Introduction to epidemiology

- with examples from Chernobyl studies -

Hajo Zeeb

Johannes-Gutenberg University

Mainz, Germany

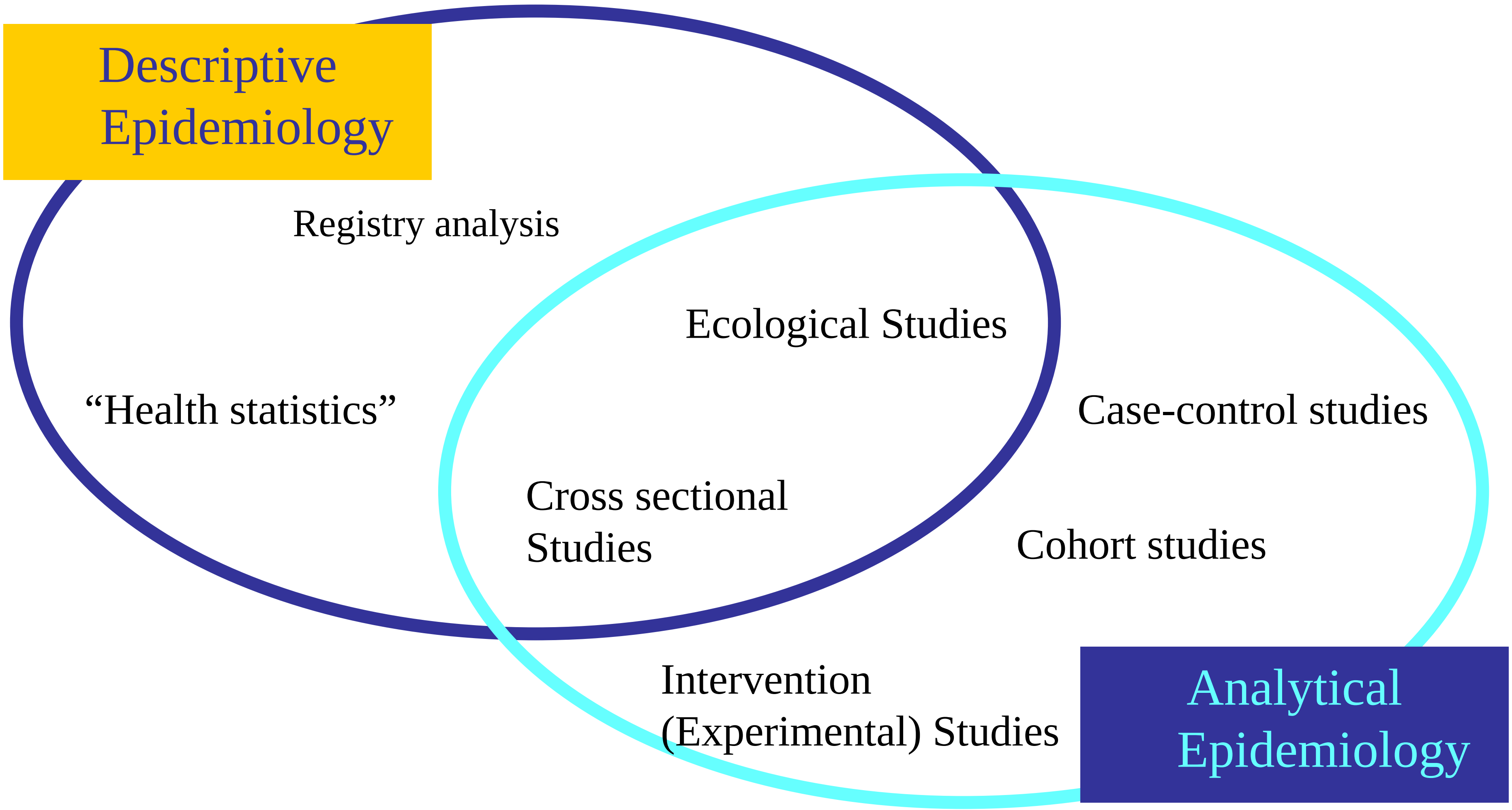
Outline

- Epidemiology – an overview
  - Observational epidemiology, challenges
- Measuring disease
- Study approaches
  - Illustrated by investigations following the Chernobyl accident
- Conclusion

Questions that epidemiology attempts to answer….

