IRSN
INSTITUT
DE RADIOPROTECTION
ET DE SÛRETÉ NUCLÉAIRE

Basics in Epidemiology

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Content

- Epidemiology of radiation-induced risks
- Study types, terms and definitions
- Risk
- Dose-risk relationship
- Limits of low dose epidemiology
- Conclusion

Effects of exposure to ionising radiation

Deterministic effects

- seriousness is function of the dose
- high doses (> 500 mGy)
- early and specific effects
- threshold model

(rash, vomiting, modification of blood formula, cataract)

→ Medical emergency

Stochastic effects

- frequency is function of the dose
- low and medium doses
- late and non specific effects
- no threshold model

(cancers, hereditary effects…)

→ Epidemiology

Epidemiology

Definition

Study of the frequency and distribution of health effects in time and space among humans, and of their determining factors

- Observation science (no control as in experimental studies)
- Considers directly the relevant issue (stochastic effects)

Objectives

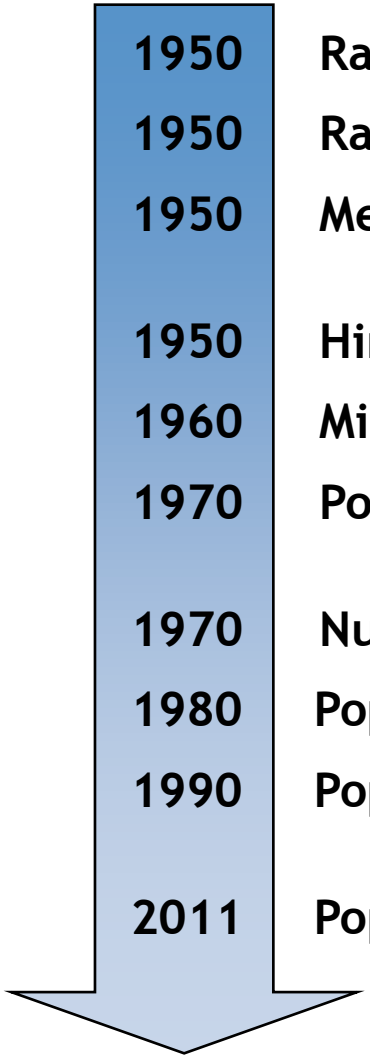
Descriptive:

- Surveillance, estimation of disease rates
- Identification of groups of population with excess risk

Analytic :

- Identification of risk factors and quantification of relative risk
- Modelling of the exposure-risk relationship

History of epidemiological studies of ionizing radiation



1950	Radiologists (1900-30)
1950	Radium dial painters (1910-30)
1950	Medical exposures for non malignant illnesses, diagnostic exposures (1920-40)
1950	Hiroshima-Nagasaki survivors (1945)
1960	Miners (uranium) (1940-90)
1970	Population exposed to fallout from atmospheric nuclear weapons (1950-60)
1970	Nuclear workers (1950-)
1980	Population exposed to natural background radiation
1990	Population exposed to releases from the Chernobyl accident (1986)
2011	Population exposed to releases from the Fukushima accident (2011)

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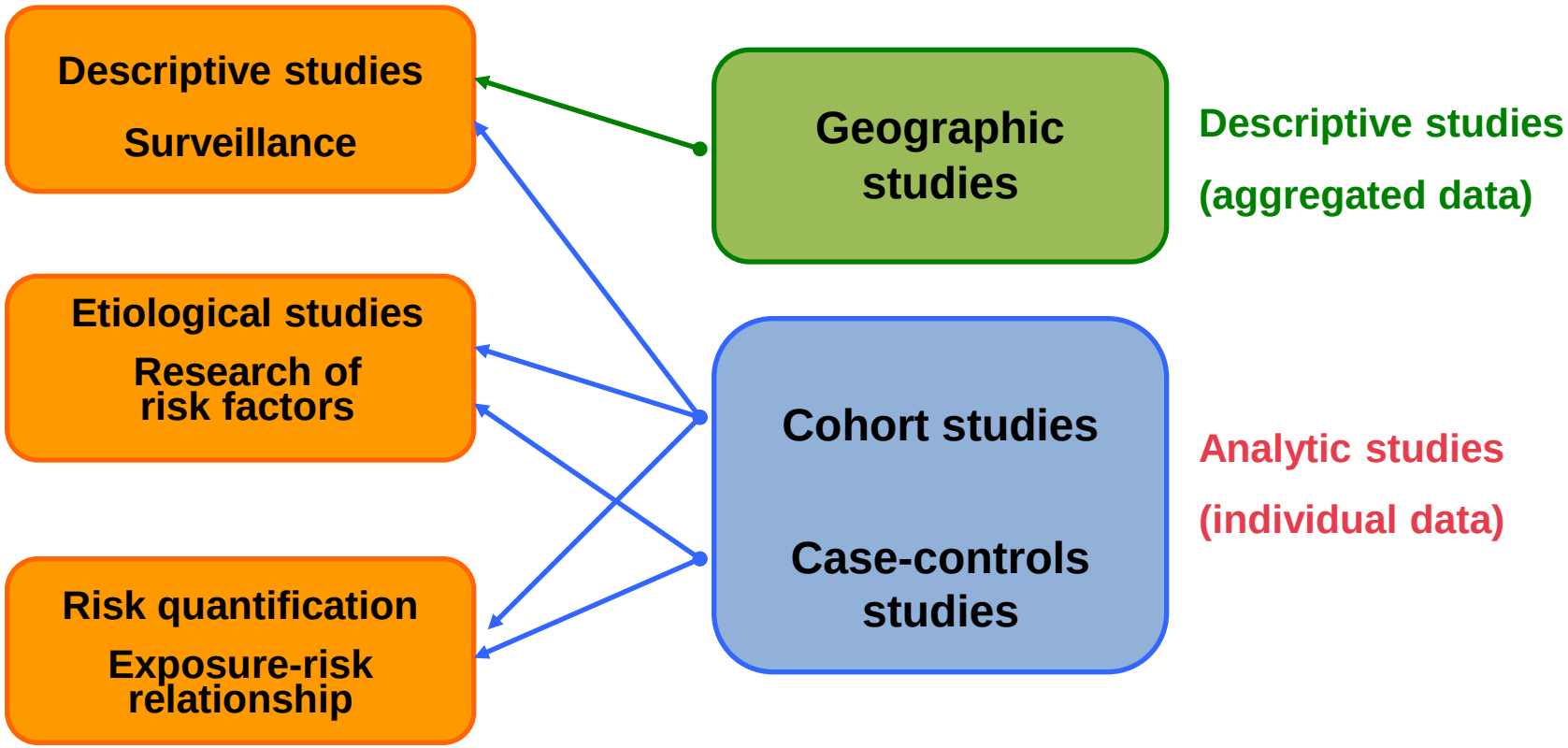
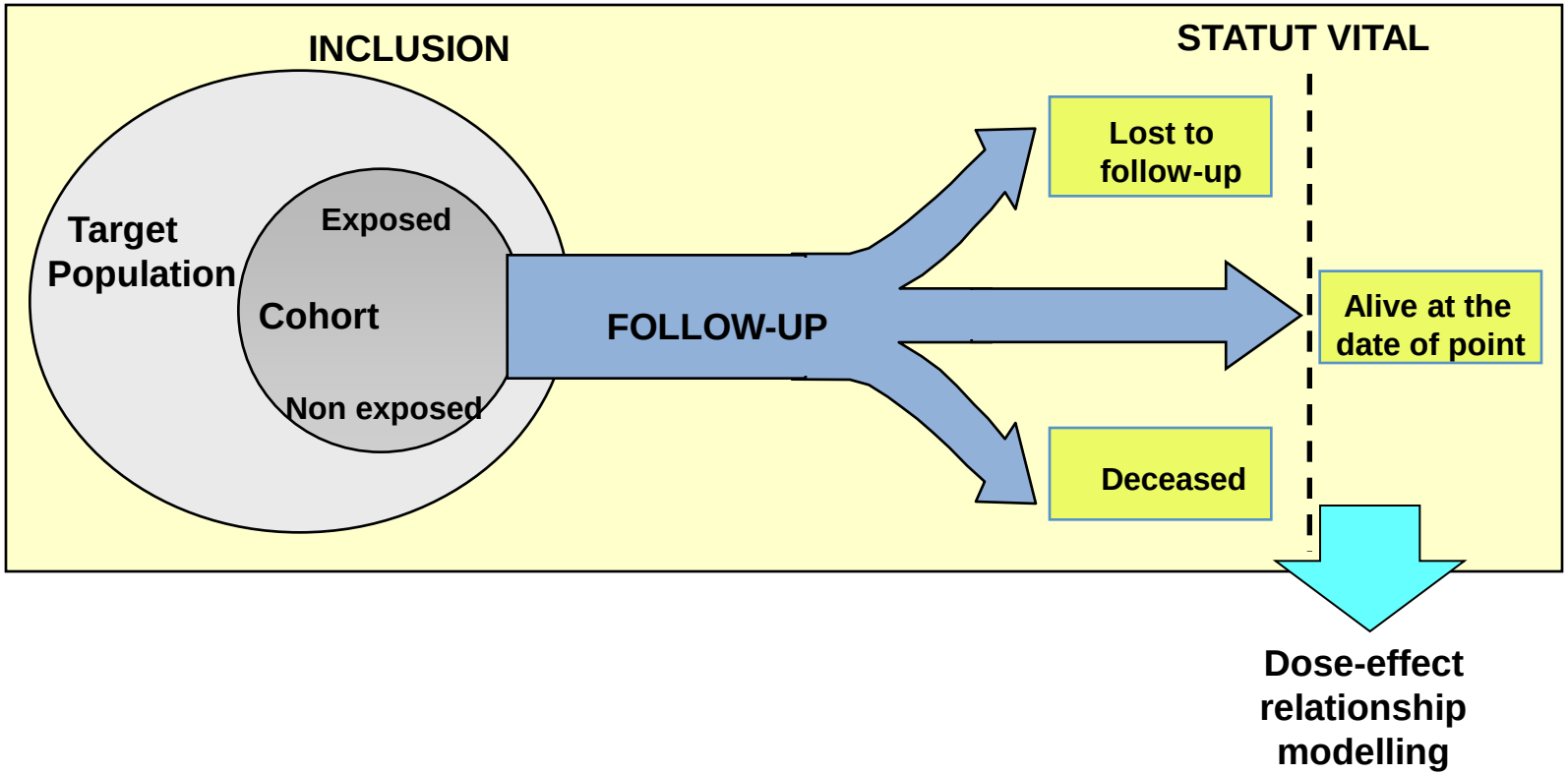
Objectives and types of epidemiological studies



