Methods to Recognize Work-related Cancers

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Spitsbergen, Norway, 78° North; coal mining area

GEORGII AGRICOLAE

DE RE METALLICA LIBRI XII▸ QVIBVS OFFICIA, INSTRVMENTA, MACHINAE, AC OMNIA DENIque ad Metallicam ſpectantia, non modò luculentiſſimè deſcribuntur, ſed & per effigies, ſuis locis inſertas, adiunctis Latinis, Germanicisq; appellationibus ita ob oculos ponuntur, vt clarius tradi non poſſint.

EIVSDEM

DE ANIMANTIBVS SVBTERRANEIS LIBER, AB AVTORE recognitus: cum Indicibus diuerſis, quicquid in opere tractatum eſt, pulchrè demonſtrantibus, atq; omnibus nunc iterum ad archetypum diligenter reſtitutis & caſtigatis.

BASILEAE M▸ D▸ LXI▸

Cum Priuilegio Imperatoris in annos v. & Galliarum Regis ad ſexennium.

Gregorius Agricola (Georg Bauer) published "*De re metallica*", Basel and Deventer, 1556.

Here he reported on "Bergsucht" = "mine-consumption"

Harting FH, Hesse W. Vjschr Gericht Med Öff Sanit 1879;30:296-309.

They reported on "endemic occurrence" of lung cancer among the Scheeberg miners.

Deaths among on average 650 miners:

1869-71 = 63

1872-74 = 42

1875-77 = 40

Subsequent studies in these mines: on average 100.000 Bq m^{-3}, peaking at 3-600.000 Bq m^{-3}.

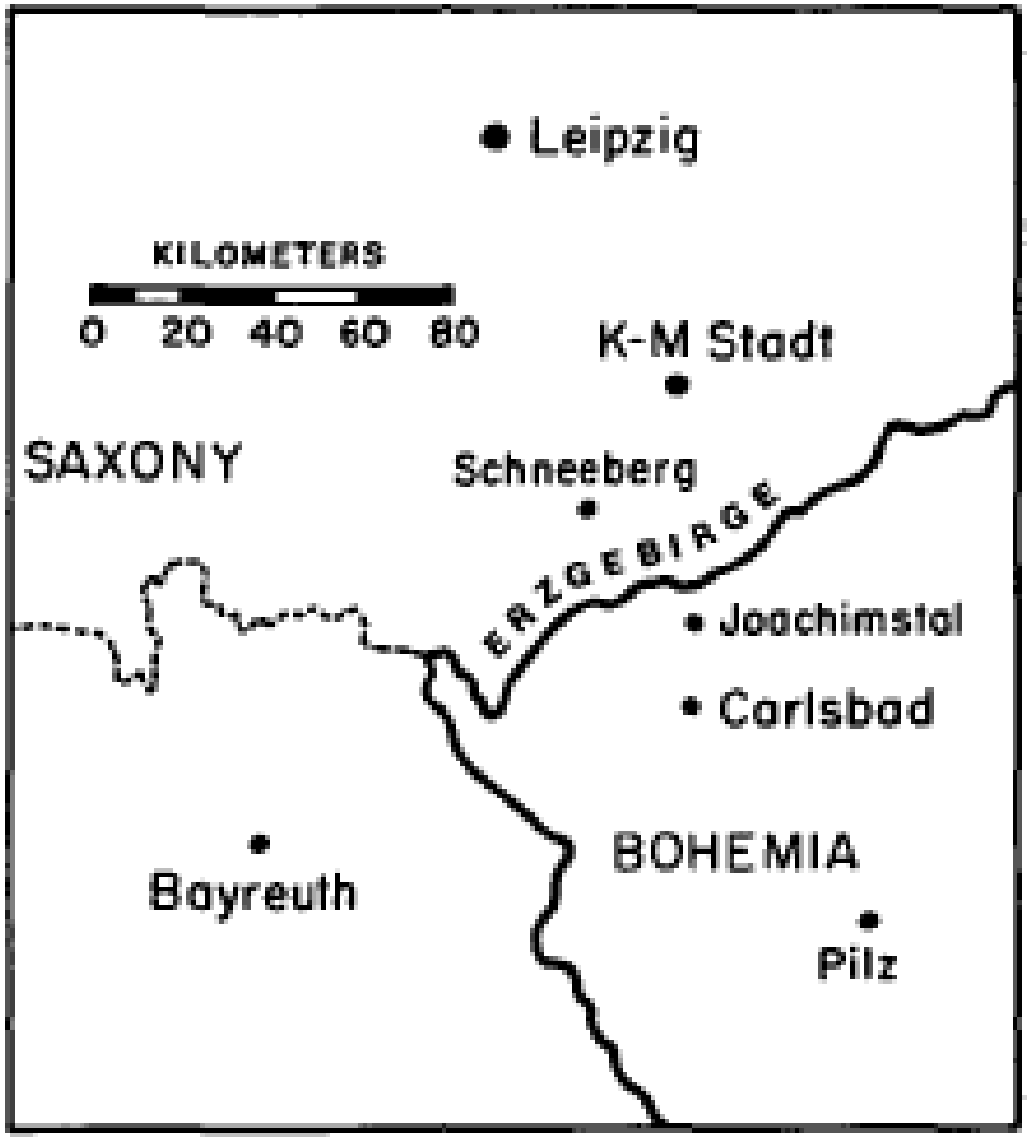


FIG. 1. Sketch map of the Erzgebirge mountain range.

Bernardino Ramazzini indicated that nuns carried an elevated risk of breast cancer.

Norway: Løken AC. [Lung cancer among *nikkel*workers]. Tidsskr Nor Laegeforen 1950;70:376-8.

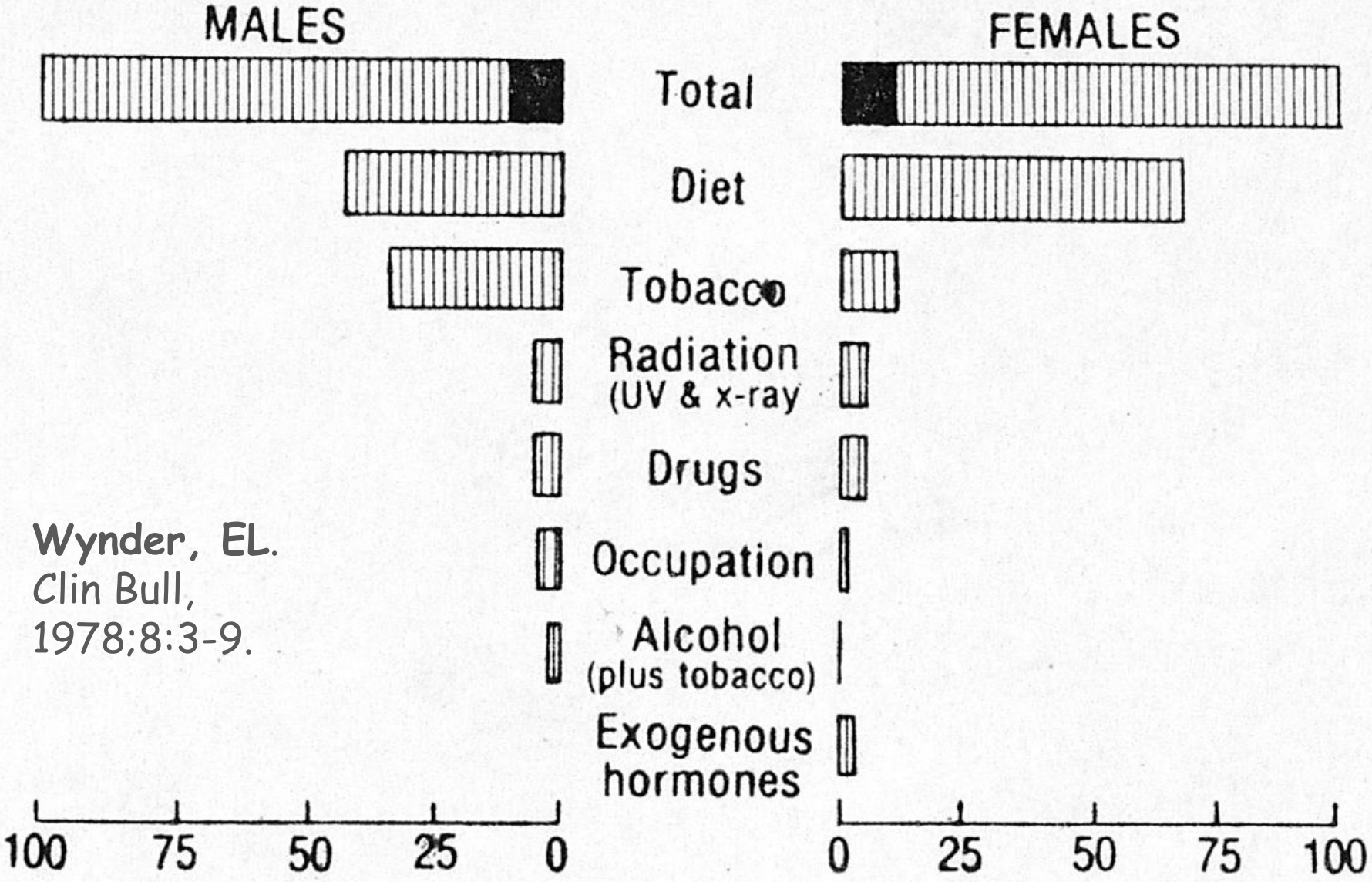
She reported on ***three cases*** of squamous-cell carcinoma of the lung occurring in in men who had been employed in the roasting and shearing areas of the Falconbridge nickel refinery at Kristansand, Norway.