- Description:
  - how frequent is a disease in a population ?
  - how does the disease develop
    - in specific groups, places, time periods ?
    - in comparison with another population ?
- Analysis and causality:
  - what are likely causes of the disease ?
  - Is a particular agent (toxin) a cause for a specific disease ?

Epidemiological Studies



Epidemiology investigates

- the distribution of
  - diseases,
  - disorders,
  - injuries,
  - risk factors (determinants)

  and the association between them

- in the general population or
  - in specific populations, e.g.
    - clinical epidemiology (patients)
    - occupational epidemiology (workers)
  - concerning particular exposures/health risks e.g.
    - radiation epidemiology
    - environmental epidemiology etc.

This knowledge is essential for health protection and prevention

Epidemiology is built on four “pillar-concepts”

- **Health and disease :** **from medicine**
- **Population :** **from demography**
- **Probability :** **from statistics**
- **Comparison, unbiased :** **from experimental methodology**

thanks to R. Saracci

Experimental versus observational epidemiology

Design	Experimental	Observational
Approach	Random allocation A B	Nonrandom allocation A B
Example	A = Aspirin B = Placebo	A = Chernobyl radiation B = non-exposed
Threat to validity - confounding	Only random differences	Random + factors associated with exposure

Common problems for epidemiology

- Bias (systematic error in study approach, measurements, etc.)
  - may produce flaws in
    - Selection of study participants
    - Exposure assessment
    - Disease information
- Confounding (an association between a exposure and outcome of interest is observed as the result of the influence of a third variable
  - Risk estimates too high or too low
- Statistical power (too low to detect small risk differences)

Observational epidemiology

- Measures of frequency and association
- Study designs
  - Ecological studies
  - Cross-sectional studies
  - Case-control studies
  - Cohort studies

Measures of frequency

- **Prevalence**
  - measures ***existing*** cases of disease
    - at a particular ***point in time*** or
    - over a ***period of time***

- **Incidence**
  - measures ***new*** cases of disease that develop over a ***period of time***
  - in a population ***at risk***
  - cumulative incidence versus incidence rate
    - CI = Incident cases in observed pop. at entry into study
    - IR = Incident cases/sum of person-time at risk
  - *Note: absolute risk refers to incidence rate*

Measures of association

- Two fundamental ratio measures of disease: **odds ratio** and **risk ratio**
- **Odds ratio**
  - Typical measure of effect used in case-control studies, but can also be used in other study types
- **Risk ratio**
  - typical measure of effect used in cohort studies,
  - Also:
    - Standardized mortality ratio SMR
    - Standardized incidence ratio SIR

Typical for radiation epidemiology

- Comparison of incident cases in persons (groups) with different radiation doses
- If IR exposed = IR unexposed, RR = 1
- ERR per unit dose of radiation
  - Excess relative risk/Sv
  - Describes the excess above RR = 1
  - RR = 1.5/Sv → ERR = 0.5/Sv
- EAR = excess absolute risk
  - excess (absolute) incidence