Protocol of a cohort study



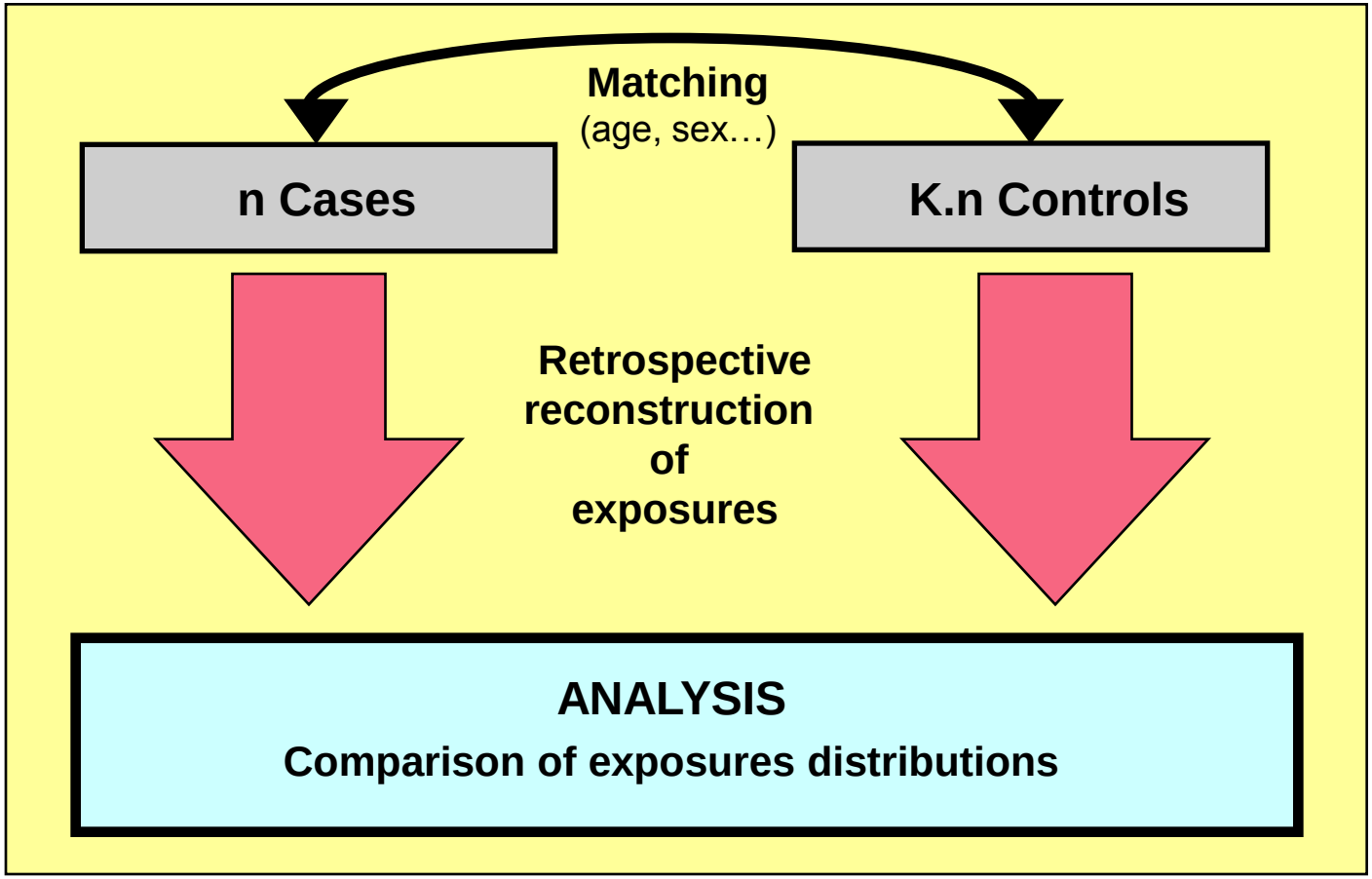
Advantages:

- Time sequence from exposure toward effect, all effects

Limits:

- Expensive: follow-up on a long duration
- Limited by the proportion of lost of follow-up

Design of a case-controls study



Advantages:

- Less expensive than cohort studies (a few years), adapted to rare diseases

Limits:

- Selection bias (representativeness of controls), memory bias (of past behaviours)

Sources of information

Identification

- Administrative files, pay-rolls,
- Population registry (evacuees, liquidators…),
- Census…

Exposures

- Archives: dosimetric files, occupational medicine files,
- Interviews, questionnaires,
- Time spent and location, job-exposure matrix,
- Biomarkers of exposure

Endpoints

- Mortality registry, cancer registry,
- Hospital and medical databases,
- Declaration, score,
- Biomarkers of effect