This was the second scientific report – after Amor, 1938* - on the association between exposure to nickel compounds and lung cancer.

* Amor AJ. Bericht über den VIII internationalen Kongress für Unfallmedizin und Berufskrankheiten, Frankfurt am Main, September 1938, Vol 2, p 941. Thieme, Leipzig.

Well known work / environment-related carcinogenic substances and agents

Acrylonitrile
Aflatoxin
4-Amino biphenyl
Arsenic
Asbestos
Benzene
Benzidine
Beryllium
β-Naphthylamine
BCME
Chromium compounds
Coal tar (aromatic hydrocarbons)
Cyclophosphamide
Diethylstilbestrol (hormone analog)
Leather and wood dust
Mustard gas (alkylating agents)
Neoprene
Nickel compounds
Nitrosamines
Radiation (ionizing and ultraviolet)
Tobacco smoke
Vinyl chloride



Wynder, EL.
Clin Bull,
1978;8:3-9.

	MALES	FEMALES
Estimated new cases for all sites, 1976	339,000	336,000
Estimated deaths for all sites, 1976	202,000	168,000

American Cancer Society, 1975

TABLE 20.—*Proportions of cancer deaths attributed to various different factors*

Text section No.	Factor or class of factors	Percent of all cancer deaths: Best estimate	Percent of all cancer deaths: Range of acceptable estimates
5.1	Tobacco	30	25–40
5.2	Alcohol	3	2–4
5.3	Diet	35	10–70
5.4	Food additives	<1	−5[a]–2
5.5	Reproductive[b] and sexual behaviour	?	1–13
5.6	Occupation	4	2–8
5.7	Pollution	2	<1–5
5.8	Industrial products	<1	<1–2
5.9	Medicines and medical procedures	1	0.5–3
5.10	Geophysical factors[c]	3	2–4
5.11	Infection	10 ?	1–?
5.12	Unknown	?	?

[a] Allowing for a possibly protective effect of antioxidants and other preservatives.

[b] *See* section 5.5 for intended meaning.

[c] Only about 1%, not 3%, could reasonably be described as "avoidable" (*see* text). Geophysical factors also cause a much greater proportion of non-fatal cancers (up to 30% of all cancers, depending on ethnic mix and latitude) because of the importance of UV light in causing the relatively non-fatal basal cell and squamous cell carcinomas of sunlight-exposed skin.

Doll R, Peto R. The causes of cancer. **Quantitative Estimates of Avoidable Risks of Cancer in the United States.** J Natl Cancer Inst *1981*;66:1192-1308.

Given that 4 % of all incident cases of cancer in Norway are work-related, **±1100 weighted cases** are related to work exposure.

Norway*: Approved occupational diseases and compensation, mean no. 2004-07

Diagnose group	Approved Workers. Comp. F	Approved Workers. Comp. M	Notified cases F	Notified cases M
C34 Lung cancer	0	95	0	125
C45 Mesotheliomas	0	41	1	51
C00-D48 Other tumors	0	11	1	12
G00-G99 Diseases CNS	3	44	3	57
H60-H95 Hearing loss	11	336	0	47
J00-J99 Lung diseases	26	160	20	132
L00-L99 Skin diseases	53	73	22	28
Other diseases	21	47	2	26

*5 mill people.

When to consider cancer cases as *work-related?*

- **Practical definition** for "work-relatedness":
  All cases of cancer to which work exposure has contributed to a certain extent by weight are work-related.
- Only in rare cases work exposure contributes close to 100% by weight.
- **When applying a low** *weight-threshold* **to consider a given case** *work-related*, **result in a large number of** *cases* **- and *vise versa*.**

Norway's *national insurance scheme* requires at least *doubling*$^{+}$ *of the case's risk* - compared to unexposed - and *15%*$^{+}$ *attribution* by weight to compensate a cancer case as *occupational disease.*

I. Gender differences; a tool to identify work-related cancers

Airways cancers **one year** in Norway:

Incident cases as of 1999

	Men	Women
• **Lung cancer**	**1.257**	**712**
• Cancer of the nasal sinuses	22	19
• **Pleural mesotheliomas**	**61**	**11**
• Larynx cancer	111	17