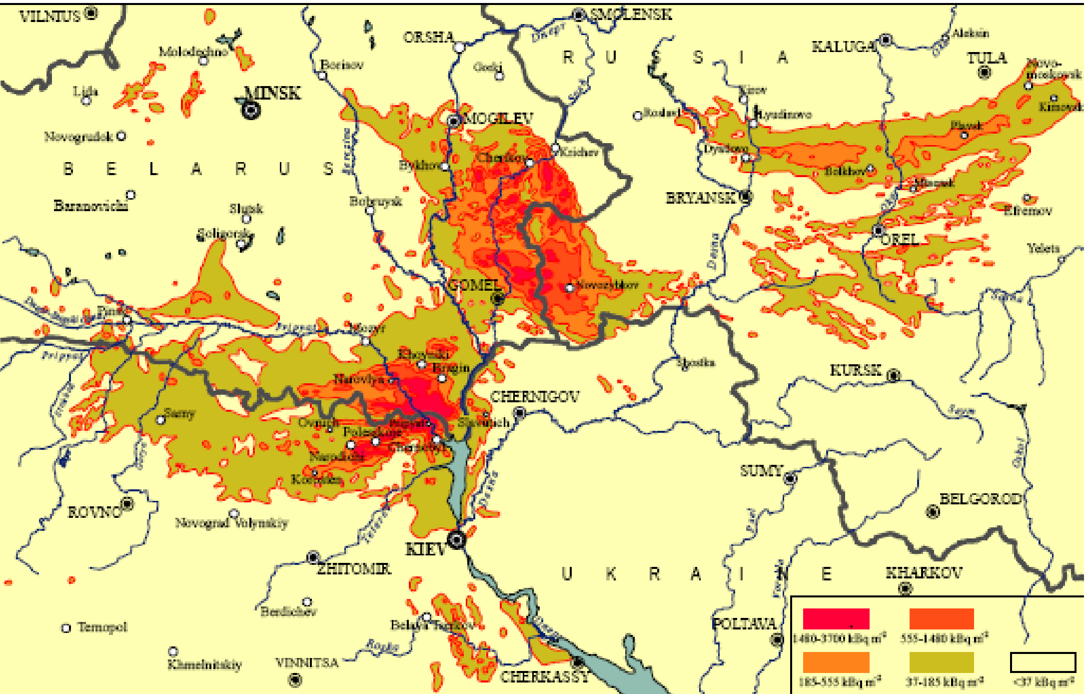
Insert

The accident at the Chernobyl nuclear power plant

Country	Area in deposition-density ranges (km^2) 37-185 $kBqm^{-2}$	185-555 $kBqm^{-2}$	555-1480 $kBqm^{-2}$	>1480 $kBqm^{-2}$
Russia	49,800	5,700	2,100	300
Belarus	29,900	10,200	4,200	2,200
Ukraine	37,200	4,200	900	600
Sweden	12,000	-	-	-
Finland	11,500	-	-	-
Austria	8,600	-	-	-
Norway	5,200	-	-	-
Bulgaria	4,800	-	-	-
Switzerland	1,300	-	-	-
Greece	1,200	-	-	-
Slovenia	300	-	-	-
Italy	300	-	-	-
Moldova	80	-	-	-

26.4.1986

Chernobyl



+ 200,000 evacuated

~ 5 Mill living in contaminated areas

Fall-out: ^{131}Iodine
^{137}Caesium
+ many other nuclides

Exposed populations

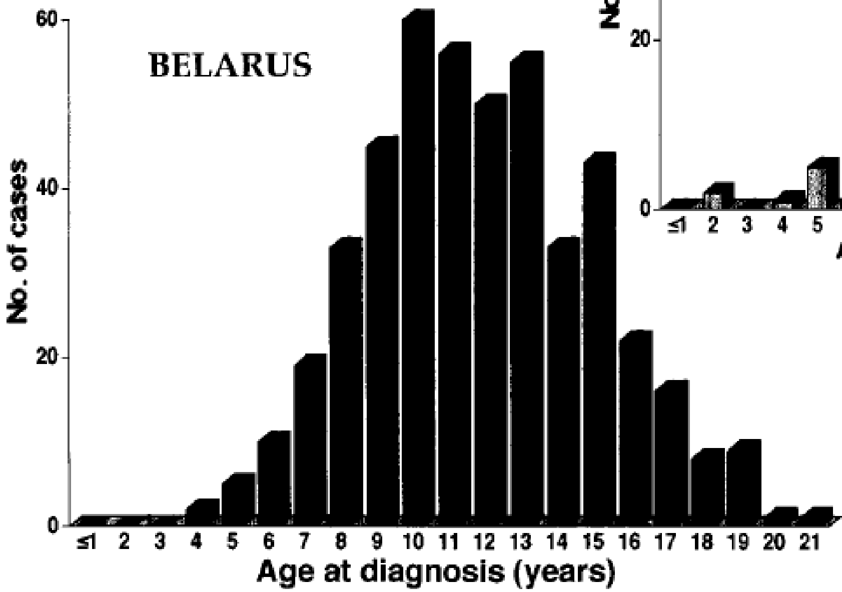
- "First day" emergency personnel
  - Several hundred, some lethally irradiated
- Liquidators (some 600,000)
  - 170 mSv mean annual dose 1986
  - 130 mSv (1987), 30 mSv (1988)
- Evacuated population
  - ~ 30 mSv
- Population of wider contaminated regions

