# Competing risks

David McAllister

3rd March 2020

# Learning outcomes

- Understand relationship between rates and risks
- Understand concept of competing risks
- Get a feel for the impact of competing risks on outcomes and treatment effects

# Overview

- Spend some time on rates and risks
- Proceed to competing risks
- Discussion, equations and interactive plots (via a Shiny app)

# Why there are some equations

- Only if you find these helpful
- Tried hard, but I am not a statistician - some errors possible, corrections are welcome

# Scenarios where we might find competing risks

# Cancer

- Trial of a cancer treatment
  - Death from relapse
  - Death from non-relapse related causes

# Cardiovascular

- Trial of a treatment for myocardial infarction (heart attack)
    - Cardiovascular death
    - Bleeding death
    - Non-cardiovascular non bleeding death

# Pregnancy

- Long-term outcomes following chemotherapy - childbirth
  - Childbirth
  - Relapse

# Rates and risks

# Rates and risks

- Rates - events per person-time
    - Single event per person - incidence rate
    - Otherwise - event rates
- Risk - % or proportion of people experiencing an event

## Synonyms

- Rates - incidence density, force of mortality, force of morbidity, hazard rate
- Risk - cumulative incidence

## Uses

- Rates - understanding causation, modelling
- Risks - prediction, magnitude, public health/policy, clinical decision-making

# Incidence rate and hazard rate

- Hazard rate
  - mathematics/statistics
  - instantaneous risk
  - Conditional probability
- Incidence rate
  - epidemiology
  - empirical examples
  - Number at risk

Equivalent concepts

# In the absence of competing risks

# 1 to 1 relationship. Constant rates

$$Risk = 1 - e^{-\lambda t}$$

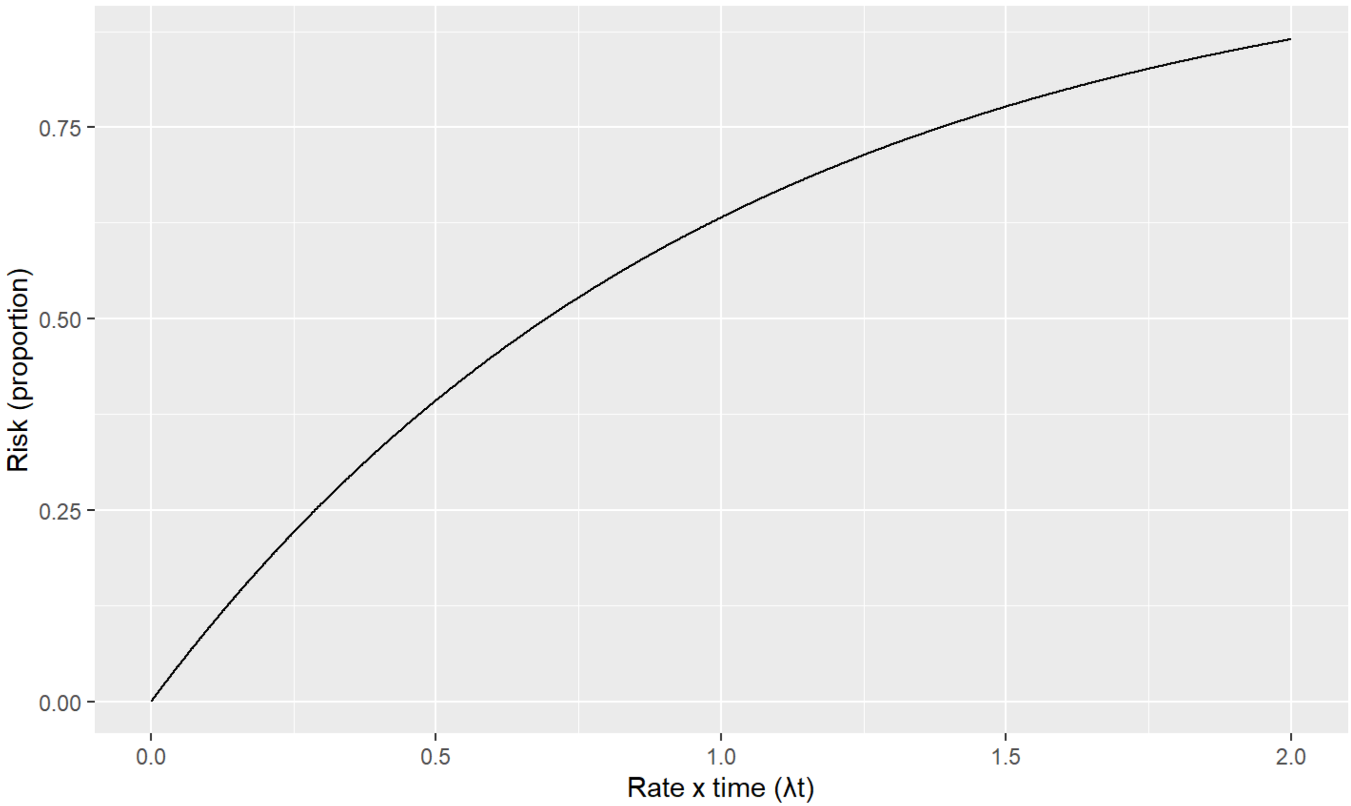
$$\frac{1}{e^{\lambda t}}, \frac{1}{2.72^{\lambda t}}, \frac{1}{2.72^{1}}, \frac{1}{2.72^{2}}, \frac{1}{2.72^{3}}, \frac{1}{2.72^{4}}$$

