Introduction to Pharmacoepidemiology
Case-Control Studies

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2014/10/24
My Training

• *B.S* in *Pharmacy*, Taipei Medical University, Taiwan, 2001

• *M.S. in Clinical Pharmacy*, Taipei Medical University, Taiwan, 2003

• *Ph.D. in Health and Welfare Policy Management*, National Yang-Ming University, Taiwan, 2007
  – Major: Pharmacoepidemiology and pharmacoeconomics
My Academia Experience

• *Post-doctoral fellow*, Collaborative drug policy research team from National Health Research Institutes and National Yang-Ming University, *2007-2008*

• *Post-doctoral fellow*, University of Maryland, Department of Pharmaceutical Health Services Research, *2008-2010*

• *Assistant professor*, National Taiwan University, Graduate Institute of Clinical Pharmacy, *2010-*
Disclosure

• No conflicts of interest to declare
Learning Objectives

• How are case-control designed?
• When is case-control study warranted?
• How to conduct a case-control study?
Study Design

Randomized controlled trials (experimental)

- Cohort studies (世代研究)
- Case-control studies (病例对照研究)
- Cross-sectional studies

Clinical observation (case reports, case series) (observational)
Cohort Study (世代研究)

Population

Population of interest

Exposed
- Develop outcome
- Not develop outcome

Unexposed
- Develop outcome
- Not develop outcome
Cohort Study

<table>
<thead>
<tr>
<th></th>
<th>Outcome develops</th>
<th>Outcome does not develop</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposed</td>
<td>a</td>
<td>b</td>
<td>a+b</td>
</tr>
<tr>
<td>Non-exposed</td>
<td>c</td>
<td>d</td>
<td>c+d</td>
</tr>
</tbody>
</table>

First, identify

- Incidence in exposed: \( \frac{a}{a+b} \)
- Incidence in non-exposed: \( \frac{c}{c+d} \)

then follow to see whether.....
Case-control Study (病例對照研究)

Exposed
Non-Exposed

Disease¹
“Case”

Exposed
Non-Exposed

No disease
“Control”

Disease¹: outcome, condition, ADR
Case-control Study (病例對照研究)

- Exposed (meal after 8pm)
  - Weight gain “Case”
  - Non-Exposed
- Exposed (meal after 8pm)
  - No weight gain “Case”
  - Non-Exposed
### Case-control Study

#### 2x2 Table

First, select

<table>
<thead>
<tr>
<th></th>
<th>Case (with disease)</th>
<th>Control (without disease)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposed</td>
<td>a</td>
<td>b</td>
</tr>
<tr>
<td>Non-Exposed</td>
<td>c</td>
<td>d</td>
</tr>
<tr>
<td>Total</td>
<td>a+c</td>
<td>b+d</td>
</tr>
</tbody>
</table>

Then measure past-exposure

Proportion of exposed in case = \( \frac{a}{a+c} \)

Proportion of exposed in control = \( \frac{b}{b+d} \)
Case-control Study
A Classic Example

• An epidemic in Boston!
  – Arthur L. Herbst, M.D., Howard Ulfelder, M.D., and David C. Poskanzer, M.D. of Massachusetts General Hospital
  • 8 cases of vaginal adenocarcinoma among young women (age 14-22) were seen in two Boston hospitals
    – Between 1966-1969
  • Vaginal adenocarcinoma
    – Very rare carcinoma, primarily in elderly women (over the age of 50)
      → What causes the occurrence of this event?