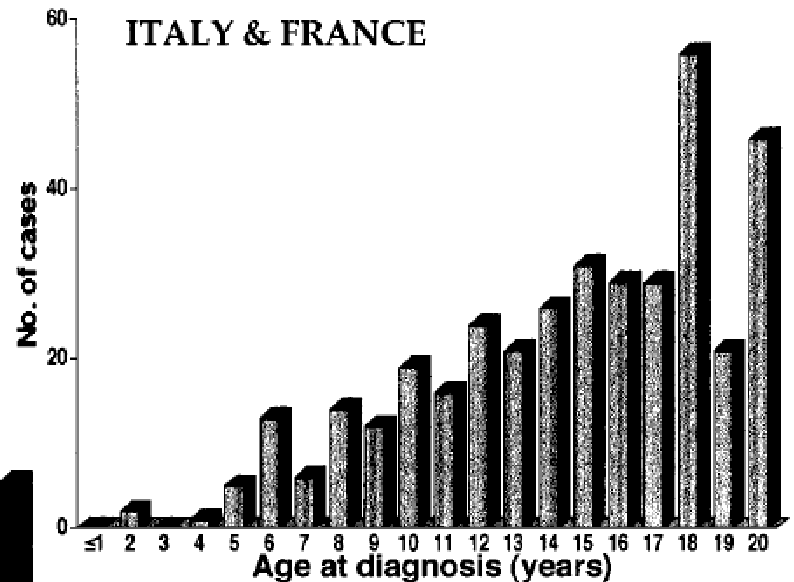
Registered thyroid cancer cases, 1986-2002

Age at exposure	No. of cases			
	Belarus	**Russian Federation**	**Ukraine**	**Total**
0 -14	1711	349	1762	3822
15 -17	299	134	582	1015
Total	2010	483	2344	4837

Health Effects of the Chernobyl Accident, WHO 2006

Ecological (correlation) studies





“ Based on the geographical and temporal distribution of the cases, there is strong evidence that the increased incidence of childhood thyroid cancer is caused by ionizing radiation…”

Pacini et al, 1997

New cases of thyroid cancer in Belarus, May 1986 –Dec 1995

Etiologic approach in ecologic studies

- Correlating
  - changes or prevalence differences in exposure

with

  - changes or disease rate differences in geographically defined populations
- Advantages:
  - practicality, costs, availability of data
- Disadvantages
  - Ecologic bias: what we see at group level does not correspond to association at individual level
  - Confounder control very difficult
    - Screening effect post Chernobyl

Thyroid cancer post Chernobyl

- UNSCEAR 2006: 6 studies listed
  - Correlating incident thyroid cancer cases and thyroid doses of individuals living in contaminated regions
  - Example: Jacob et al, 2006, Belarus and Ukraine
    - Population: born 1968-April 1986
    - 1034 settlements where thyroid dose measurements had been performed (to a varying extent) → average area doses computed
    - Cancers: all surgically removed cancers 1990-2001
    - Estimates of EAR (2.66 / 10^4 Person years Gray)
    - Estimate of ERR (18.9 / 10^4 Person years Gray)

Also many ecological studies from others countries, e.g. Greece, Germany

Cross-sectional studies

- Classical survey approach
  – measuring exposure and disease at the same time
    → prevalence
- Example: Hatch et al, 2008, Ukraine
  – Population: 2,582 mother-child pairs
    - “Exposed” and “comparison” group
  – Dose measurements (to mothers) shortly after accident
  – Clinical, ultrasound, blood tests
    - 7 thyroid cancers (+1) , 6 in exposed group
    - Excess OR of 11.6 (not significant), p trend = 0.12
  – Further analysis similar to case-control study