Bias

Well-defined limitation linked to the epidemiological approach
Depends on the study design
Can be controlled from the protocol or evaluated afterward

- **Selection bias:** the population is not representative of the source population
  - Can be due to recruitment, randomisation, migration
  - Problem if the selection is linked to the pathology or the exposure
  - Selection of controls in a CC design, loss of follow-up in a cohort study

- **Misclassification bias**: the exposure is not well estimated
  - Can be due to memory, missing data, subjectivity
  - Problem if systematic error or if it leads to large miss of information
  - Memory bias in CC studies, measurement error and error propagation

- **Confusion bias**: a third factor modifies or hides the true relationship between exposure and effect
  - Confounding factor should be linked to both exposure and effect
  - Collect of information on known risk factors
  - Stratification of adjustment

Ethics and data protection

Justification of research

- Agreement by an ethic committee
- Evaluation of the objectives, protocol and analysis methods

Information of the study subjects

- Information of individuals (website, newsletter…) or signed informed consent
- Possibility to have access to personal data and/or to withdraw

Protection of data

- Anonymity/confidentiality of individual data (medical or not)
- Data safety (specific disk, encryption, limited conservation…)

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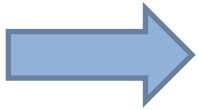
Definition: absolute risk

$$\frac{\text{Numerator}}{\text{Denominator}}$$

Numerator: number of cases (morbidity) or deaths (mortality)

Denominator: number of persons at risk over a given period (person-years)



Absolute risk or **Rate**: in cases per 100,000

Prevalence rate: number of cases at a given time

Incidence rate: number of new cases over a given period

Definition: relative risk

Relative risk (RR): ratio of the absolute risk in the exposed group on the absolute risk in the control group

a RR of 1 indicates an absence of excess risk
a RR of 2 indicates a doubling of the risk
a RR of 0.5 indicates a reduction of the risk by 2

Excess relative risk (ERR): RR minus 1.

an ERR of 0 indicates an absence of excess risk.
an ERR of 0.2 indicates an increase of 20% of the risk

Standardised Mortality Ratio (SMR): estimate of the RR

$$SMR = O / E$$

where O = number of observed cases
E = number of expected cases (number of cases that should be if rates where that of a reference population)

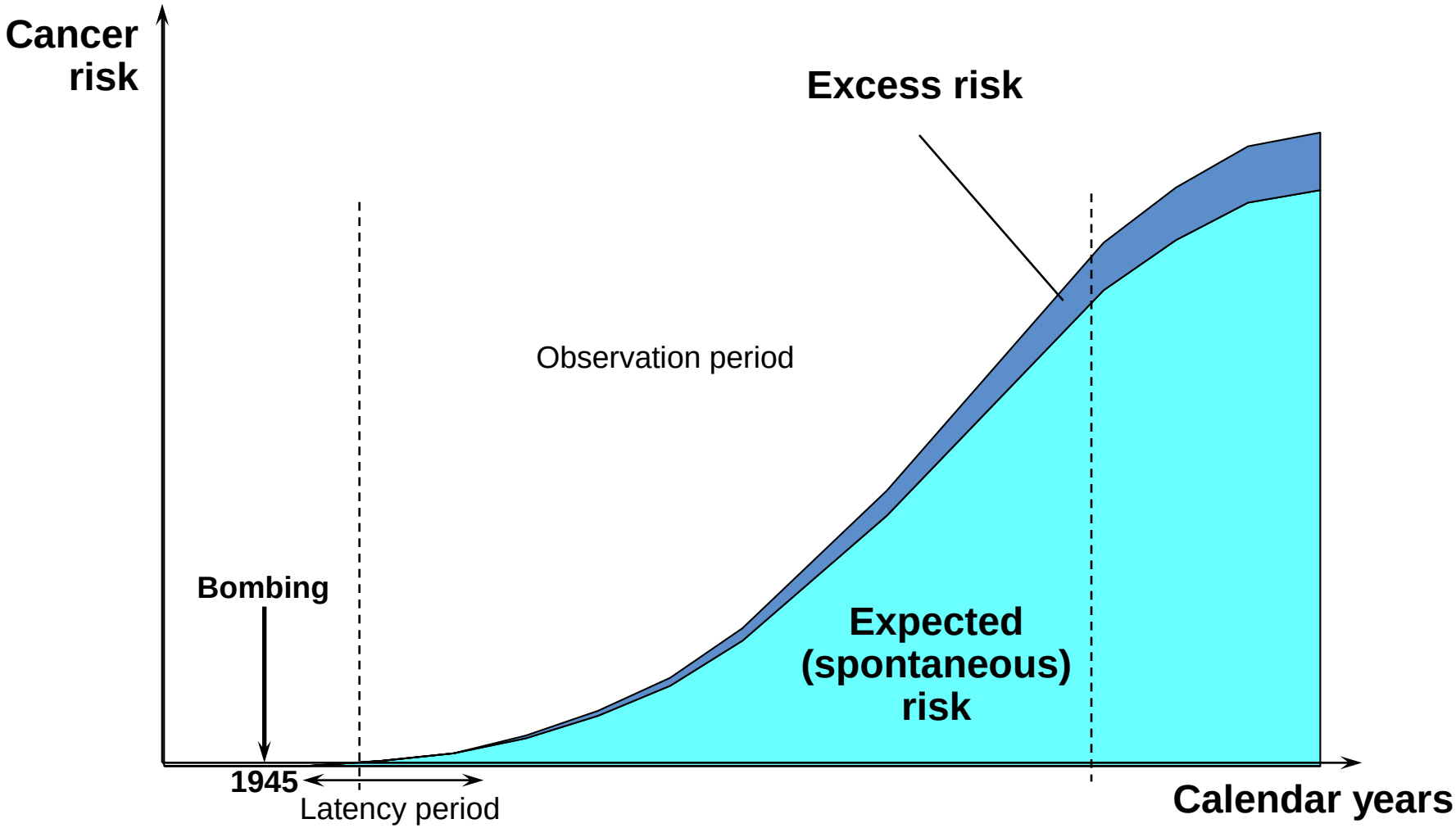
Study of Hiroshima and Nagasaki A-bomb survivors

The Life Span Cohort Study (LSS)

120 000 individuals alive in 1950
86 611 individuals with reconstructed dose
high dose rate
both sexes - all ages (and *in utero*)
mortality follow-up from 1950 to 2003
50 620 deaths (58%)

