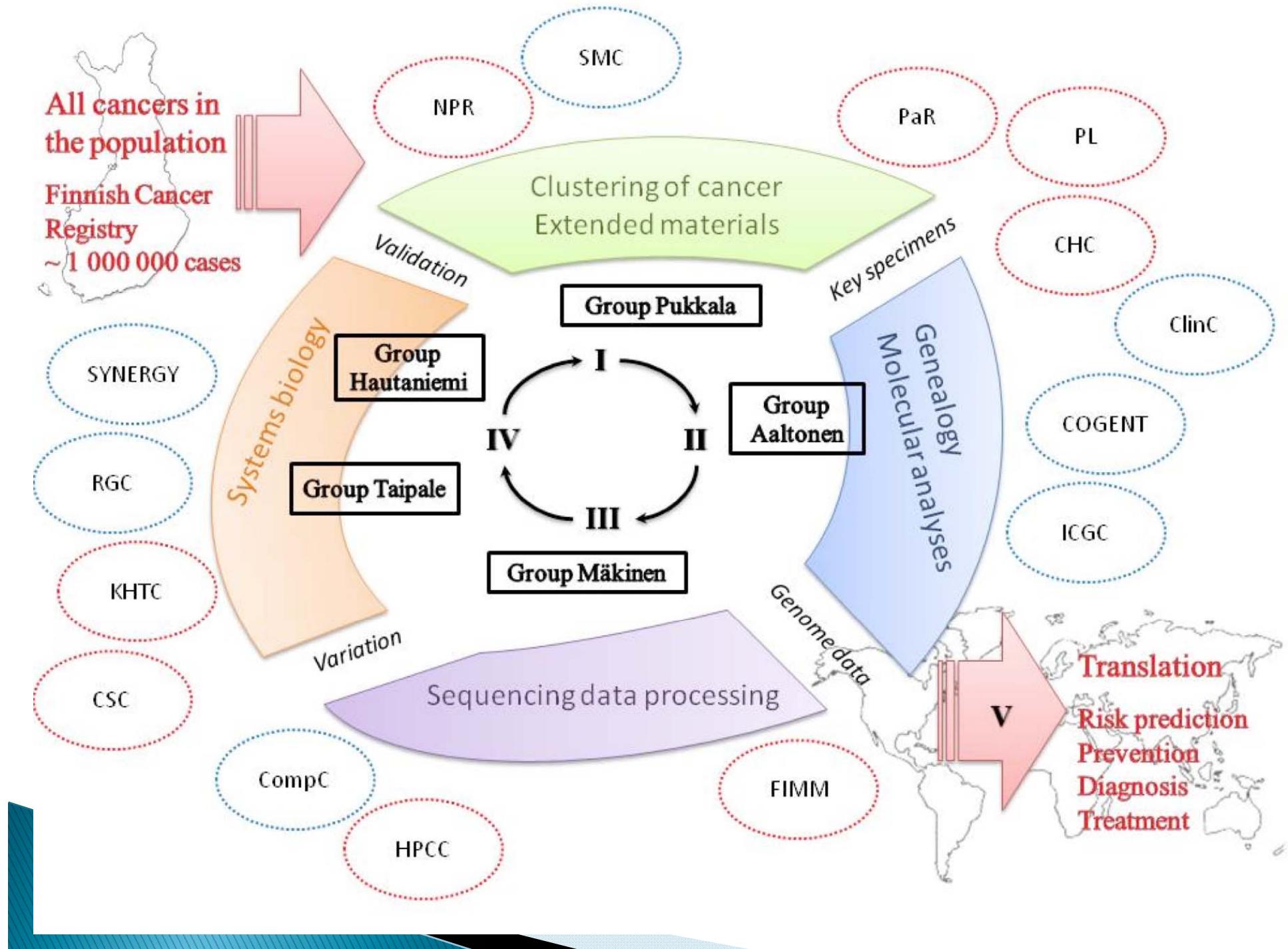
**Nationwide cancer family ascertainment using
Finnish Cancer Registry data on family names
and places of birth for 35,761 prostate cancer
patients.**

Int. J. Cancer 2000; 88: 307-312

Spatial and familial clustering of different tumour types in Finland –

**Finnish Cancer Registry as key
element of the**

**Center of Excellence
on Cancer Genetics**



Tumor types showing significant evidence for familial occurrence

Topography	Morphology	Cluster score	Number of patients in clusters**	Suggestive predisposition gene
central nervous system	hemangioblastoma	4.98	13	VHL
thyroid gland	medullary carcinoma	3.55	22	RET
skin	Kaposi sarcoma	1.91	19	
pancreas	neuroendocrine carcinoma	1.40	10	MEN1, RET
kidney	nephroblastoma	1.26	10	WT1
small intestine	neuroendocrine ca	0.98	21	
vulva and vagina	squamous cell ca	0.63	36	
mesothelium	mesothelioma	0.62	20	
breast	mucinous (cystic) ca	0.57	27	
thyroid gland	papillary adenoca	0.56	82	
central nervous system	neurofibroma	0.55	21	NF1
central nervous system	neoplasm malignant	0.51	22	
haematopoetic	polycythemia vera	0.50	20	
haematopoetic	chronic lymphatic leukemia, b-cell	0.48	66	
kidney	neoplasm malignant	0.47	26	
lymph node	Hodgkin lymphoma	0.46	47	
prostate	epithelial ca	0.44	26	

Kaasinens, E., Aavikko, M., ..., Aaltonen LA, Pukkala E. Nationwide registry-based analysis of cancer clustering detects strong familial occurrence of Kaposi sarcoma. PLoS ONE 2013.

Nordic Summer School in Cancer Epidemiology

(-30°C)

Next call opens soon:
apply at ANCR.nu



Kiitos.