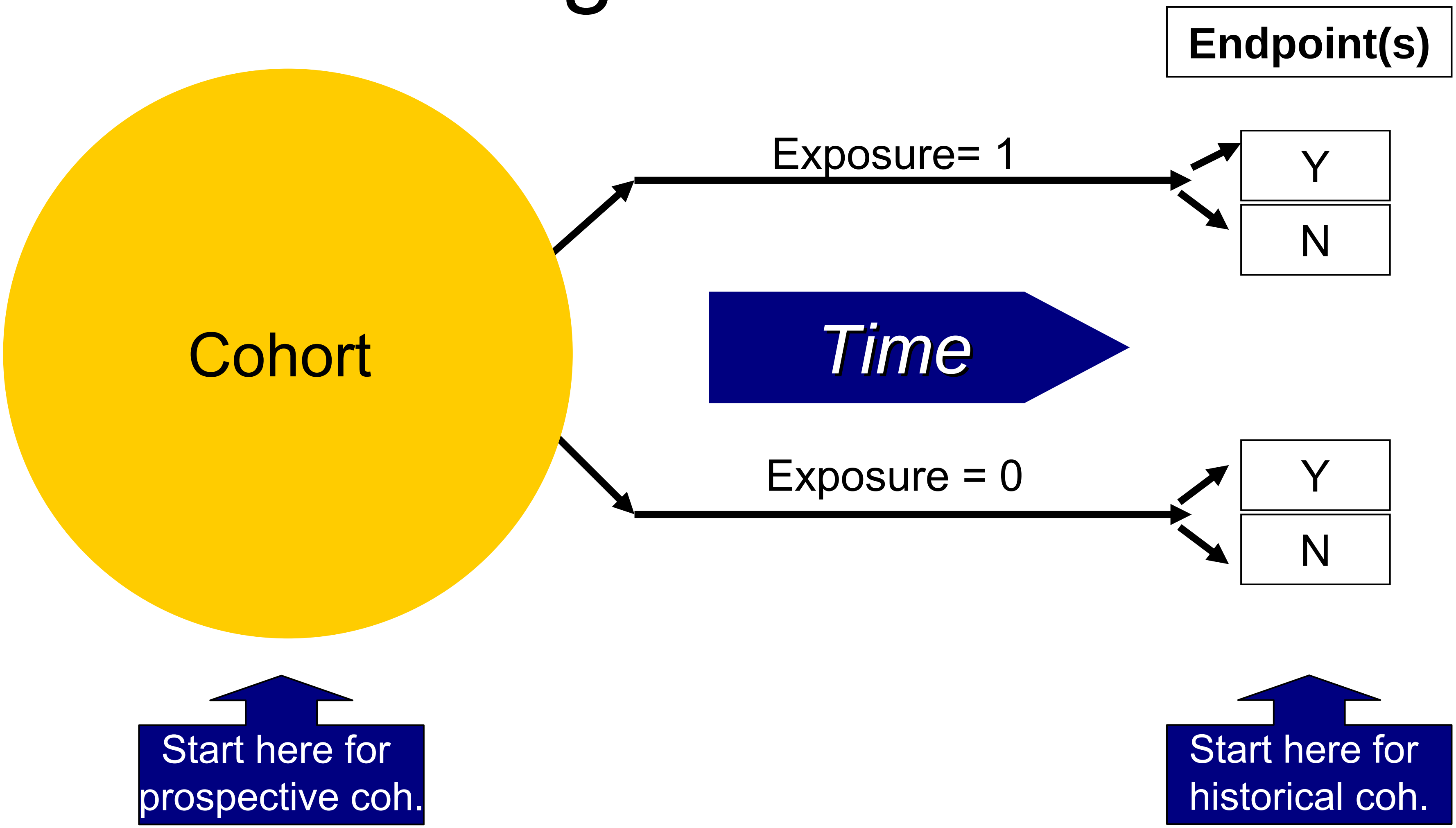
Cohort studies

- the core approach of (radiation) epidemiology
- Requires
  - Defined cohort
  - Individual exposure and co-factor assessment
  - Mechanism for follow-up over time
    - Disease (mortality) registry
    - Study specific mechanisms (e.g. repeat exams)
- Allows
  - Direct risk estimation, incidence measurement
  - Important for assessment of causal associations