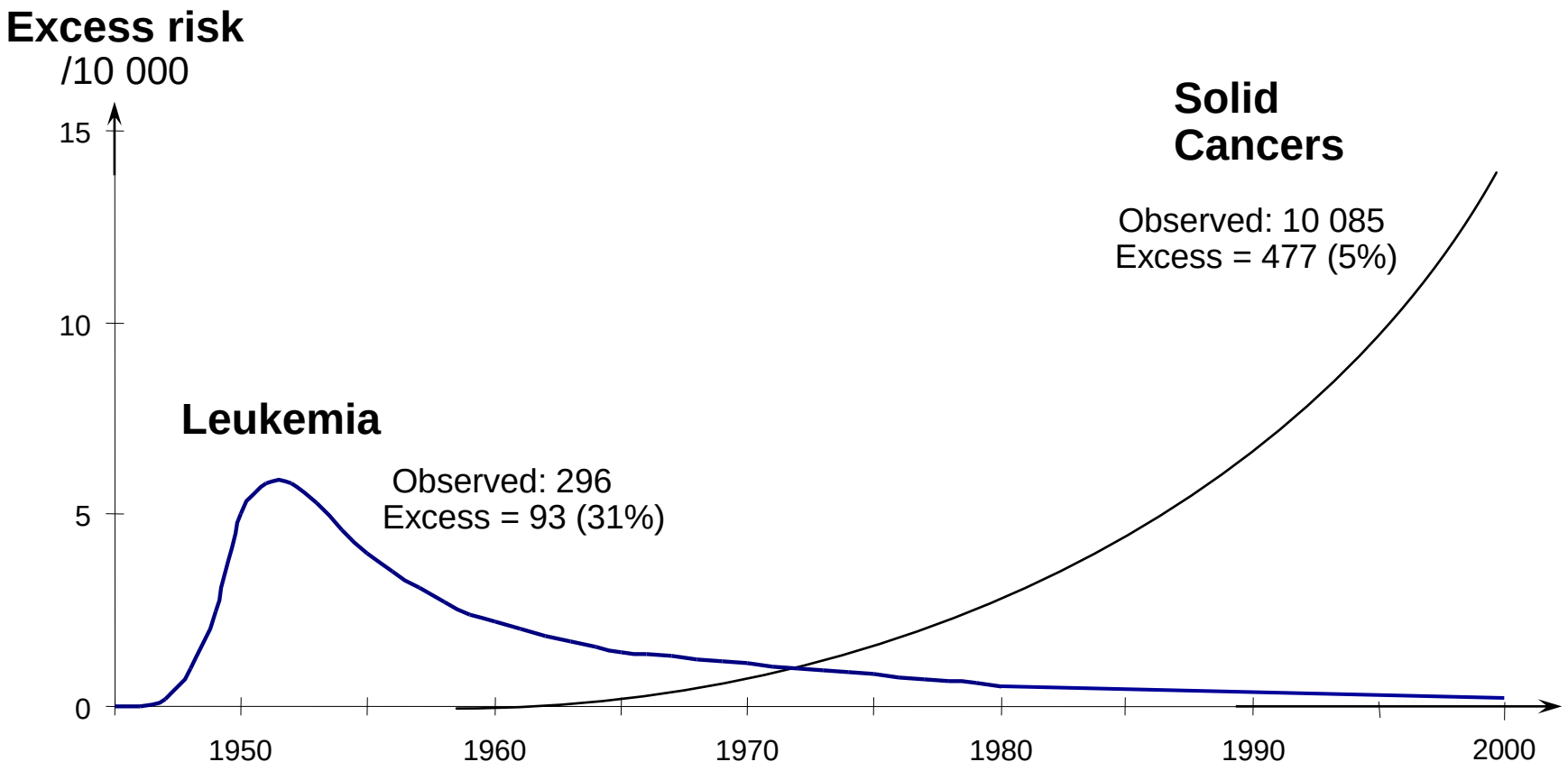
radiation induced cancers
estimates of the dose-risk relationship
latency between exposure and increased risk
effect of age
non cancer diseases

Follow-up of cancer risk



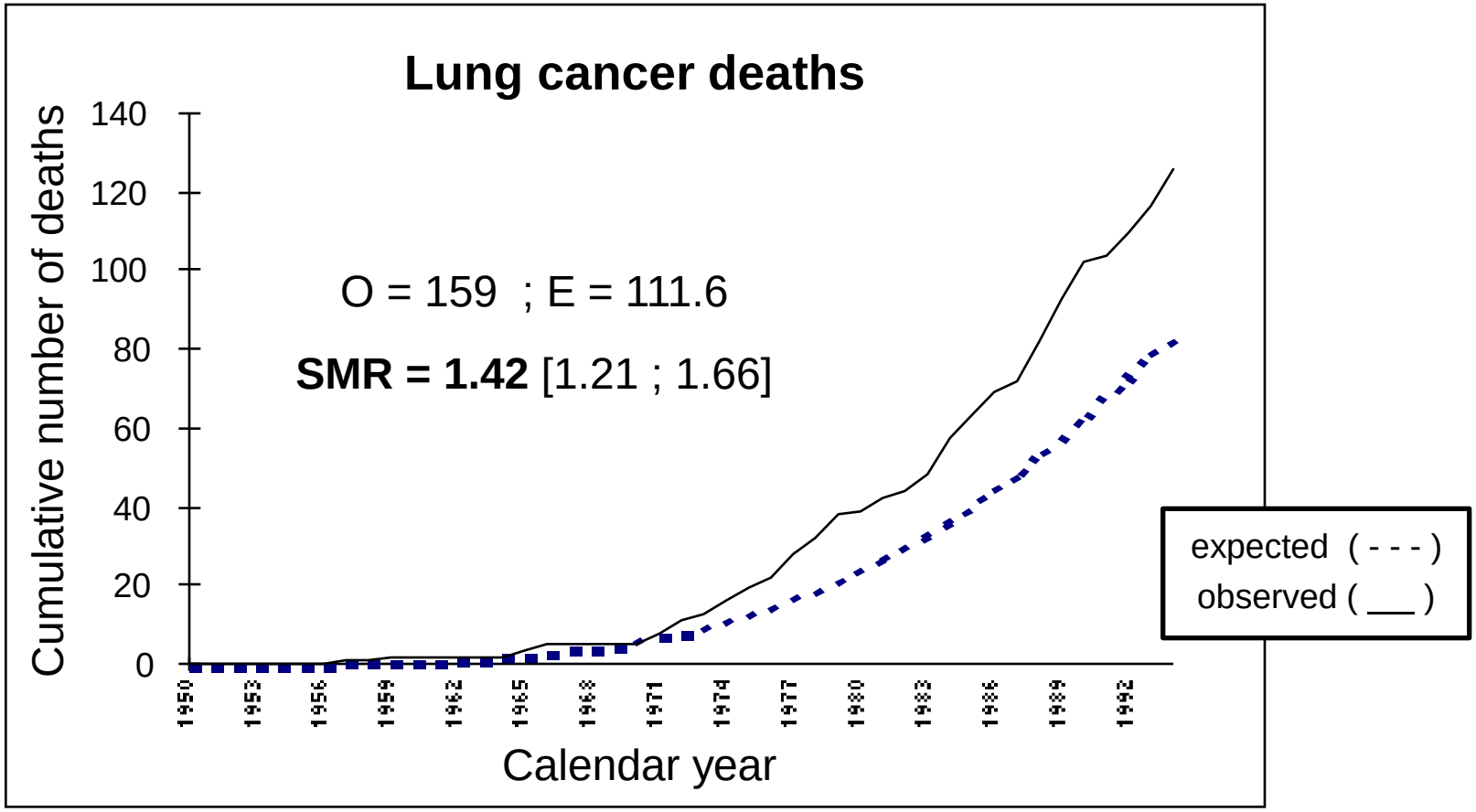
Excess cancer mortality among A-bomb survivors

Mortality 1950-2000
(Preston *et al*. Radiat Res 2004)



Mortality from lung cancer among French uranium miners

(cohort study, 5000 miners, Follow-up >30 years)



[Vacquier et al. OEM 2008]

Definition: confidence interval and significance

Confidence interval (CI): range of values that contains the theoretical value with a probability 1-α (α is conventionally fixed to 5%)

For a given estimated relative risk, the CI depends on the number of cases

O=4, E=2 => SMR=2 $CI_{95\%}$=[0.54 - 5.12]

O=1000, E=500 => SMR=2 $CI_{95\%}$=[1.88 - 2.13]

Significance (p) : a RR is significant different from 1 if the probability to wrongly reject the hypothesis of no difference is lower than 5%