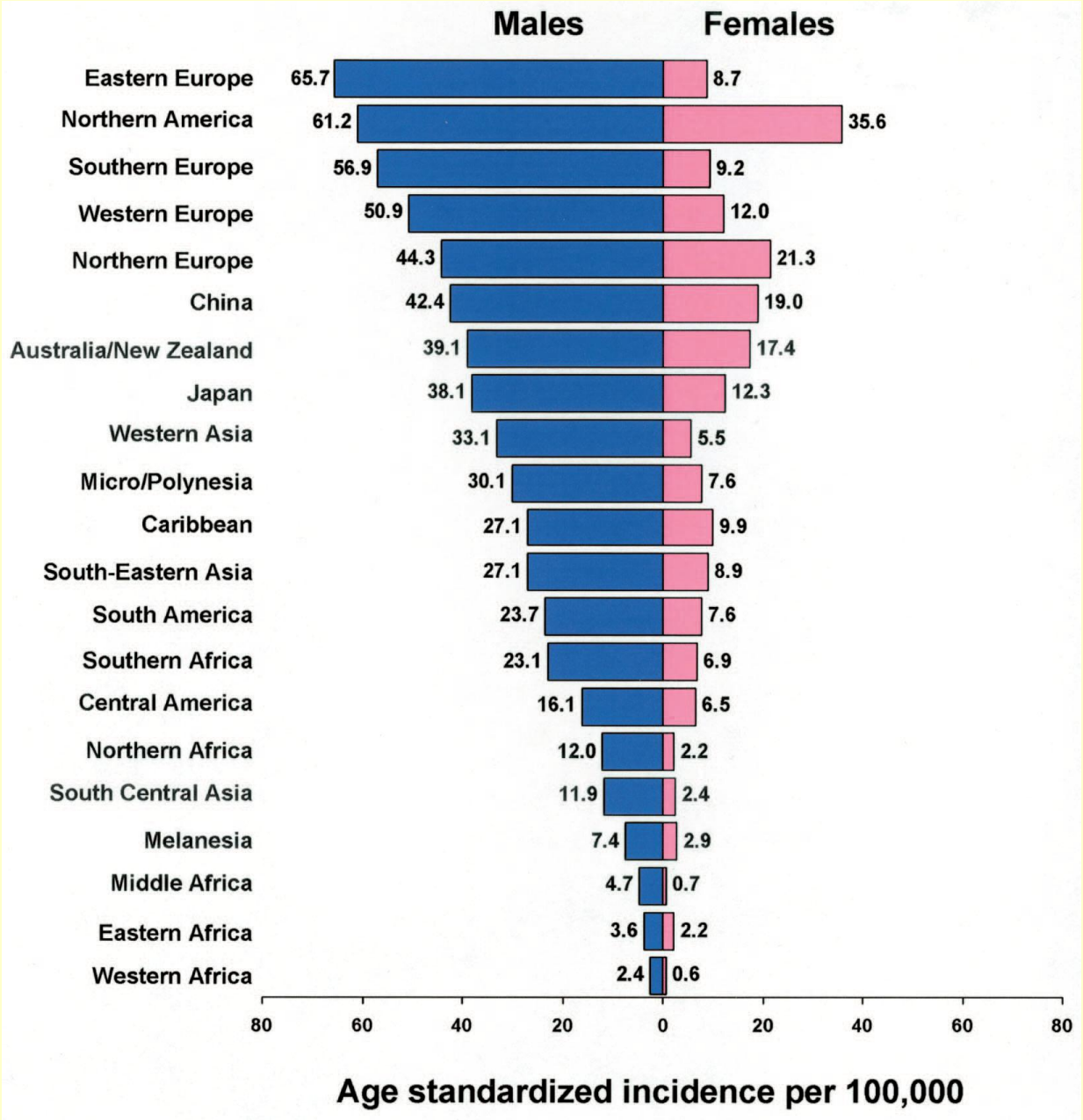
Source: The Cancer Registry of Norway

Also: Comparing incidence / mortality for specific sites in different counties or municipalities to identify large incidence differences.

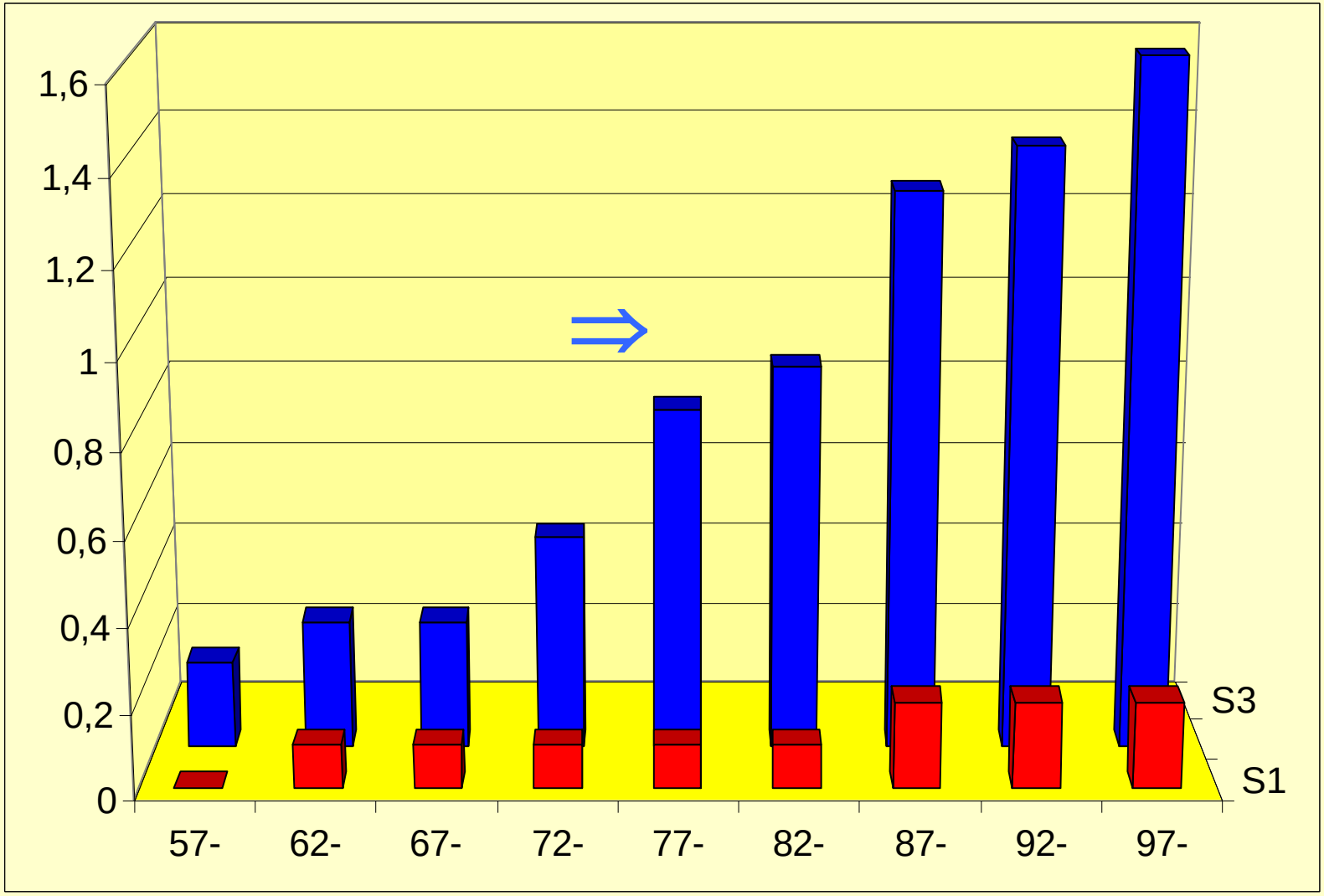
Identifying gender differences in the incidence for a cancer-location, is a port of entry to recognize work-relate cancers.

World: Lung cancer.

Parkin DM, et al. *CA Cancer J Clin* 2002;55:74-108.



