EPID 765
Pharmacoepidemiology

Lesson 12:
Immortal Time Bias



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## Immortal Time

- First described by Mitch Gail 1972
- Systematic underestimation of RR
  - Not towards the null!
  - Treatment looks better than it actually is
    - E.g., no effect when actually harmful
    - E.g., beneficial when actually no effect
- Term introduced by Samy Suissa 2003
- Alarming number of PE studies affected
  - E.g., COPD, metformin -> CA

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## Immortal Time

- Time during which outcome could not have occurred by design (logic, not chance)
- Often before person initiates treatment
- Subject had to remain event free to be classified as treated (exposed)
- Incorrect assignment of this zero risk untreated pt as treated pt leads to
  - Underestimation of risk I treated
  - Overestimation of risk in untreated

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## Immortal Time: Example I

Heart Transplant Study

- Cohort of potential heart transplant recipients ($t_0$: registry enrollment)
- Exposure: getting transplant
- Outcome: survival after $t_0$
- Result: Longer survival in those actually transplanted
- Causal interpretation?

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## Heart Transplant Study

- Important reason not to receive transplant: †
- Patients who got transplanted:
  - Person-time includes waiting time to transplant
  - pt is zero risk = immortal
  - pt actually un-transplanted instead of transplanted
- Both mortality rates biased
  - Too low in transplanted (immortal person-time)
  - Too high in un-transplanted (missing immortal pt)
- Correct classification: no survival advantage
- Separate issue: confounding by indication!

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## Immortal Time: Example II

Academy award study

- Longer survival in OSCAR winners vs. those nominated (Redelmeier & Sing 2001)
- "Survival" defined as age at death
- Implicit baseline: birth!
- Winners older than those nominated
- Immortal time before OSCAR!
- Proper reanalysis (baseline at OSCAR win or nomination): no difference (Sylvestre et al. 06)

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## Immortal Time in PE

- Time-based cohorts
  - Baseline: calendar date
  - Exposure: defined during follow-up
- Immortal time before first script
- Solution:
  - Time-varying exposure assignment
  - Time before 1st script is unexposed
  - [TS solution: new user design]

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## Immortal Time in PE

- Event-based cohorts
  - Baseline: event date (e.g., cancer dx)
  - Exposure: defined during follow-up
    - Within certain period after event
  - Time between baseline and end of exposure definition period: immortal
    - Chemotherapy vs. no chemotherapy
    - Second script
  - Solutions
    - Time-varying exposure assignment
    - "Landmark" $t_0$ to allow treatment assignment
    - "Treatment regimen", repeated trials analyses

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## Immortal Time in PE

- Exposure-based cohorts
  - Baseline for exposed: script date
    - E.g., first combined LABA + inhaled steroid
  - Baseline for unexposed: arbitrary date
    - E.g., first any bronchodilator
    - And no LABA or steroid **during follow-up**
  - Hierarchical definition of exposure
  - Time before LABA + steroid: immortal
    - Excluded from unexposed pt!
  - Solution: never exclude patients based on future treatments ("clean" cohorts)

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## Immortal Time in PE

- Multiple-event-based cohorts
  - Exposure: several events over time
  - Immortal time if baseline is first event
    - E.g., between first and second script
  - Solution: use last event as baseline
    - Use 2nd script as baseline
- Similar issue:
  - Requiring 2 claims to define outcome

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## Immortal Time in PE

- Event-exposure-based cohorts
  - Baseline exposed: event plus script
  - Definition unexposed: no script during follow-up
  - Anyone starting exposure during follow-up excluded from unexposed group: immortal
  - Solution (same as exposure-based):
    - You shall not exclude unexposed based on exposure during follow-up!