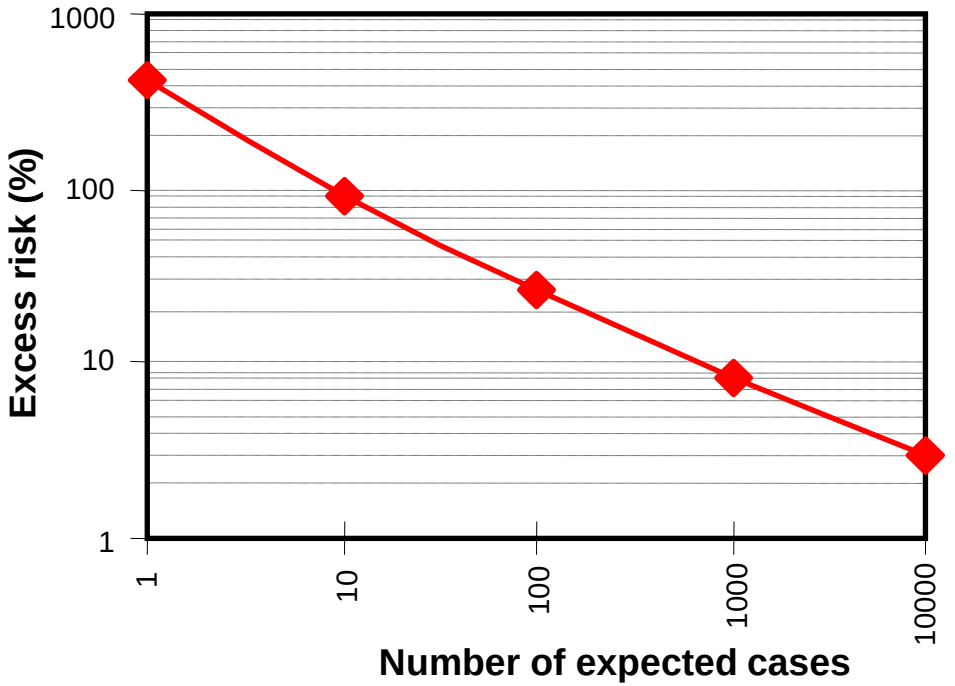
O=4, E=2 => SMR=2 p=0.14, not significant

O=1000, E=500 => SMR=2 p<0.001, significant

Definition : statistical power

Capacity of a study to demonstrate an excess risk if it exists (probability)

- ↗ with the size of the effect
- ↗ with the number of expected cases, and therefore with the size of the studied population (number and duration)



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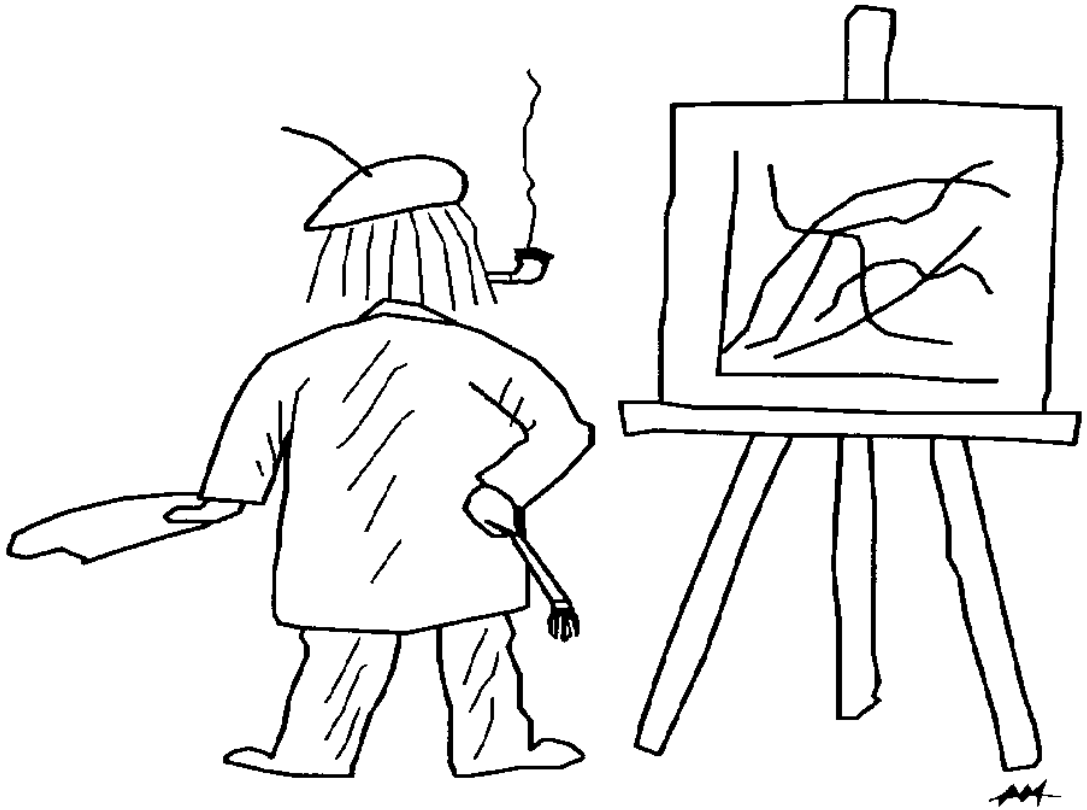
Quantifying the dose-risk relationship



"Which line do you like best ?"

Modelling the dose-risk relationship

Models

Linear (L)

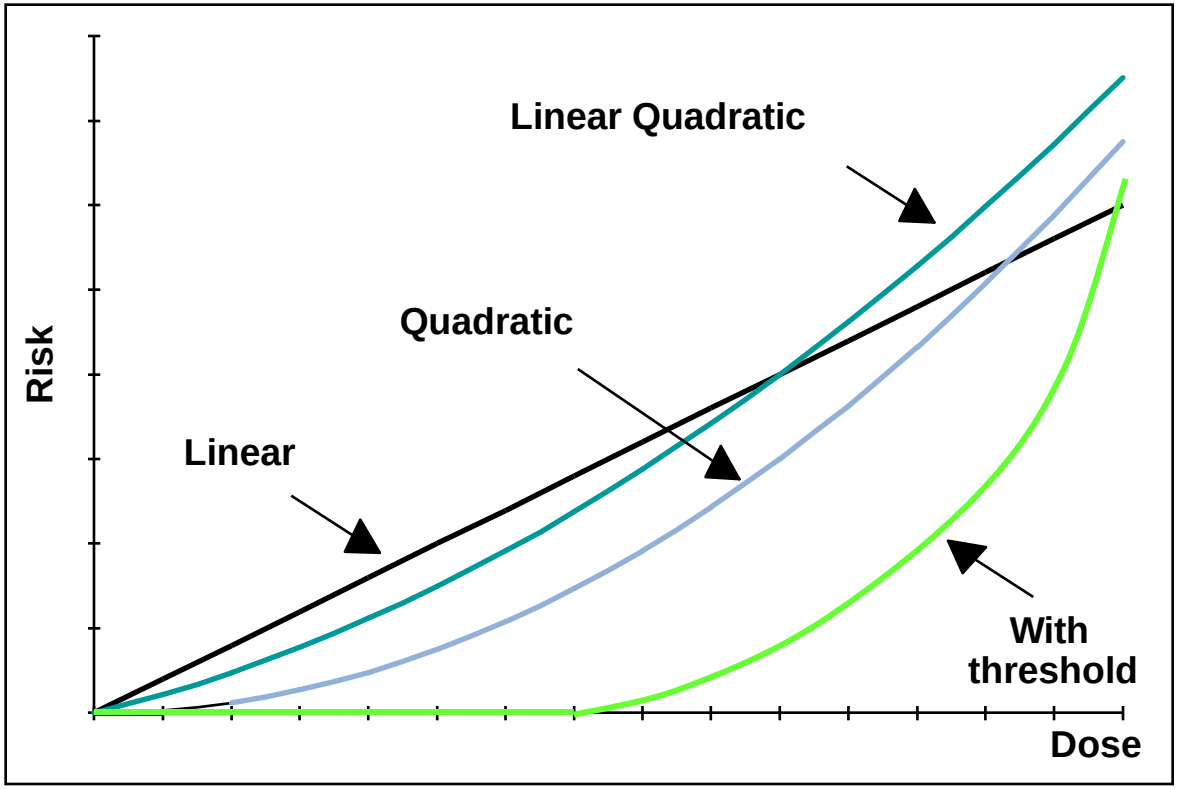
$$Y=\alpha + \beta_1 * D$$

Quadratic (Q)