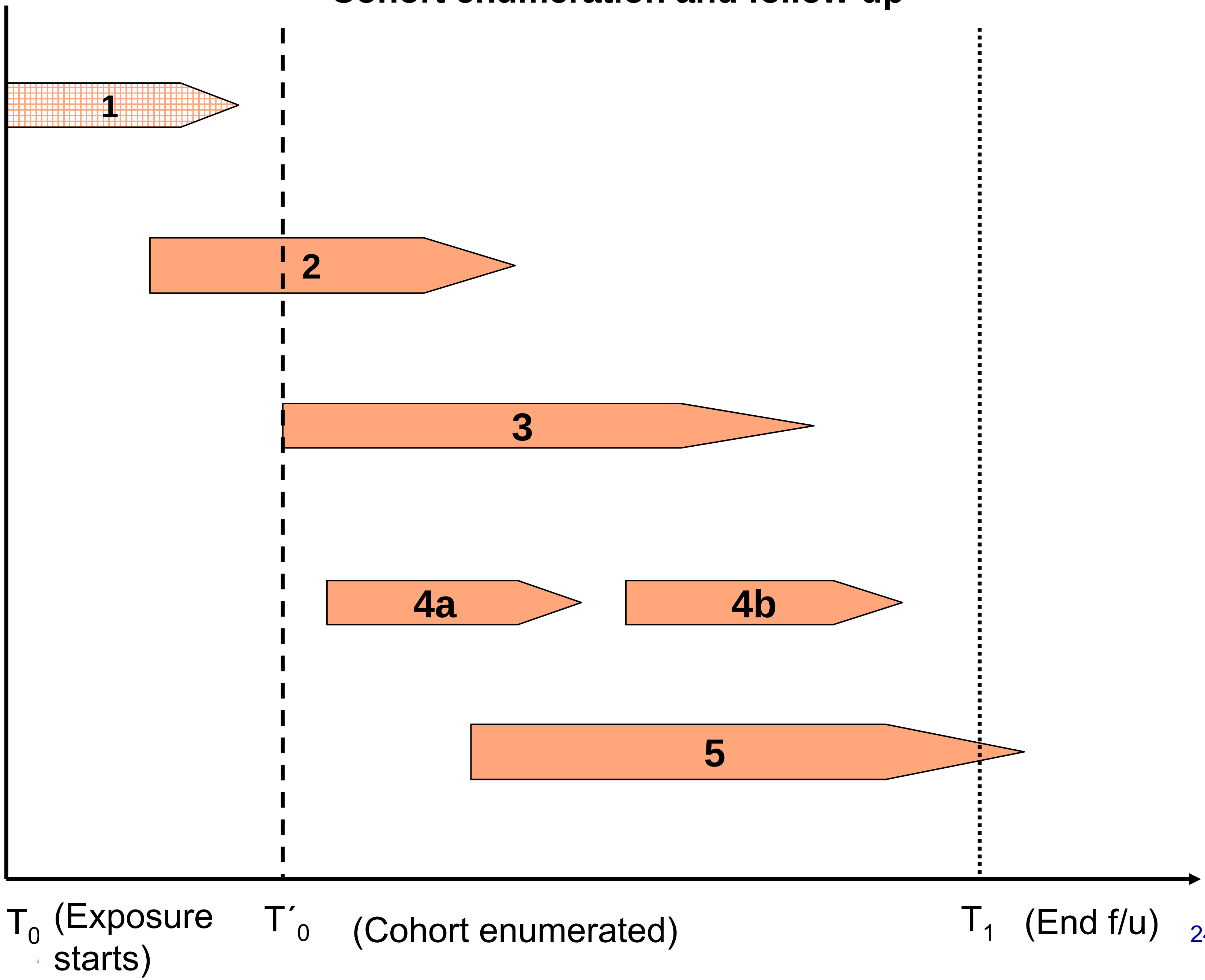
General aspects

- Baseline – cohort definition
  - Exposed subjects (at different levels)
- Comparison group
  - Non – exposed
  - General population
- Direction of investigation: prospective
- Study type:
  a) prospective
  b) retrospective
- Endpoints
  - Multiple endpoints (cancer, non-cancer)

Design Scheme



Cohort enumeration and follow-up



Chernobyl: cohort studies of clean-up workers (“liquidators”)

Cohort studies initiated in Russia, Belarus, Ukraine, Baltic countries

ORIGINAL PAPER

V. K. Ivanov · A. I. Gorski · A. F. Tsyb · S. I. Ivanov · R. N. Naumenko · L. V. Ivanova

Solid cancer incidence among the Chernobyl emergency workers residing in Russia: estimation of radiation risks