I Gender differences: mesotheliomas, Norway, nx10^{-5}, 1957-01

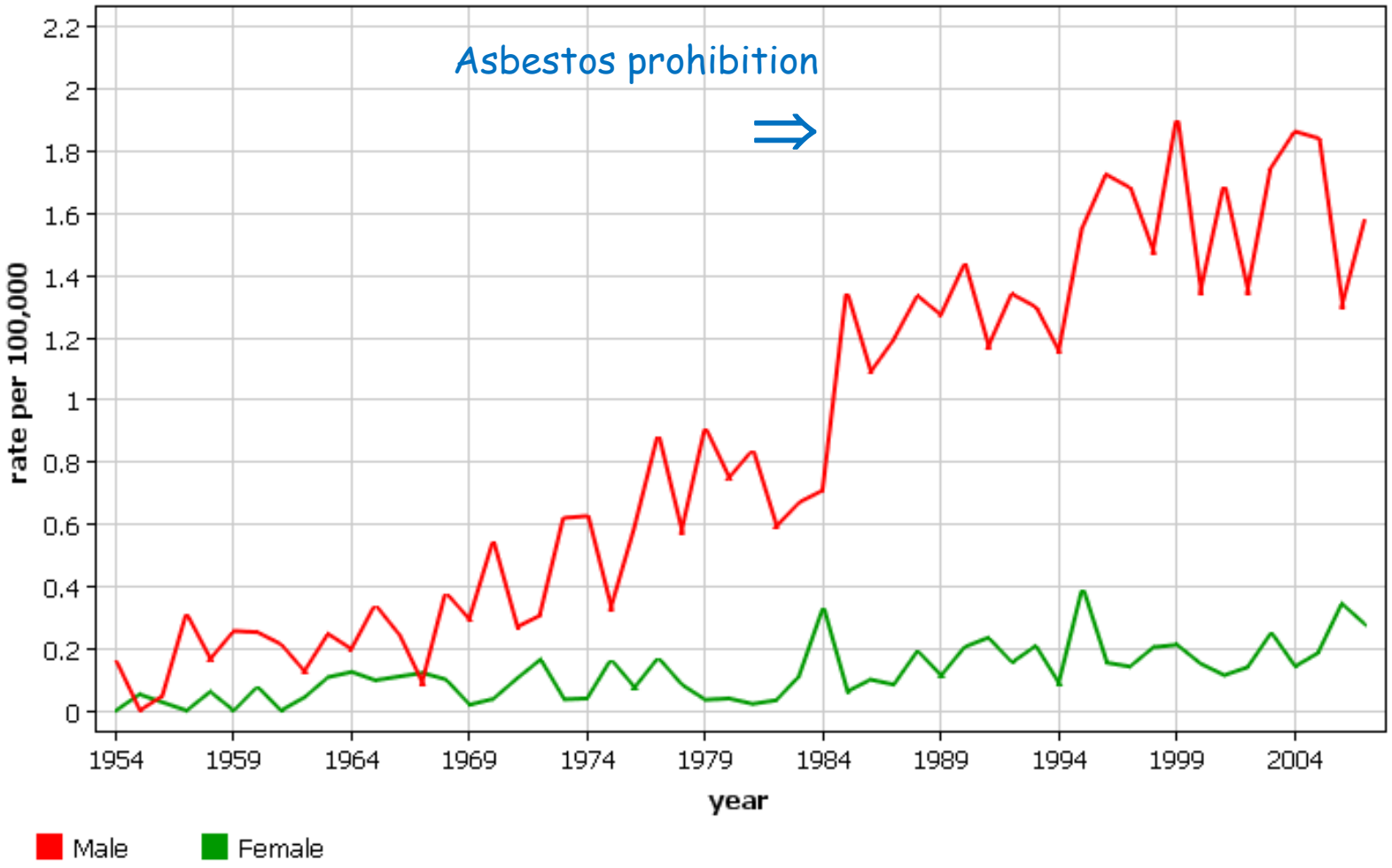


Males Females

Cancer Registry of Norway, 2001

Incidence pleural mesotheliomas, Norway

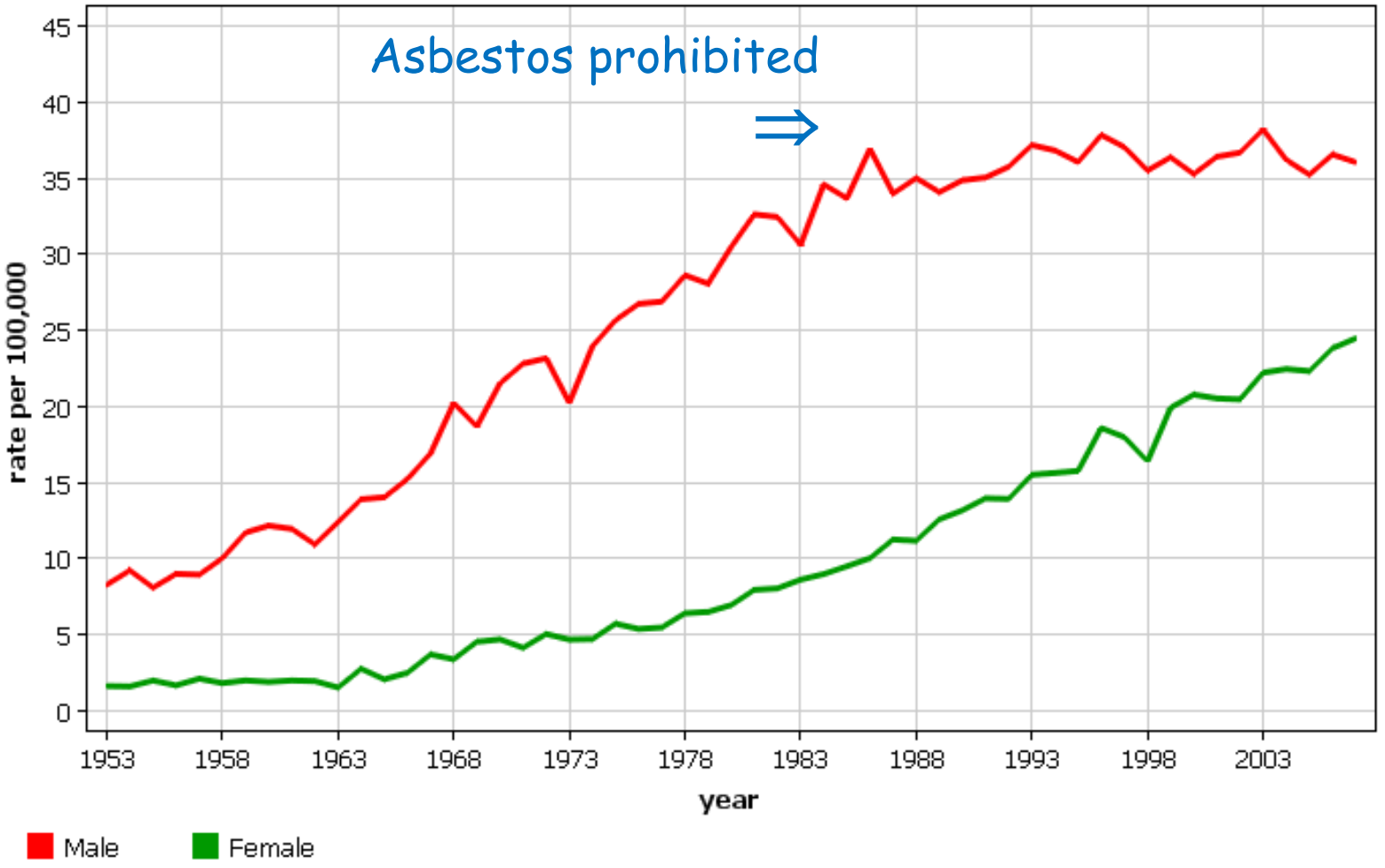
Norway
Pleura
Incidence: ASR (World) age (0-85+)



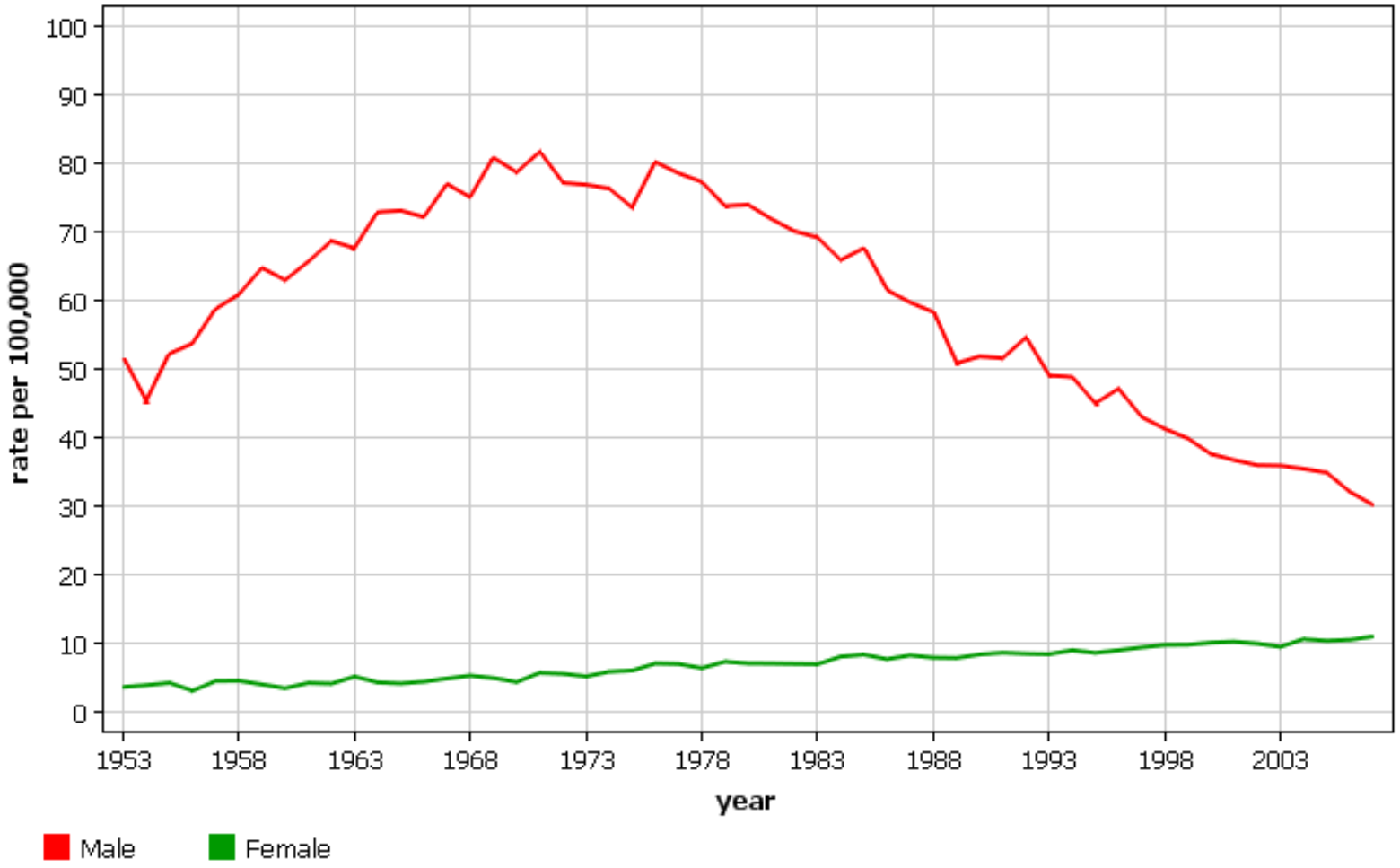
Norway Incidence of lung cancers 1953-2008