$$Y=\alpha + \beta'_2 * D^2$$

Linear-quadratic (LQ)

$$Y=\alpha + \beta_1 * D + \beta_2 * D^2$$



Risk models

Relative risk

$$RR(d) = \frac{\lambda(c, s, b, a, e, d)}{\lambda_0(c, s, b, a)}$$

c city
s sex
b birthyear
a attained age
e age at exposure
d dose

Linear ERR model with modifying factors

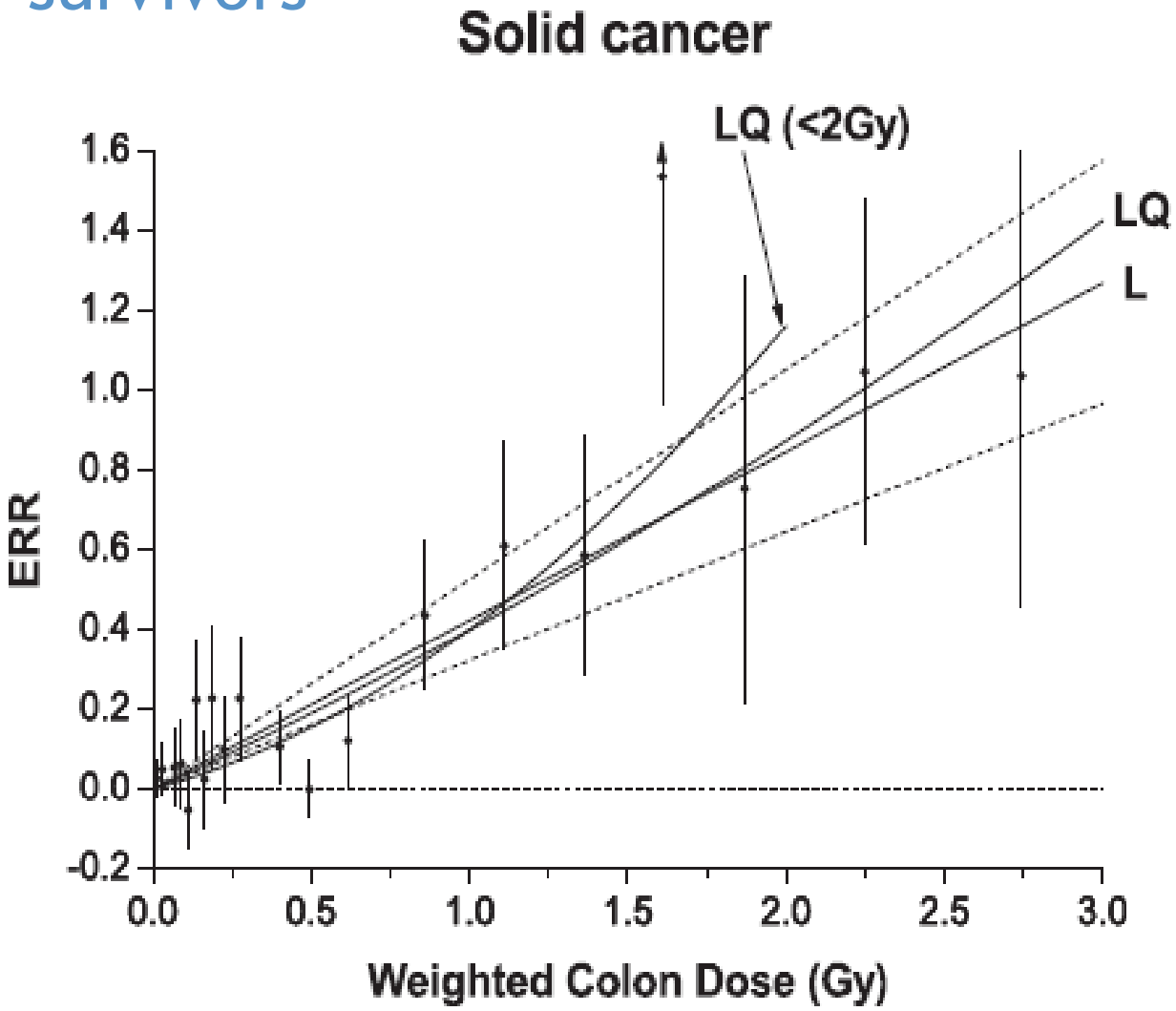
$$\lambda(c, s, b, a, e, d) = \lambda_0(c, s, b, a)[1 + \beta_1 d \cdot \exp(\tau e + \upsilon \ln(a)) \cdot (1 + \sigma s)]$$

Linear ERR model with modifying factors

$$\lambda(c, s, b, a, e, d) = \lambda_0(c, s, b, a) + \beta_1 d \cdot \exp(\tau e + \upsilon \ln(a)) \cdot (1 + \sigma s)$$

[Osaza Radiat Res 2012]