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## Immortal Time Bias

**TABLE 1. Hazard ratios of death associated with antithrombotic drugs using the five different cohort definitions applied to patients with a lung cancer diagnosis, estimated by the Cox proportional hazards model using the biased and correctly classified approaches**

| | No. of subjects | No. of deaths | No. of person-years (immortal time*) | Biased HR† | 95% CI† | Corrected HR | 95% CI |
|---|---|---|---|---|---|---|---|
| Time-based cohort | | | | | | | |
| No ATD† during a 1-year period | 1,749 | 659 | 1,411.2 | 1 | Reference | 1 | Reference |
| ATD during a 1-year period | 146 | 50 | 128.3 (34.4) | 0.83 | 0.63, 1.11 | 1.13 | 0.84, 1.50 |
| Event-based cohort | | | | | | | |
| No ATD during a 90-day period | 7,896 | 5,402 | 4,068.3 | 1 | Reference | 1 | Reference |
| ATD during a 90-day period | 280 | 162 | 189.5 (23.7) | 0.66 | 0.56, 0.77 | 1.02 | 0.85, 1.22 |
| Exposure-based cohort | | | | | | | |
| No ATD | 500 | 352 | 248.6 | 1 | Reference | 1 | Reference |
| ATD exposure | 476 | 260 | 308.1 (316.5) | 0.73 | 0.63, 0.85 | 1.05 | 0.87, 1.28 |
| Multiple-event-based cohort | | | | | | | |
| No ATD | 500 | 357 | 242.5 | 1 | Reference | 1 | Reference |
| ATD exposure | 388 | 188 | 276.3 (291.1) | 0.48 | 0.40, 0.57 | 0.91 | 0.76, 1.10 |
| Event-exposure-based cohort | | | | | | | |
| No ATD | 6,392 | 4,131 | 3,545.0 | 1 | Reference | 1 | Reference |
| ATD exposure on the same day | 174 | 101 | 109.1 | 0.80 | 0.66, 0.98 | 0.95 | 0.83, 1.09 |
| ATD exposure in the follow-up year | 232 | 122 | 172.7 (61.0) | | | | |

* Immortal time either misclassified in the analysis or excluded by design and unaccounted for.
† HR, hazard ratio; CI, confidence interval; ATD, antithrombotic drugs.

Suissa S. Immortal Time Bias in Pharmacoepidemiology. Am J Epidemiol 2008;167:492–499

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**Risk of malignancies in patients with diabetes treated with human insulin or insulin analogues: a cohort study**

*Definition of cohorts* We defined four study groups according to the treatment received: human insulin, aspart, lispro and glargine. Eligible participants were those exposed to only one of these agents during follow-up. Patients who received any concomitant insulin prescriptions were excluded, as were patients who received porcine or bovine insulin.

Cave: likely includes treatment changes during follow-up

Hemkens LG, Grouven U, Bender R, et al. Risk of malignancies in patients with diabetes treated with human insulin or insulin analogues: a cohort study. *Diabetologia*. 2009;52(9):1732-1744.

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## Association of Aspirin Use With Major Bleeding in Patients With and Without Diabetes

period of 60 days of treatment. All those individuals who did not receive aspirin throughout the study period were considered controls, and were assigned an index date corresponding to the same year of the cases.

Former aspirin users, who were those who had prescriptions for aspirin at the beginning of follow-up but had their last prescription of aspirin more than 75 days before an event, were excluded from the analyses.

De Berardis G, Lucisano G, D'Ettorre A, et al. Association of aspirin use with major bleeding in patients with and without diabetes. *JAMA*. 2012;307(21):2286-2294

Lund JL, Stürmer T, Toft-Sørensen H. **Benefits and Risks of Aspirin Use.** *JAMA.* 2012;308(11):1088-1089

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## Summary Immortal Time Bias

- Definition of cohorts at $t_0$ (exposed, unexposed) based on future information
- PE studies vulnerable ("crystal ball")
- Can easily be avoided:
  - Define cohorts as of baseline (think prospective!)
  - Start follow-up at cohort definition date (not before)
  - Never exclude from cohort based on follow-up data
  - "Safest" design: active comparator new user (ACNU)
- You still need to account for treatment changes after $t_0$ (e.g., IT, AT)

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