•
Case-control Study

• Retrospective study
  – To evaluate the histories of the offspring and their families, as well as factors related to the mothers’ pregnancies

• Case and control
  – 8 cases of vaginal adenocarcinoma
    • All of the patients had been born in New England
      – The mother of one of them, who had been treated by Howard Ulfelder, indicated to him that she had taken diéthylstilbestrol (DES) during the pregnancy that produced her daughter
  – 4 controls matched to each cohort (32)
    • Same gender
    • Born within 5 days in the same hospital and same service of the case
Case-control Study

• Mothers of the 40 study subjects (8 cases and 32 controls) were interviewed
  – Smoking, bleeding during pregnancy, prior pregnancy loss, estrogen use during pregnancy, X-ray exposure, breast feeding
  ➔ 7/8 cases were exposed to diethylstilbestrol (DES)
  ➔ 0/32 controls were exposed to diethylstilbestrol (DES)
## Case-control Study

2x2 Table (N Engl J Med 1971; 284: 87)

<table>
<thead>
<tr>
<th></th>
<th>Vaginal carcinoma (with disease)</th>
<th>Control (without disease)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DES</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Non-Exposed</td>
<td>1</td>
<td>32</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>8</strong></td>
<td><strong>32</strong></td>
</tr>
</tbody>
</table>

First, select

Proportion of exposed in case = \(\frac{7}{8} = 87.5\%\)

Proportion of exposed in control = \(\frac{419}{845} = 0\%\)
Case-control Study

• Investigator as medical detectives
  – Facing a series of adverse outcomes, need to identify causes/risk factors

• Efficiency
  – No need for lengthy follow-up
  – Small/moderate number of cases and controls for rare diseases
    • 8 cases of vaginal adenocarcinoma
    • 4 controls matched to each cohort (32)
When is case-control study warranted? (1)

- It is usually conducted before a cohort or an experimental study to identify the possible etiology of the disease
  - Can be conducted in a shorter time in a relatively small population ➔ Costs less!
- Long latent period between an exposure and the disease ➔ case-control maybe the most feasible one!
When is case-control study warranted? (2)

• It is usually conducted **before** a cohort or an experimental study to identify the possible etiology of the disease
  – Can be conducted in a **shorter time** in a **relatively small population** → Costs less!

• **Long latent period** between an exposure and the disease → case-control maybe the most feasible one!

•
When is case-control study warranted? (3)

- Unless target pre-specified risk factors, for a given disease, a case-control study can investigate **multiple exposures** (when the real exposure is not known)
  - Vs. cohort study → relatively difficult!
    - Remember you first need to **identify**
      - “exposure/non-exposure group”
How to Conduct a Case-control Study?
First step: Identify Cases

• Ideally
  – The cases studied should be a random sample of all the patients with the disease
    → Impossible in real life!

• Practically
  – Identify “homogenous” cases
  – Criteria or definition of cases must be well formulated and documented
Second Step: Identify Controls

• Conceptually
  – Controls should come from the same population at risk of disease from which cases develop
    • Real life: you don’t know who they are

• Practically
  – Controls are often selected to be similar to cases on key factors but without the disease
Second Step: Types of Controls

• Convenient control
  – Hospital/outpatient control
    • Attending the same hospital
      – Pros: Similar quality of information
      – Cons: they may have characteristics or diseases that led to hospitalization
  – Best friend or neighbor controls (for interview or survey)
    – Pros: convenient
    – Cons: may share similar characteristics (too similar?)
    – e.g. Socioeconomic: community and income

• Population control
  – Random sample
Second Step: “Matching”

• “Matched”
  – Controls are similar to the cases with regard to certain key characteristics—such as age, sex, and race
    • Pros: Logically understandable; statistical power
    • Cons:
      – Matching on many variables may make it difficult to find an appropriate control
      – Can’t explore the possible association between any variable on which the cases and controls have been matched and the disease
Case-control Study: Hospital Setting
(J Formos Med Assoc 2003;102:305-12)

- **Cases:**
  - 776 patients with newly diagnosed and histologically confirmed colorectal cancer treated at a Hospital in Taiwan

- **Controls:**
  - 736 controls were selected from subjects who visited the health examination department for comprehensive health examinations including colonoscopies.
  - age- and gender-matched controls
Case-control Study: Hospital Setting
(J Formos Med Assoc 2003;102:305-12)