Solid cancer excess relative risk among A-bomb survivors

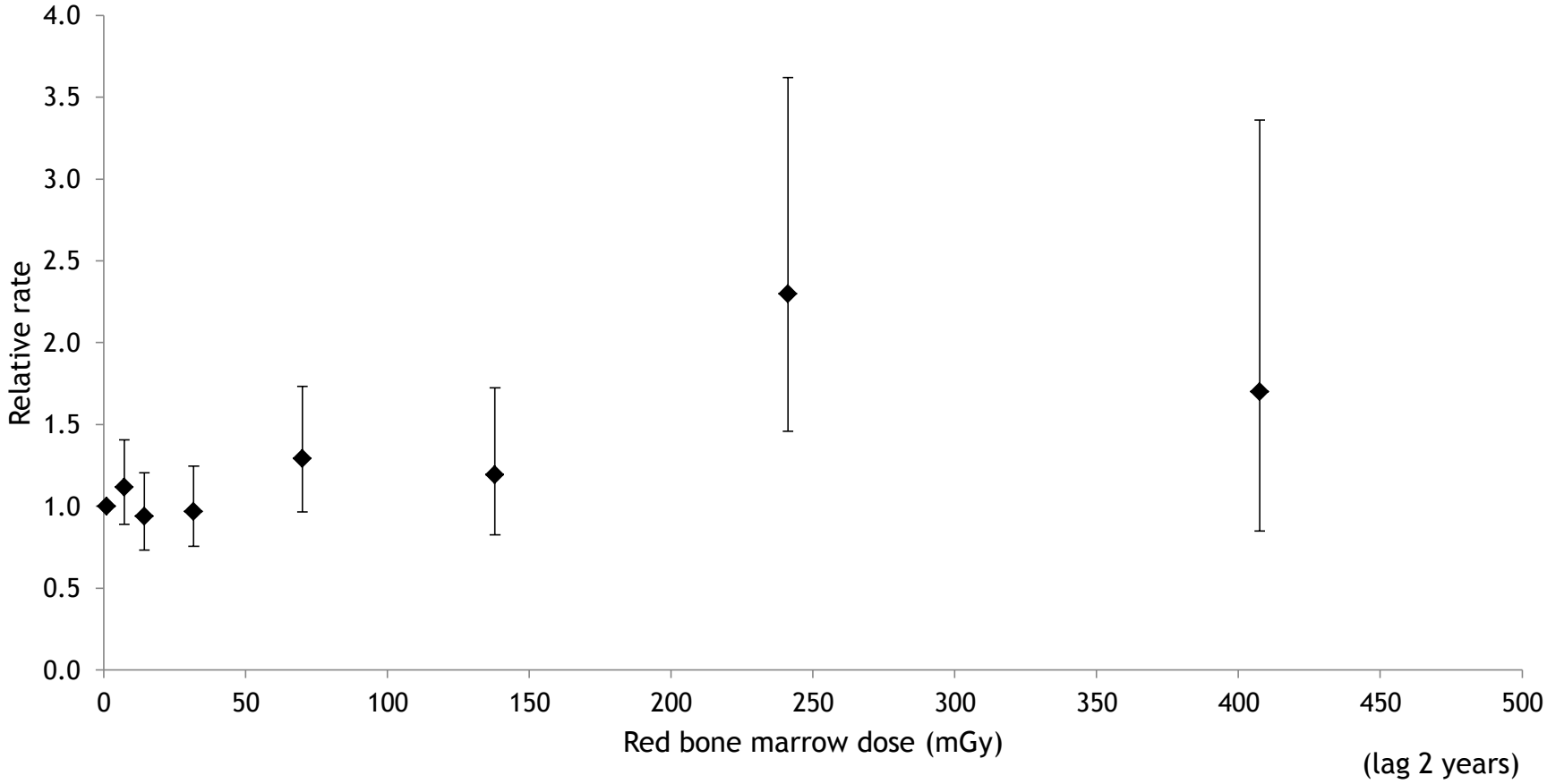


Linear model:

ERR = 0.42 per Gy
95%CI = [0.32 ; 0.53]

[Ozasa et al, Rad Res 2012]

INWORKS: Relative risk of non-CLL leukemia associated with red bone marrow dose



(Combined analysis of cohorts in France, US, UK, > 300,000 workers, follow-up 25y)

[Leuraud et al. Lancet Haematol 2015]

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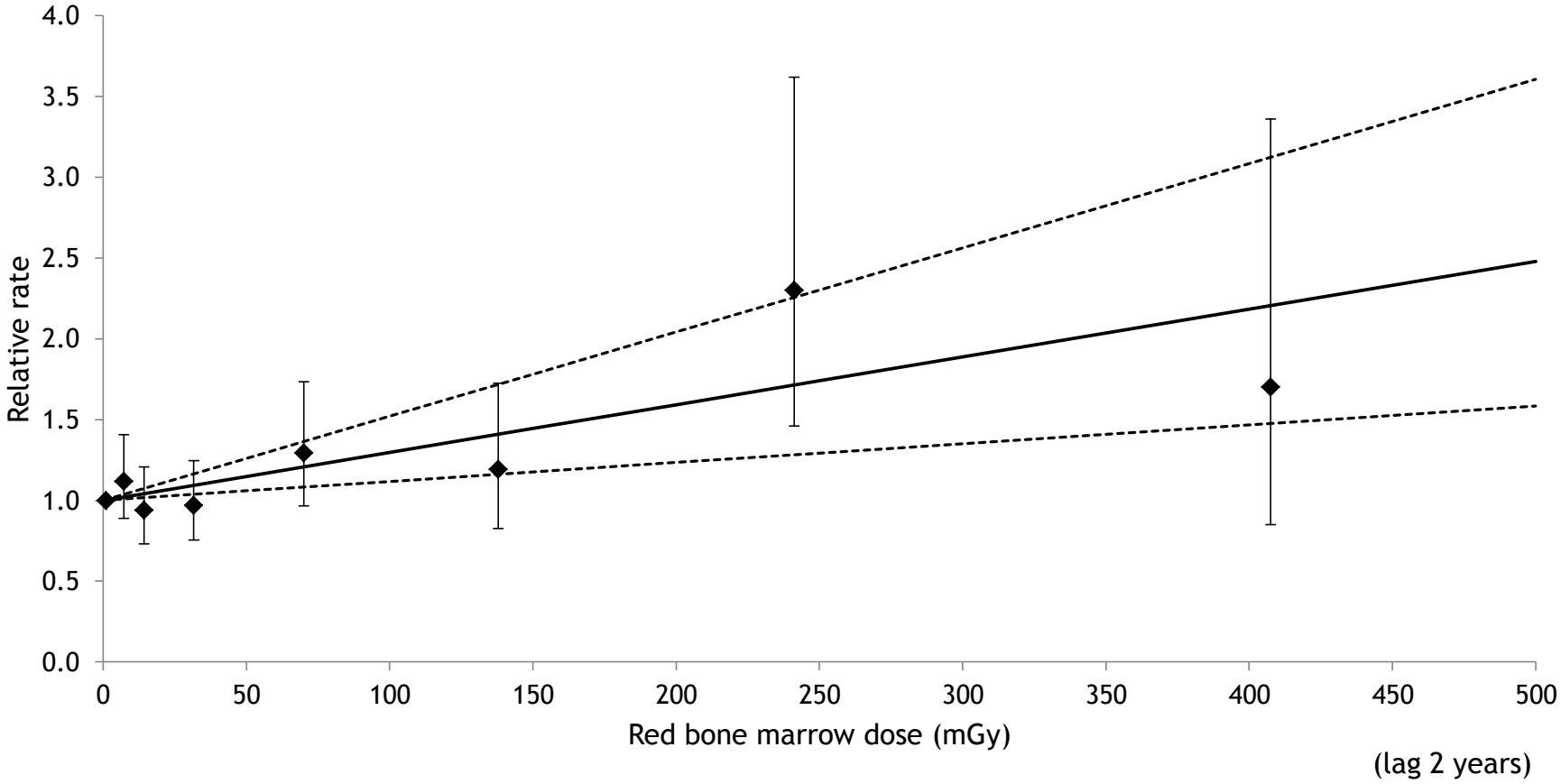
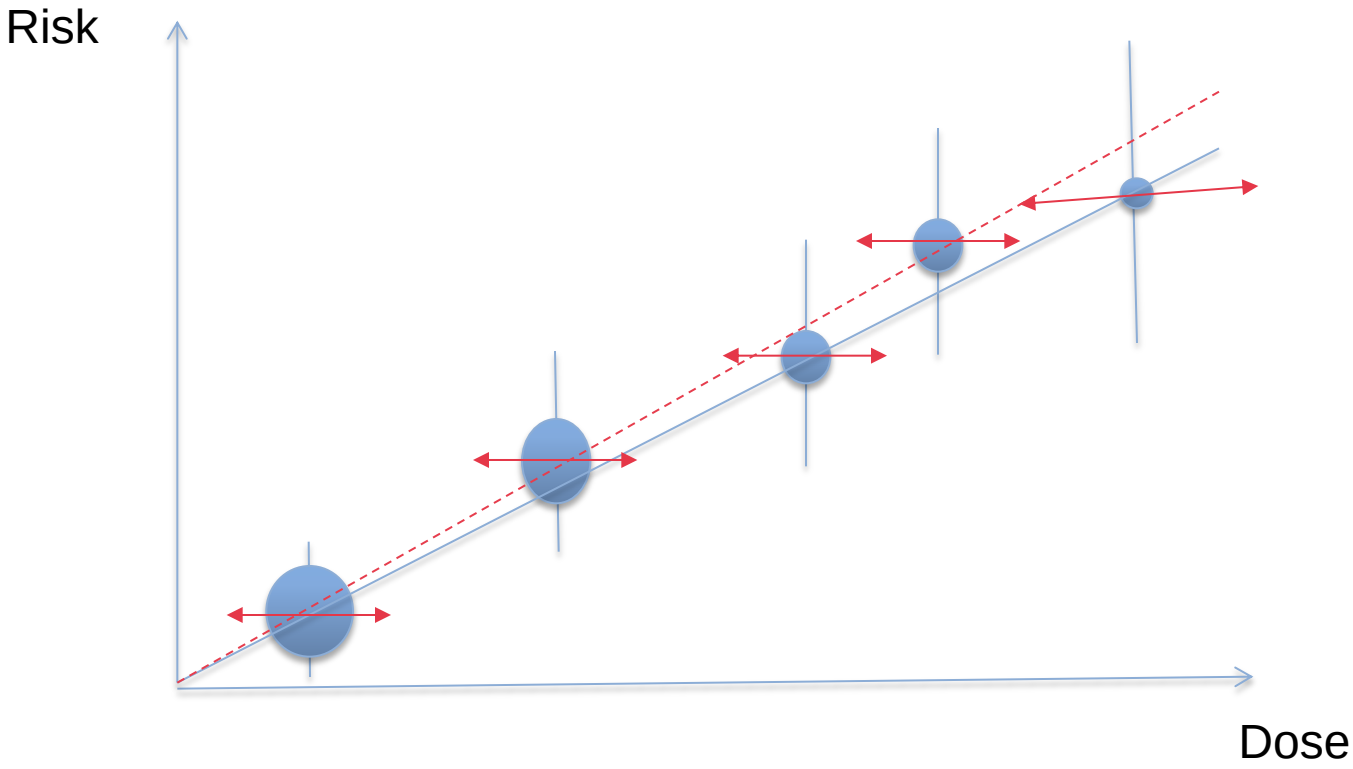