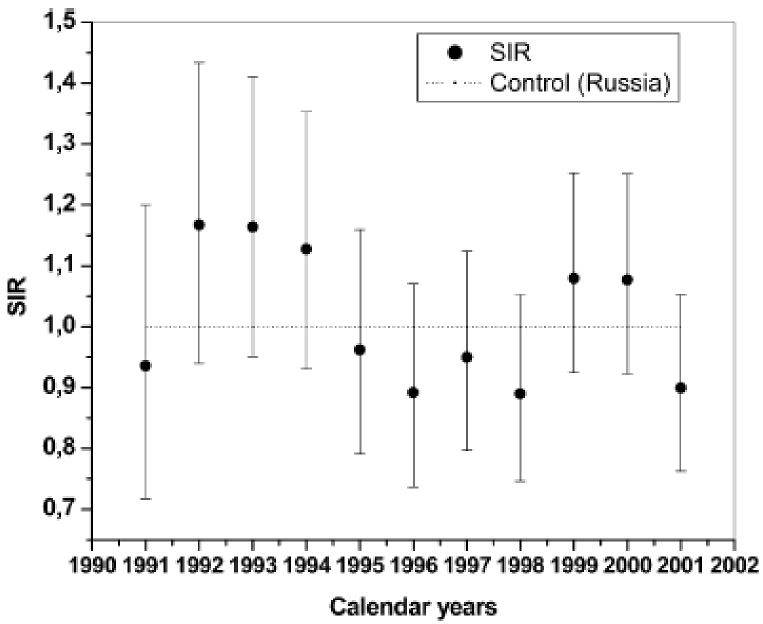
Ivanov et al, 2004

- Cohort: 55,718 male clean-up workers living in Russia → defined cohort
- Documented doses (mostly indiv. meas.)
  - exposure in 30 km zone
- Mean age at exposure: 34.8 y
- Mean external dose: 130 mGy
- Follow-up for cancer <u>incidence</u>: 1991-2001
  - 1370 solid cancers registered

Risk measures

- Standardized incidence ratio SIR (95% CI)
  - Comparison: Russian reference population

$$SIR = \frac{\Sigma Obs}{\Sigma Exp}$$



Consider:
- varying mortality level in Russian population
- selection effects

SIR and other measures can be calculated for
- different periods,
- exposure classes,
- individual cancer sites

Risk measures

- Excess Relative Risk / Gray for all solid cancer
  - 0.33 (-0.39 - 1.22)
  - Differs over time, lower in later f/u period
  - Previous finding for mortality (Ivanov 2001)
    - ERR = 2 (1.31 – 2.92)

- Problems illustrated
  - Even with relatively large numbers of cases, power to show small differences remains limited
  - Quality of dosimetry and of endpoint data crucial

Case-control studies

Rare diseases

- cohort studies not efficient
- need very long follow-up, large size

But

cases occuring in a population can be identified through health system

appropriate (“healthy”) **controls** needed

efficient **in-depth assessment** of exposures and other factors

- Useful for cc studies nested in cohorts

Case-control studies

- Cases
  - E.g. all persons with thyroid cancer diagnosed in a defined region over defined time period
- Controls
  - Population-based: persons randomly selected from population registry (same region, period)
  - Hospital-based: patients visiting same hospital as cases, for other problems
- Exposure assessment
  - Individual questionnaires, medical records, other sources, (retrospective dose assessment, e.g. radon)
  - focus on past exposures

Risk measures – case-control 2x2 table

	Cases	Controls	Total
Exposed	a	b	a+b
Not exposed	c	d	c+d
	a+c	b+d	a+b+c+d

$$\text{Odds ratio} = \frac{\text{Odds that a case was exposed}}{\text{Odds that a control was exposed}} = \frac{a/c}{b/d} = \frac{a \cdot d}{b \cdot c}$$

Estimation of Odds ratio with logistic regression models

Chernobyl: leukemia among clean-up workers

- Romanenko et al, 2008 (Ukrainian-US study)
  - 71 leukemia cases
  - 501 healthy controls
  - Interviews (some with proxies) and individual dose reconstruction
  - ERR/Gy (really: EOR)
    - 3.44
- Kesmiene et al, 2008 (Belarus, Russia, Baltic)
  - 70 haematological cancers
  - 287 healthy controls
  - Interviews, dose reconstruction
  - ERR/100mGy
    - 0.6 (= 6/Gy)
    - 90%CI = -0.02 – 2.35

Typical situation in epidemiology: studies with limited powers, somewhat different results → metaanalysis (analysis of pooled data)

Summary

- Several core design approaches used in observational epidemiology
- Plenty of design variations, see Chernobyl
- Sensible approaches to common problems (bias, confounding, power) needed
- Chernobyl
  - Increased thyroid cancer in young people
  - Liquidators: overall cancer ↔, thyroid, leukemia ↑
- Epidemiology provides real-life picture
  - and cannot answer all questions

Thank you

zeeb@imbei.uni-mainz.de