Taiwan, X hospital

Age 55, female (CRC)

Age 55, female (NO CRC)

Age 67, male (NO CRC)

Age 67, male (CRC)

Age 67, male (NO CRC)
• Cases:
  – all individuals in the study cohort with first occurrence of incident hip fracture

• Control:
  – Up to 10 controls were selected for each case
  – Matched for
    • sex, index date, year of birth, and both calendar period and duration of up-to-standard follow-up before the index date
Case-control Study
Secondary Data (*JAMA* 2006;296:2947-2953)

- Case vs. control (1:10)

**Table 1. Characteristics of Hip Fracture Cases and Controls**

<table>
<thead>
<tr>
<th></th>
<th>Cases (n = 13,556)</th>
<th>Controls (n = 135,386)</th>
<th>Crude OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex</td>
<td>79.90</td>
<td>79.89</td>
<td>NA</td>
</tr>
<tr>
<td>Age at database enrollment, mean (SD), y</td>
<td>77 (9.3)</td>
<td>77 (9.3)</td>
<td>NA</td>
</tr>
<tr>
<td>Body mass index†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td>6.77</td>
<td>3.59</td>
<td>1.95 (1.82-2.10)</td>
</tr>
<tr>
<td>&gt;30</td>
<td>4.51</td>
<td>6.71</td>
<td>0.65 (0.60-0.71)</td>
</tr>
<tr>
<td>Medication use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiolytic</td>
<td>14.95</td>
<td>9.20</td>
<td>1.76 (1.67-1.85)</td>
</tr>
<tr>
<td>Antidepressant</td>
<td>8.42</td>
<td>4.09</td>
<td>2.17 (2.03-2.32)</td>
</tr>
<tr>
<td>NSAID/aspirin</td>
<td>9.16</td>
<td>6.84</td>
<td>1.38 (1.30-1.47)</td>
</tr>
</tbody>
</table>
Third Step: “Exposure”

• By questionnaire
  – Risk factors of colon cancer in Taiwan
  – A structured questionnaire
    • covering sociodemographic characteristics, lifestyle factors (including physical activities, cigarette and alcohol use, and coffee intake), dietary consumption, and medical history
      – for the 5 years preceding the date of study selection.
### Third Step: “Exposure”

<table>
<thead>
<tr>
<th>Variable†</th>
<th>Controls (n)</th>
<th>Cases (n)</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Staple</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>133</td>
<td>65</td>
<td>1.0</td>
<td>0.42–1.15</td>
</tr>
<tr>
<td>Medium</td>
<td>92</td>
<td>31</td>
<td>0.69</td>
<td>0.42–1.15</td>
</tr>
<tr>
<td>High</td>
<td>184</td>
<td>89</td>
<td>1.01</td>
<td>0.68–1.50</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Meat</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>53</td>
<td>15</td>
<td>1.0</td>
<td>0.61–2.39</td>
</tr>
<tr>
<td>Medium</td>
<td>112</td>
<td>38</td>
<td>1.21</td>
<td>0.61–2.39</td>
</tr>
<tr>
<td>High</td>
<td>244</td>
<td>132</td>
<td>1.97</td>
<td>1.06–3.64</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Vegetable/fruit</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>57</td>
<td>48</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Medium</td>
<td>86</td>
<td>49</td>
<td>0.67</td>
<td>0.40–1.13</td>
</tr>
<tr>
<td>High</td>
<td>266</td>
<td>73</td>
<td>0.32</td>
<td>0.20–0.51</td>
</tr>
</tbody>
</table>

*p = 0.89*†

*Meat Exposure in the past 5 years

*p < 0.01*
Third Step: “Exposure”

- From secondary data
  - (JAMA 2006;296:2947-2953)
  - Long-term use of PPI and risk of hip fracture
    - >= 1 year
Third Step: “Exposure”