Lung

Incidence: ASR (World) age (0-85+)



Lung cancers 1953-2008, Finland



II Cancer-epidemiological studies

- No cases of work-related cancers in Norway prior to 1950. A few cases of nickel-related cancers diagnosed in the 1950's.
- In the late 1960's a small number of mesotheliomas were diagnosed as work-related.
- A significant number of cases were identified as work-related in in the wake of epidemiological studies on nickel*- and chromium-related** cancers in the early 1970's. The studies elicited an interest in identifying work-related cancers in our country.

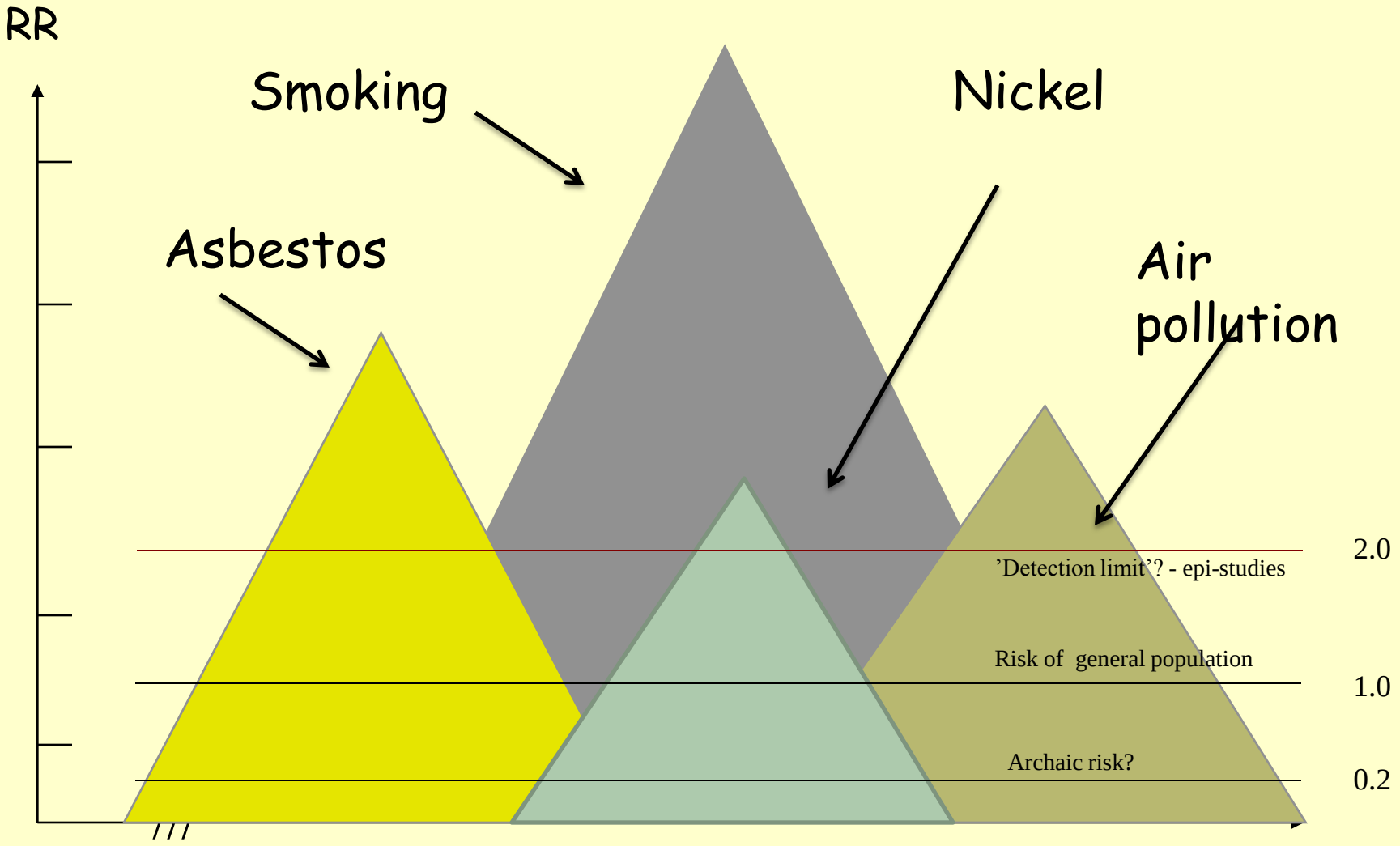
* Pedersen E, Høgetveit AC, Andersen Aa. Int J Cancer 1973;12:32-41.

** Langård S, Norseth T. Br J Ind Med 1975;32:62-5.

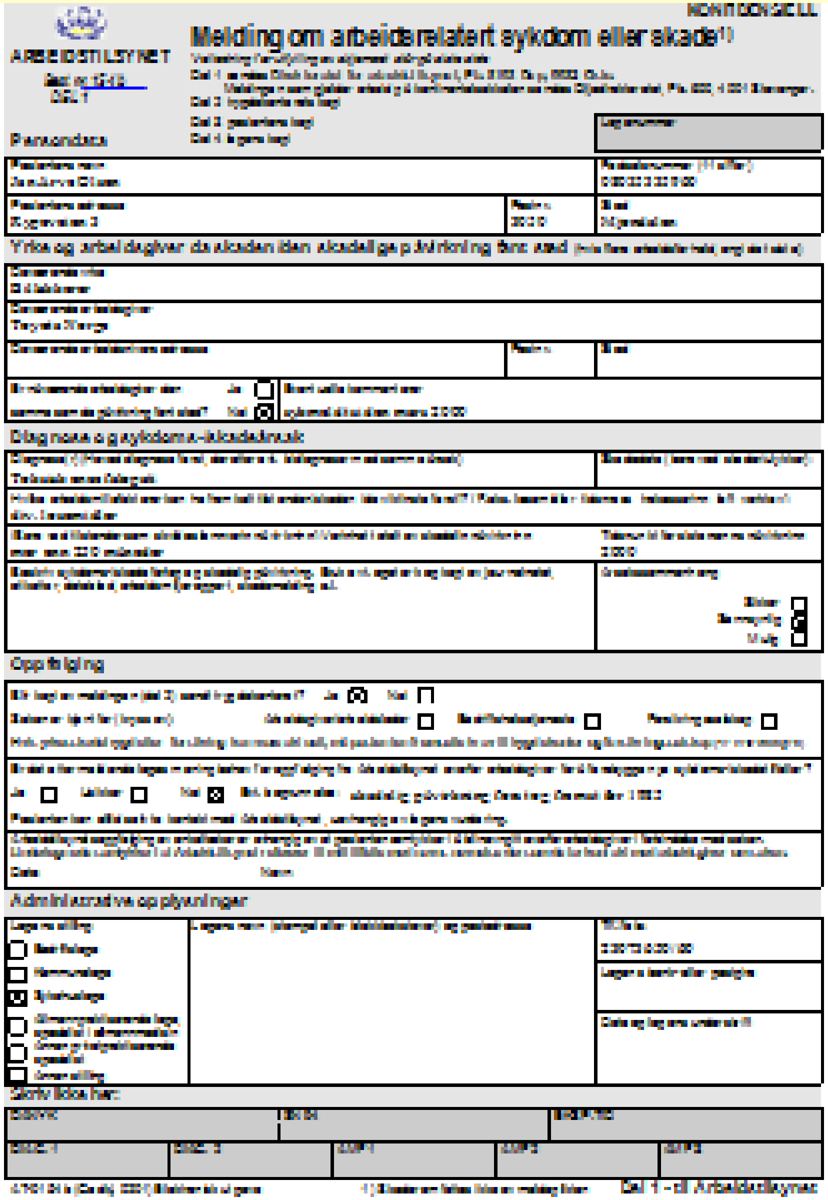
II Norway: epidemiological studies in the late 70's and early 80's *enhanced the interest* on work-related cancers

