Methods in Epidemiology & Nutrition

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Observation vs. Experimentation

- *Observations de populations ou d'individus*
  - ne donne pas de preuve directe
- *Expérimenter au labo ou "sur le terrain"*
  - preuve directe que l'action a un effet
Observation vs. Experimentation

• To observe populations or individuals
  – Correlation studies (international)
  – Retrospective case-control studies
  – Prospective cohort studies
  –
• To do Experimental studies (lab or field)
  – In vitro, cell culture or bacteria
  – In vivo, animal studies (pre-clinical studies)
  – In volunteers: intervention trial

Observation at Population Level

international correlation studies

E.g.:
International correlation between
Fat Intake & Breast cancer mortality
(correlation is NOT a proof)
International Correlation shown on a map

Red meat eating countries
Are also Colorectal cancer high risk countries
(correlation is NOT a proof)

Observation: Population Level
Time Trends Studies

- Generates hypotheses on causes of disease: is there a change in the lifestyle that can explain the change in disease rate?
- Also migrant studies: Observe changes in disease rate when a population migrates from a low-risk country to a high-risk country
  (still not a proof!)
**Change with Time**
ex.: Colon cancer in the UK (stability) & in Japan (increase!)
Evolution of cancer mortality in France 1950-2000 WOMEN

Migrants Japan=>Hawaï
Cancer Incidence /100 000 (Haenszel JNCI 1968)
Analytical Observation of **Individuals**: case-control studies (retrospectives)

- Go to the hospital, at the patient's bed (case)
- Ask many questions on past life
- Make a similar survey for similar controls
- Compare cases answers to controls answers, many questions, many people
- Ex: Stomach cancer and fruits & veg. intake

Analytical Observation of **Individuals**: Case-Control studies (retrospectives)

- Population cut in 3 to 5 groups (tertiles, quartiles, quintiles)
- Relative Risk to get the condition (e.g., cancer) in the "big eater" group compared to the "small eater" group

Exemple: Risques relatifs de cancer de l'estomac selon la consommation quotidienne de légumes
Analytical Observation of Individuals: Case-Control studies (retrospectives)

- Relative Risk (precisely, Odd Ratio)
- And 95% Confidence Interval
  \[ RR=2.1 \ (95\% \ C.I.= 1.2 \ - \ 4.3) \]
- If **ONE** is not included in the 95%CI, the risk is significant
- Other example (protection):
  \[ RR=0.38 \ (IC95= 0.15-0.89) \]

Analytical Observation of Individuals: Case-Control studies (retrospectives)

- Advantage: fast & cheap (all cases & controls are "already" there : you only need to ask them questions)
- Drawbacks: Hard to remember past diet (recall bias): elapsed time, and illness yield false answers
- No ideal control (Hospital? Home? Street?)
- And multiple confusion factors
Analytical Observation of Individuals: Cohort Studies (prospective)

- Choose a large **healthy** cohort
- Ask them how they live **now**
- Wait a long time till some of them get ill (cancer, CVD, diabetes, … any condition you want to study)
- Compare answers from "cases" and "controls" (= the whole cohort, minus the "cases")
- Calculate relative risks (RR) and confidence intervals 95%. If excludes ONE, it's significant
Analytical Observation of **Individuals**: Cohort Studies (prospective)

- Nurses' Health Study = 72000 American nurses (Harvard, USA)
- colorectal cancer & processed meat intake
- (Willet, 1990 : quintiles 1 & 5 are reported here)

**Drawback:**
- Very long (*attendre que gens "tombent malades"*)
- Very expensive (*faut énormément de gens*)

**Advantages:**
- No "recall bias": questions address present time, to healthy people
- Ideal controls: everybody is similar to start with

**But confusing factors still possible…**
The people of Kratovilla have low rates of cancer. It must be all the sarsaparilla they drink... ...unless it's all the pickles they eat... ...unless it's the mayonnaise they put on the pickles... ...unless it's the chocolate they dip the pickles in... ...unless it's the Coca beans the chocolate comes from... ...unless it's...

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**Meta-Analysis of Many Cohort Studies**

Larsson & Wolk  
IJC 2006

Colorectal cancer & Red meat Intake

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative risk (95% CI)</th>
<th>Red meat</th>
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</thead>
<tbody>
<tr>
<td>Bostick et al., 1994^10</td>
<td>1.04 (0.62-1.76)</td>
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<tr>
<td>Kato et al., 1997^11</td>
<td>1.23 (0.68-2.22)</td>
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<tr>
<td>Chen et al., 1998^13</td>
<td>1.17 (0.68-2.02)</td>
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<tr>
<td>Hsing et al., 1998^16</td>
<td>1.90 (0.90-4.30)</td>
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<tr>
<td>Singh et al., 1998^14</td>
<td>1.41 (0.90-2.21)</td>
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<tr>
<td>Pietinen et al., 1999^17</td>
<td>1.10 (0.70-1.70)</td>
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<tr>
<td>Järvinen et al., 2000^18</td>
<td>1.50 (0.77-2.94)</td>
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<tr>
<td>Tiemersma et al., 2002^19</td>
<td>1.60 (0.90-2.90)</td>
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<tr>
<td>Flood et al., 2003^20</td>
<td>1.10 (0.83-1.45)</td>
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<tr>
<td>Wei et al., 2004^21</td>
<td>1.21 (0.72-2.03)</td>
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<tr>
<td>Wei et al., 2004^22</td>
<td>1.24 (0.78-1.96)</td>
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<tr>
<td>English et al., 2004^23</td>
<td>1.40 (1.00-1.90)</td>
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<tr>
<td>Larsson et al., 2005^24</td>
<td>1.32 (1.03-1.68)</td>
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<tr>
<td>Chao et al., 2005^25</td>
<td>1.36 (0.93-2.00)</td>
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<tr>
<td>Norat et al., 2005^26</td>
<td>1.35 (0.96-1.88)</td>
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**Summary estimate** 1.28 (1.15-1.42)

Test for heterogeneity:  
Q = 4.86; p-value = 0.99; I² = 0%
Observation & Expérimentation

- **Observations de populations ou d'individus**
  - Études de corrélation. Evolution dans le temps
  - Études cas-témoin rétrospectives
  - Études de cohorte, prospectives

  **Do not give a direct proof**

- Experimental studies: in the lab or "on the field"
  - In vitro, In vivo, in volunteers
  **Direct solid proof of a cause-effect relationship**
Experimental Studies in Laboratories

In vitro, cell culture or bacterial
- Mutagens (Ames' test)
  – Clastogens (human cells chromosomes)
  – Comet Test (single cell gel electrophoresis)
Experimental Studies in Laboratories

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In vivo, animal studies (preclinical)
- Physiological biomarkers
- Carcinogens
- Carcinogenicity studies: protection or promotion
Human Clinical Trials in Volunteers

**Intervention Studies**

- Gold standard: clinical trials for drugs
- **Randomized** trial: treated ones chosen at random
- Treatment compared to a **placebo**
- **Double blinded** study:
  Volunteer AND Investigator
do not know if placebo or treatment is taken
Human Clinical Trials in Volunteers

Intervention Studies

- Randomized, placebo-controlled, double-blind intervention studies are the only valid proofs that a given diet/agent can change a disease risk.
- But testing one agent once costs $10 to 70 millions US dollars, and lasts 3 to 10 years.
- This explains why so few agents/diets have already been tested!