ERR per Gy = 2.96 ; 90%CI [1.17 – 5.21]

[Leuraud et al. Lancet Haematol 2015]

Uncertainties



- Characterisation of errors associated to exposure and dose
- Application of dose-error correction methods

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Limits of epidemiology at low doses

- **Low dose:** Low risks, RR close to 1
- **Epidemiological design**: need for well defined protocol and good data quality
- **Power**: large numbers needed to show small effects
- **Latency**: need long duration of follow-up (decades)

- **Baseline rates**: large variations between countries and populations
- **Multiple exposures:** background exposure, medical sources..
- **Multifactorial aetiology**: numerous non-radiation confounding factors
- **Errors in exposure assessment**: measurement errors

- **Mechanisms**: different at low and high dose
- **Low dose rate**: effect controlled by repairing systems / threshold ?

Pre-requisites of low dose studies

- Avoid biases: Good quality designed protocol

  ⇒ **Cohort and case-control studies**

- To demonstrate low excess risks: Increasing the statistical power

  ⇒ **Large numbers, combined international studies**

- Latency period long and varying between cancer sites
- Modifying factors of the dose-risk relationship (age, time since exposure)

  ⇒ **Long duration of follow-up**

- Control for confounding factors

  ⇒ **Collection of additional data, nested studies**

- To limit the uncertainties: Precision of exposure data estimates

  ⇒ **Correction for measurement errors**

Epidemiological studies at low dose and dose rate

Lung cancer risk and indoor radon: **European Pooling study**

13 case-controls studies in European countries
> 7000 cases (lung cancers) / > 14,000 controls
reconstruction of past indoor radon concentration over 30 years
control for smoking and other lung cancer risk factors
(Darby 2005, Darby 2007)

Nuclear workers: **INWORKS**

Cohorts from France, the UK and the USA
> 308,000 workers, followed-up for 25 years
> 66,000 deaths, including 20,000 from cancer
external exposure: cumulated mean dose 25 mSv
(Hamra 2015, Thierrychef 2015, Leuraud 2015, Richardson 2015)

Childhood CT scan: **Epi-CT**

EPI-CT

9 national cohort studies in European countries
Children with CT-scan exam during childhood
Objective: cohort of 1 million children
(Pearce 2012, Krille 2015, Bosch de Basea 2015, Journy 2015)

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Causal Criteria

Evaluation of the existence of a causal association between cancer mortality and cumulative exposure to radon among French miners

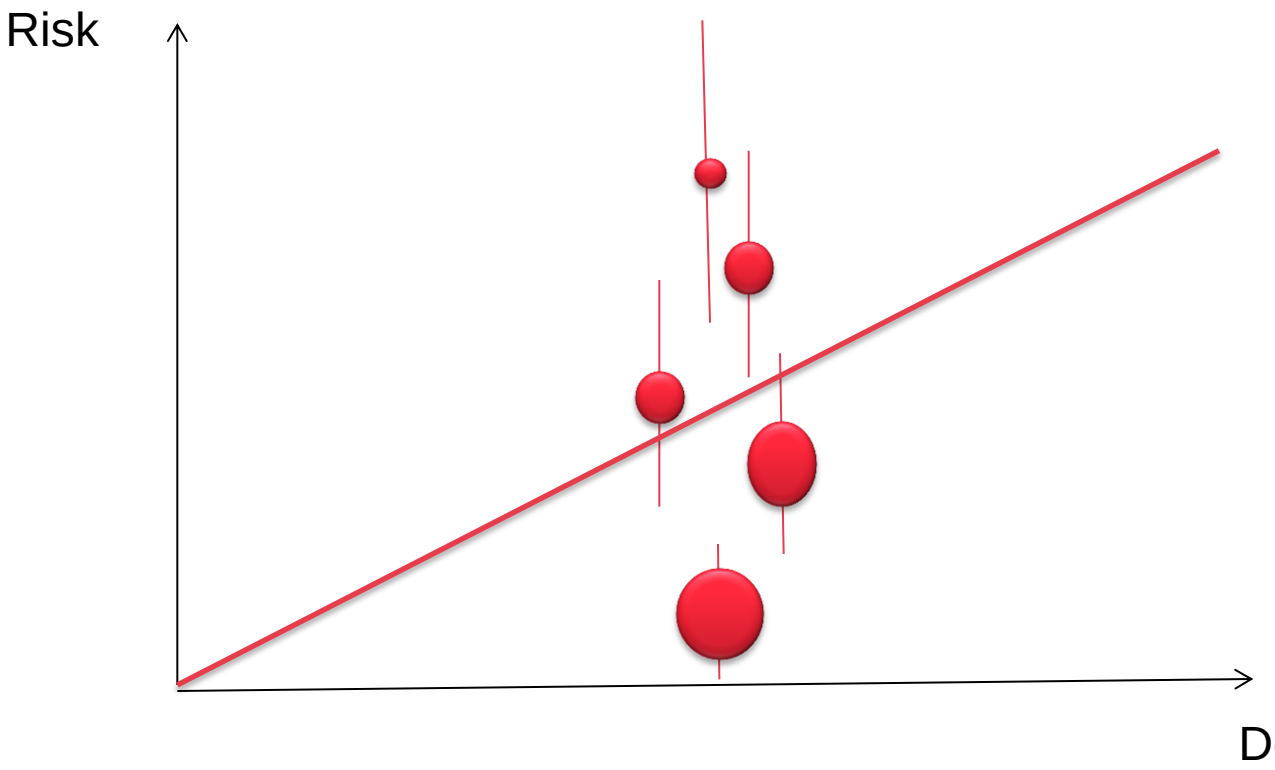
Criteria	Lung cancer	Cancer of larynx
• strength of the association	+	+
• temporality	+	+
• dose-response gradient	+	-
• consistency	+	-
• plausibility	+	-
• coherence	+	-
• experimental evidence	+	-
• specificity	-	-

according to A Bradford Hill 1965

Epidemiology at low doses: routes of improvement

- **International pooled analyses** (increasing power, standardization)
- **Multifactorial analyses** (complex exposures, other risk factors…)
- **Consideration of uncertainties** (error propagation)
- **Multidisciplinary integration** (epidemiology, dosimetry, statistics, biology)
- **Development of molecular epidemiology** (biomarkers to refine dosimetry, improve disease detection, assess inter-individual variability)

Collaboration between epidemiology and dosimetry



Epidemiologist

+

Dosimetrist

=

Good dose-risk quantification

Thank you
for your attention