- These were studies –
- Among workers in **ferrochromium-**, **ferrosilicon-**, **magnesium-** and **aluminum** smelters.
- **Welders**, workers manufacturing **vinyl chloride**, and **niobium**(-miners). **Fertilizer manufacturers** were also studied and also **asphalt workers**.
- However, workers using ***asbestos*** appeared to be the **largest** group of exposed and was subsequently extensively studied.

Populations comprises numerous "risk pyramids"; limitations inherent in epi-studies



III All physician should report 'suspected' cases to the Work Inspectorate – copy to NIS


ARBEIDSTILSYNET

Melding om arbeidsrelatert sykdom eller skade[1)]

Persondata

Yrke og arbeidsgiver da skaden/den skadelige påvirkning fant sted

Diagnose og sykdoms-/skadeårsak

Oppfølging

Administrative opplysninger

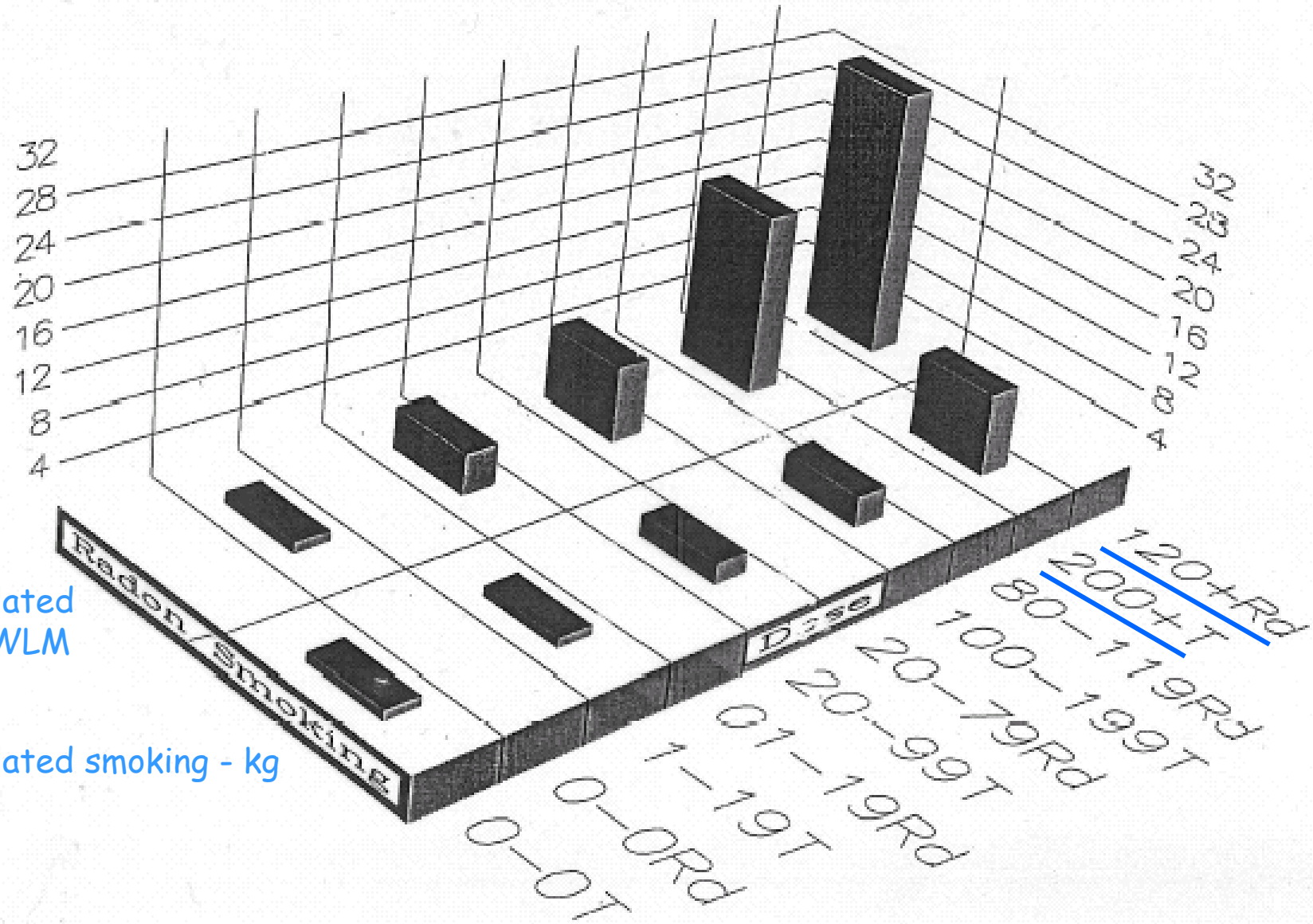
Skriv ikke her:

Del 1 - til Arbeidstilsynet

IV The clinical departments of occupational medicine boosted identification of cases

- Only few work-related cancer cases were recognized before we establish clinical departments for occupational- and environmental medicine in the 1970's and onwards.
- These clinics boosted the regional interest on work-related cancers/diseases, and have enhanced the knowledge on work-related diseases among primary- as well as occupational health physicians.
- Regional education in this field has also improved the consciousness among workers that their cancer/illness could relate to previous work exposure.

V Incidence of lung cancer in relation to Rd daughters and smoking



Cumulated Rd - WLM

Cumulated smoking - kg

Langård S, Andersen Aa, Møller B, Solli HM. 26th Int Cong Occup Health, Singapore Aug. 27-Sept 1, 2000.

