Basics in Epidemiology

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• 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)

**Stochastic effects**
- frequency is function of the dose
- low and medium doses
- late and non specific effects
- no threshold model
  (cancers, hereditary effects...)

Medical emergency

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

- **Descriptive studies**
  - Surveillance
- **Etiological studies**
  - Research of risk factors
- **Risk quantification**
  - Exposure-risk relationship

**Geographic studies** (aggregated data)

**Cohort studies**

**Case-controls studies** (individual data)
Protocol of a cohort study

INCLUSION

Target Population
- Exposed
- Non exposed

Cohort

Exposed Non exposed

FOLLOW-UP

STATUT VITAL

Lost to follow-up

Alone at the date of point

Deceased

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

Matching (age, sex…)

n Cases

K.n Controls

Retrospective reconstruction of exposures

ANALYSIS
Comparison of exposures distributions

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

<table>
<thead>
<tr>
<th>Numerator</th>
<th>number of cases (morbidity) or deaths (mortality)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Denominator</td>
<td>number of persons at risk over a given period (person-years)</td>
</tr>
</tbody>
</table>

**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

\[
\text{SMR} = \frac{O}{E}
\]

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

Cancer risk

Excess risk

Expected (spontaneous) risk

Observation period

Calendar years

Bombing

Latency period

1945
Excess cancer mortality among A-bomb survivors

Mortality 1950-2000

Excess risk
/10 000

Solid Cancers
Observed: 10 085
Excess = 477 (5%)

Leukemia
Observed: 296
Excess = 93 (31%)
Mortality from lung cancer among French uranium miners
(cohort study, 5000 miners, Follow-up >30 years)

Lung cancer deaths

O = 159 ; E = 111.6

SMR = 1.42 [1.21 ; 1.66]

[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

<table>
<thead>
<tr>
<th>O</th>
<th>E</th>
<th>SMR</th>
<th>CI 95%</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>2</td>
<td>2</td>
<td>[0.54 - 5.12]</td>
</tr>
<tr>
<td>1000</td>
<td>500</td>
<td>2</td>
<td>[1.88 - 2.13]</td>
</tr>
</tbody>
</table>

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

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<tr>
<th>O</th>
<th>E</th>
<th>SMR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>2</td>
<td>2</td>
<td>0.14, not significant</td>
</tr>
<tr>
<td>1000</td>
<td>500</td>
<td>2</td>
<td>&lt;0.001, significant</td>
</tr>
</tbody>
</table>
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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"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

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

### Linear ERR model with modifying factors

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

[Osaza Radiat Res 2012]
Solid cancer excess relative risk among A-bomb survivors

Linear model:

$\text{ERR} = 0.42 \text{ per Gy}$

$95\% \text{CI} = [0.32; 0.53]$

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

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
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
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 according to A Bradford Hill 1965

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Lung cancer</th>
<th>Cancer of larynx</th>
</tr>
</thead>
<tbody>
<tr>
<td>strength of the association</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>temporality</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>dose-response gradient</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>consistency</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>plausibility</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>coherence</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>experimental evidence</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>specificity</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
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

Risk

Epidemiologist

+ Dosimetrist

= Good dose-risk quantification

Dose
Thank you for your attention