<table>
<thead>
<tr>
<th>Table 2. Risk of Hip Fracture Associated With Increasing Cumulative Duration of Proton Pump Inhibitor Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cumulative Proton Pump Inhibitor Therapy Duration, y</strong></td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>OR (95% CI)*</td>
</tr>
<tr>
<td>Crude</td>
</tr>
<tr>
<td>Adjusted†</td>
</tr>
<tr>
<td>Crude</td>
</tr>
</tbody>
</table>
Potential Bias

• Selection bias
  – Inappropriate selection of control

• Recall bias
  – Past 5-year? (memory issue)
  – The recall is better among cases than controls because of the presence of the disease
    • Birth defect
      – Mother: What (medicine) did you take during the pregnancy?
Nested Case-control Study

- Both cases and controls are from a known, defined population at risk of disease
  - If you have a cohort of interest
    - is less costly than a cohort study because fewer subjects are required
Nested Case-control Study

Patients with familial adenomatous polyposis

Age 55, female (CRC)
Age 55, female (NO CRC)
Age 67, male (CRC)
Age 67, male (NO CRC)
Age 67, male (NO CRC)
Age 55, female (NO CRC)

Taiwan, X hospital
Case Study
Risk of bladder cancer in diabetic patients treated with rosiglitazone or pioglitazone: a nested case–control study.
Nested Case-control Study


Diabetic patients

Exposed (TZDs)
Non-Exposed

Exposed (TZDs)
Non-Exposed

Bladder cancer “Case”

No bladder cancer “Control”
• **Exposure**
  
  – Use of TZDs is divided into four categories: Current user, recent user, past user and non-user.

Entry → Index

**Past user:** Prescription end date = > 180 days before index date

**Recent user:** Prescription end date = 90-180 days before index date

**Current user:** Prescription end date = 0-90 days before index date
### Nested Case-control Study

*Drug Saf. 2013 Aug;36(8):643-9*

<table>
<thead>
<tr>
<th></th>
<th>Total (n=20472)</th>
<th>Case (n=3412)</th>
<th>Control (n=17060)</th>
<th>Adjusted odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td><strong>Pioglitazone</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-users</td>
<td>19796 (96.7)</td>
<td>3259 (95.5)</td>
<td>16537 (96.9)</td>
<td>1.00 (Reference)</td>
</tr>
<tr>
<td>Current users</td>
<td>262 (1.3)</td>
<td>82 (2.4)</td>
<td>180 (1.1)</td>
<td><strong>2.39 (1.75-3.25)</strong></td>
</tr>
<tr>
<td>Recent users</td>
<td>50 (0.2)</td>
<td>13 (0.4)</td>
<td>37 (0.2)</td>
<td>1.62 (0.79-3.33)</td>
</tr>
<tr>
<td>Past users</td>
<td>364 (1.8)</td>
<td>58 (1.7)</td>
<td>306 (1.8)</td>
<td>1.10 (0.79-1.52)</td>
</tr>
<tr>
<td><strong>Rosiglitazone</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-users</td>
<td>18541 (90.6)</td>
<td>3066 (89.9)</td>
<td>15475 (90.7)</td>
<td>1.00 (Reference)</td>
</tr>
<tr>
<td>Current users</td>
<td>539 (2.6)</td>
<td>154 (4.5)</td>
<td>385 (2.3)</td>
<td><strong>1.89 (1.51-2.38)</strong></td>
</tr>
<tr>
<td>Recent users</td>
<td>121 (0.6)</td>
<td>19 (0.6)</td>
<td>102 (0.6)</td>
<td>0.78 (0.46-1.35)</td>
</tr>
<tr>
<td>Past users</td>
<td>1271 (6.2)</td>
<td>173 (5.1)</td>
<td>1098 (6.4)</td>
<td>0.95 (0.78-1.14)</td>
</tr>
</tbody>
</table>
Thank you very much.
Any Questions?