V *A method* is based in the Cancer Registry

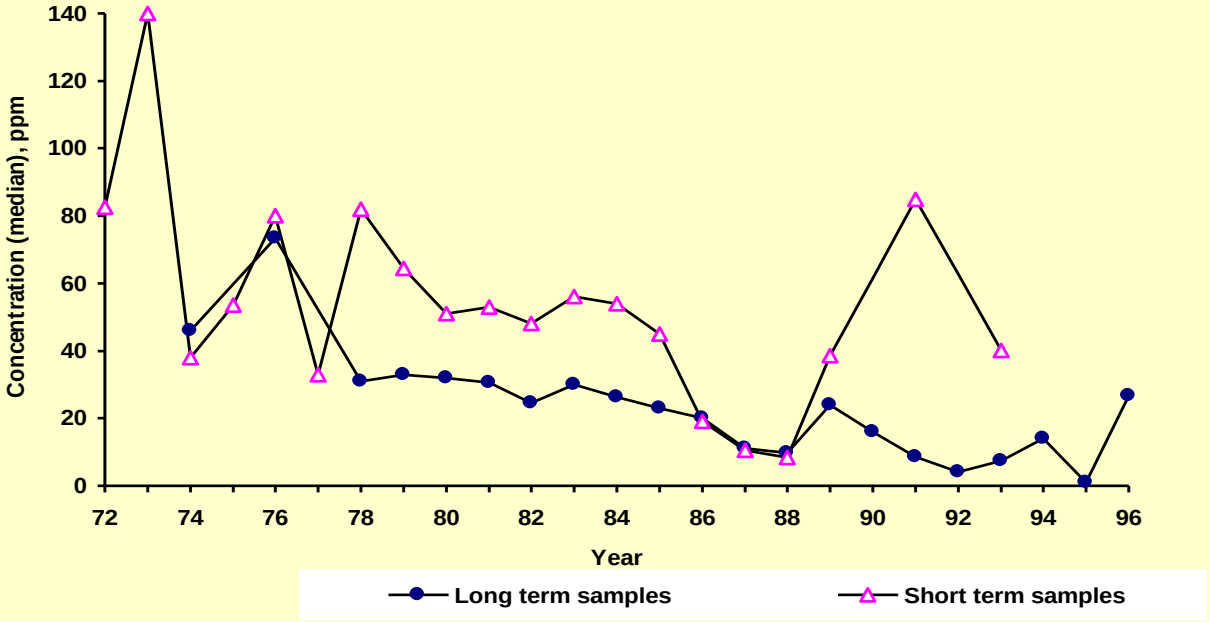
- Based on an unfortunate incident in the mid 1980's, when the "confidentiality inspectorate" stopped us from notifying deceased case subjects with *lung cancer* when they were detected in epidemiological studies, we initiated *a letter to be sent from the Cancer Registry* to *patients* with *cancer diagnoses* experienced resulting frequently from work exposure.
- The letter informs the patient that his/her disease could be work-related, and suggests *referral* to a *department of occupational medicine* to have the possible work-relation scrutinized.
- *Subjects* to *receive the letter* are identified by linkage to occupations, with frequent exposure to carcinogens, given at two different censuses, i.e. 1960, 1970, 1980, or 1990, respectively.

VI Cases of lung cancer with asbestos-typical pleural plaques/calcifications to be scrutinized on work-relatedness*

- Instruct the radiologist to refer all such cases of lung cancer to clinical occupational physicians for further scrutiny.
- This should be done for other possible asbestos-related cancers with such pleural plaques, i.e. cancers of the kidneys, bladder, oesophagus and stomach.

* Langård S. [When is cancer work-related?] Tidsskr Nor Lægeforen 2011;131:965-7.

VII Exposure-info: National expo-bases is a source of exposure information; the survey (1996) by the *German Berufgenossenschaften* an other one



Asbestos/lung cancer: When in doubt, fresh lung tissue may be collected for ***EM analyses*** of ***fibre-content***.

Fig.1. The average annual air concentration of styrene (for all the styrene measurements registered in the database).

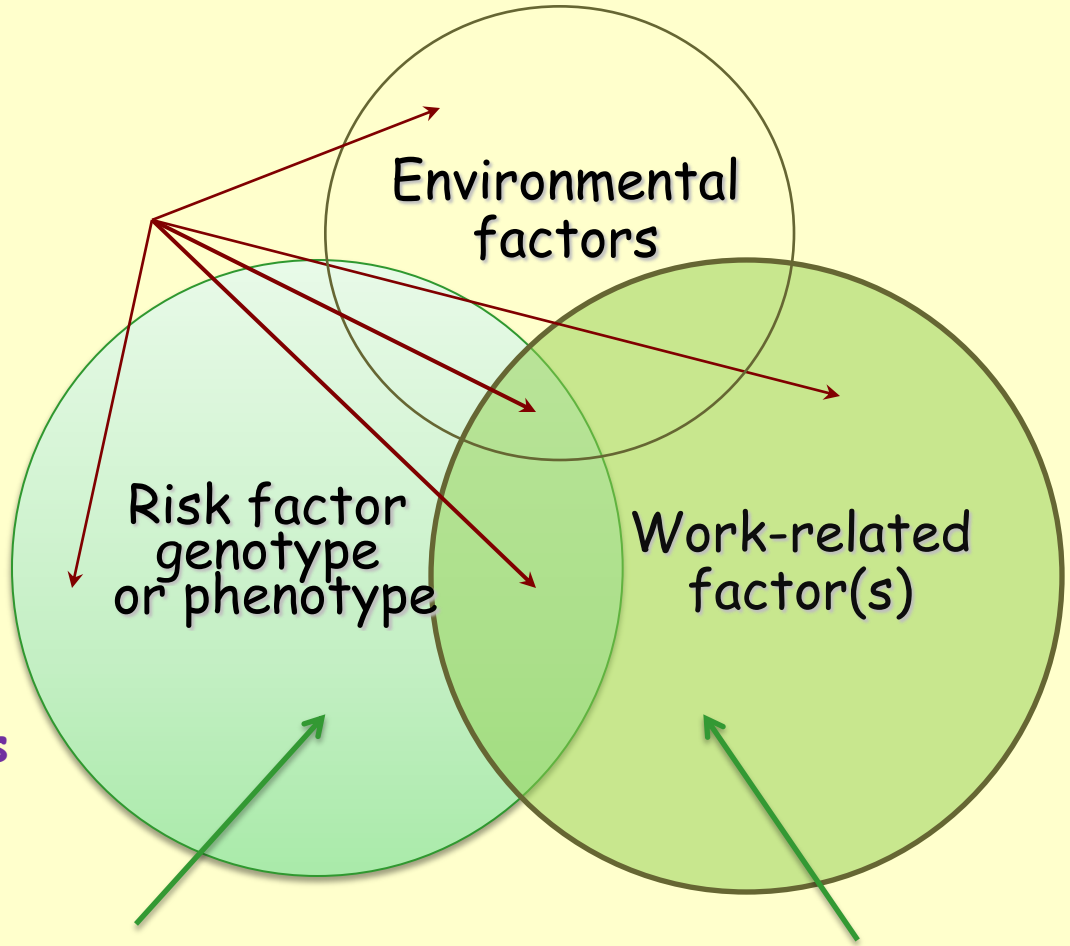
VIII Clinical verification: How to distinguish *work-related cancers* from non work-related?

- Work-related cancers are histological in-distinguishable from the non work-related ones.
- Thus, identification of work-related cases depends on a precise exposure history - documenting *all time periods of exposure* and *(semi)quantifying* all exposures possibly having contributed to enhanced risk of cancer in the case patient.

Clinical cases: Cases of exposure-related cancer are always recruited from either of these partly overlapping exposure-related sub-populations

Patients with work- and environment-related cancers are always recruited from one or more of these sub-populations:

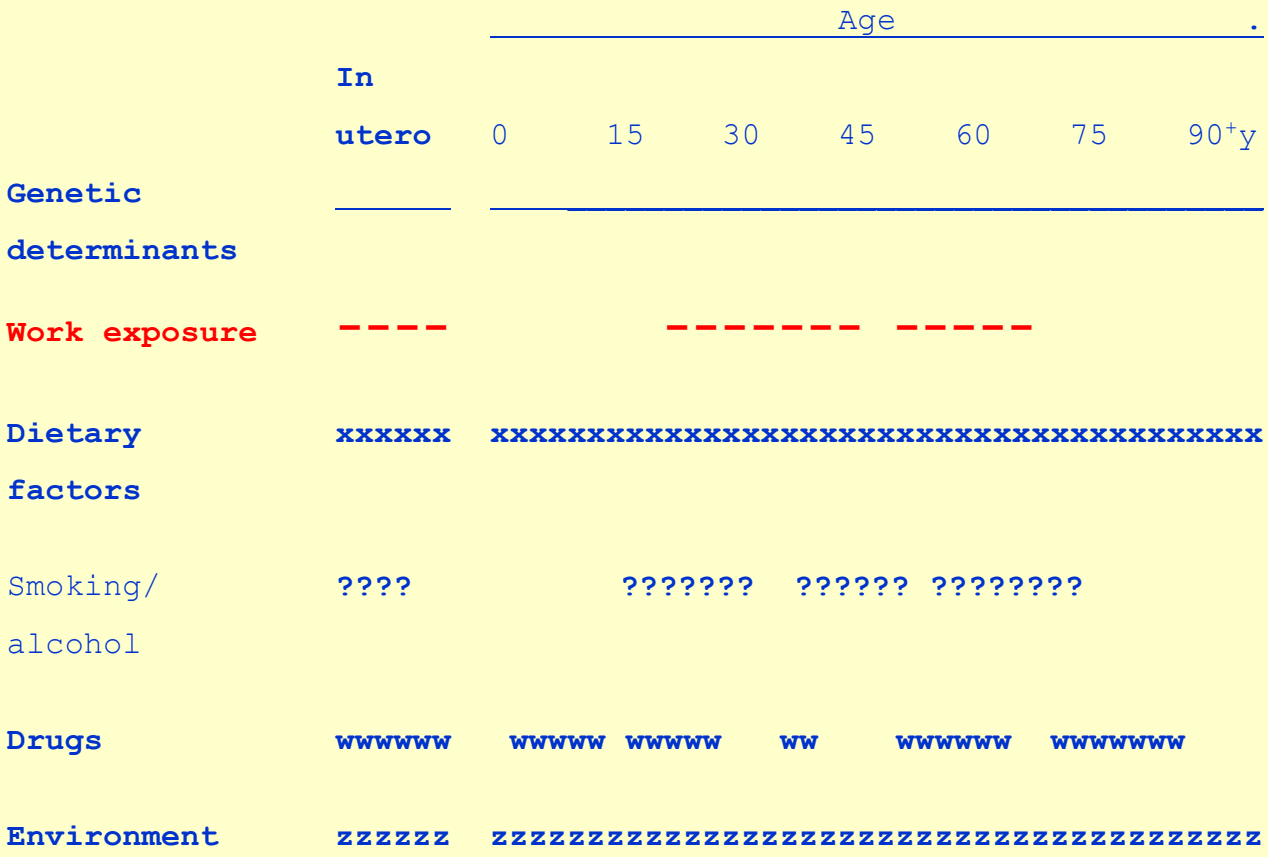
How to partition the weights of the different cases in this case?



To determine attribution to the different causes, the expert MD has to sort out all **major causes** of cancer.

A precise **work- and exposure-history** is ***a prerequisite*** to estimate individual disease risks

Potential disease determinants during all phases of life



Langård, S. Scand J Work Environ Health 1994;20;100-7.

What is obligatory to permit individual quantification of *á priori* caner risk

- Compiling **in-depth life-long exposure history** necessary to quantify disease risks.
  - Work exposures; ***time periods***, ***durations***, ***intensity***, and ***data on measurements***.
  - **Home-environment**; i.e. radon-daughters, passive smoking and cooking methods/habits.
    - **Smoking**; time relations and intensity.
    - **Passive smoking at work / at home.**
      - Genetic determinants?
      - **Possible other factors?**

When is a given cancer case ***work-related***?

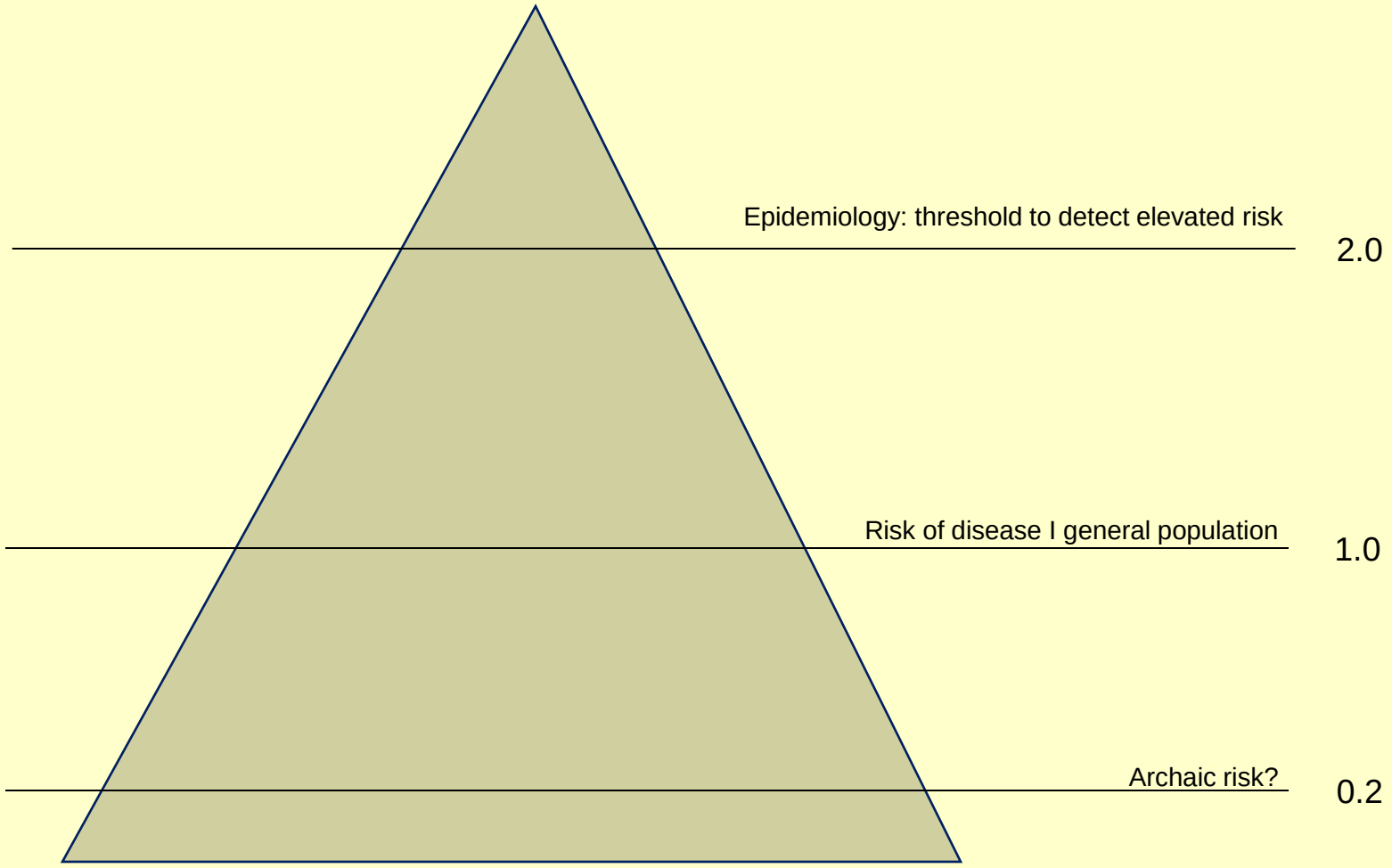
- **Sufficient exposure** to substances/ elements, known from the literature for its *intrinsic cancer-causing potential*, as ***based on*** matching ***dose-response data*** in scientific literature.
- "Latency": Sufficient exposure ***a long time ago*** (15-30 years or more).
- All ***major competing causes*** of the disease should be identified and accounted for.

Reference literature as basis for assessment of *á priori* risk

Whenever adequate information on past exposure is available:

- Identify literature with quantifiable estimates on risk at two or more 'dose'-levels (dose-response) for the exposure of concern.
- Put the patient's exposure into the dose-response-curve. That gives you the ***risk of cancer prior to diagnosis***.
- Do this for all exposure factors.

One out of many exposure-related "risk-pyramides" in any population



WHO: NATIONAL PROGRAMMES FOR ELIMINATION OF ASBESTOS-RELATED DISEASES: REVIEW AND ASSESSMENT; **07-08 June 2011, Bonn**

"Armenia in 2009 -2010, about 200 tons of chrysotile asbestos were imported. Roofing slates used in the rural areas mostly contain asbestos. Old pipes and slabs used for heating purposes also often contain asbestos. Asbestos related diseases have not been registered in the country, and doctors do not investigate the occupational causes of the illness in general. Even high-level officials are practically unaware of the hazards of asbestos."

Armenian participant: Dr Soso Hovhannisyan, Head. Division of Occupational Health and Radiation Safety State Hygienic and Antiepidemic Inspectorate, Ministry of Health, Yerevan

Thank you for your attention!

Photo: S Langård; Danshui, Taiwan

The 'mudskipper' may teach us how humanity can rise again after extinction!