$$\frac{1}{e^{\lambda t}}, \frac{1}{2.72^{\lambda t}}, \frac{1}{2.7}, \frac{1}{7.4}, \frac{1}{20.12}, \frac{1}{54.74}$$

$$\frac{1}{e^{\lambda t}}, \frac{1}{2.72^{\lambda t}}, 0.4, 0.14, 0.05, 0.02$$

100 events per 1,000 person years, 0.1 events per person-year; 10 years; $\lambda t = 1$

# Risk and rates



# Risk of event at different follow-up periods

| rate | 1 year(s) | 2 year(s) | 3 year(s) | 4 year(s) |
|---|---|---|---|---|
| **0.1** | 0.10 | 0.18 | 0.26 | 0.33 |
| **0.2** | 0.18 | 0.33 | 0.45 | 0.55 |
| **0.3** | 0.26 | 0.45 | 0.59 | 0.70 |
| **0.4** | 0.33 | 0.55 | 0.70 | 0.80 |

# Time-varying rates

- Rates varying continuously

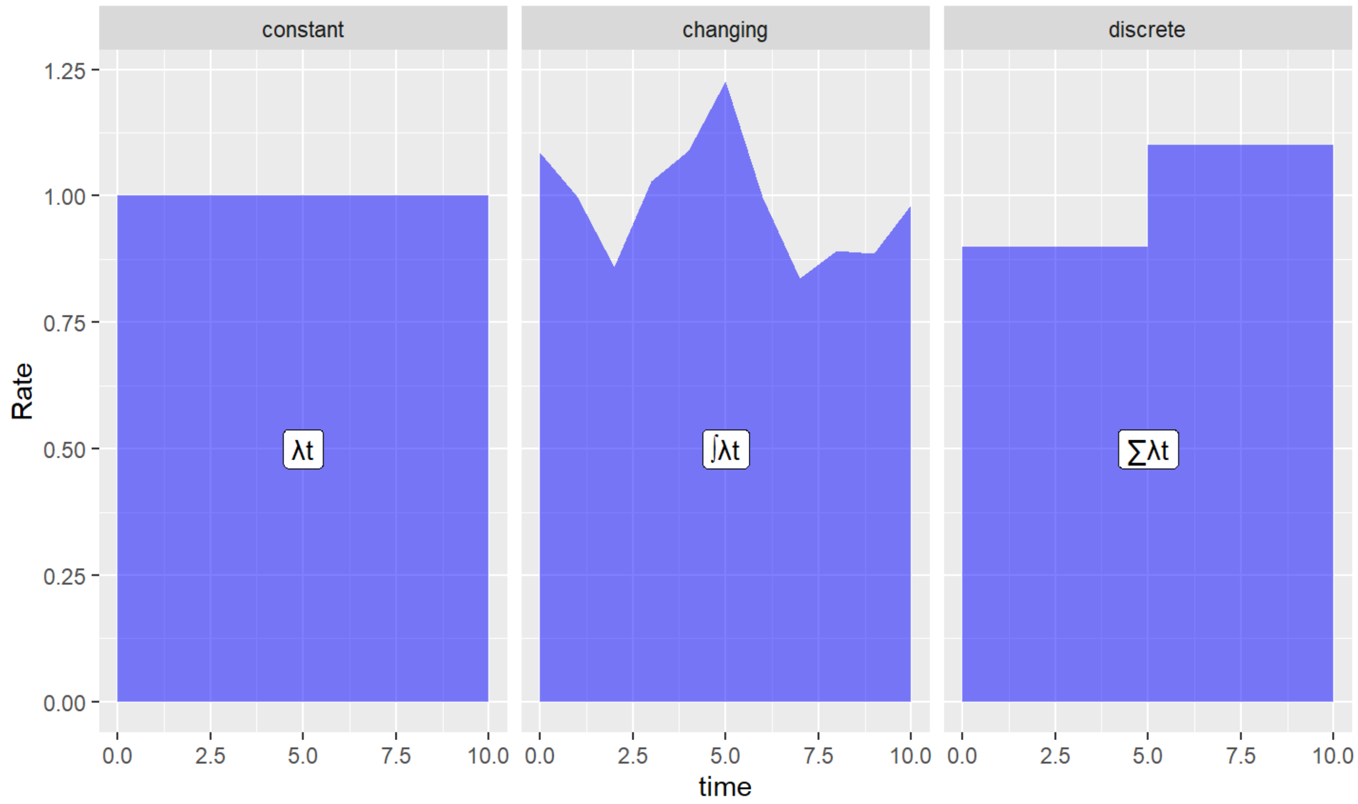
$$Risk = 1 - e^{-\int(\lambda_t dt)}$$

- Rates constant within discrete time periods

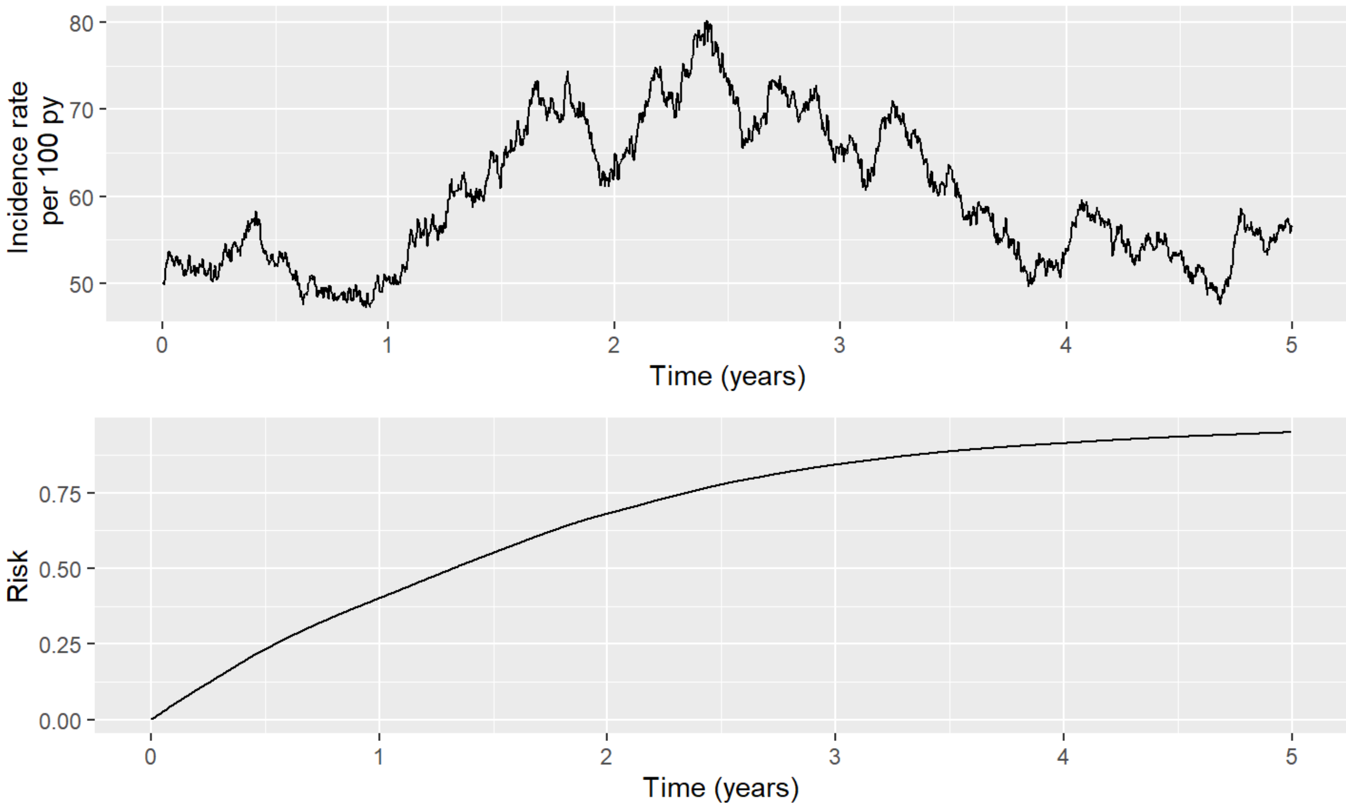
```
- 0-3 months 2.5 per 1000 person years
- 4-12 months 1.0 per 1000 person years
```

$$Risk = 1 - e^{-\sum(\lambda_t t_t)}$$

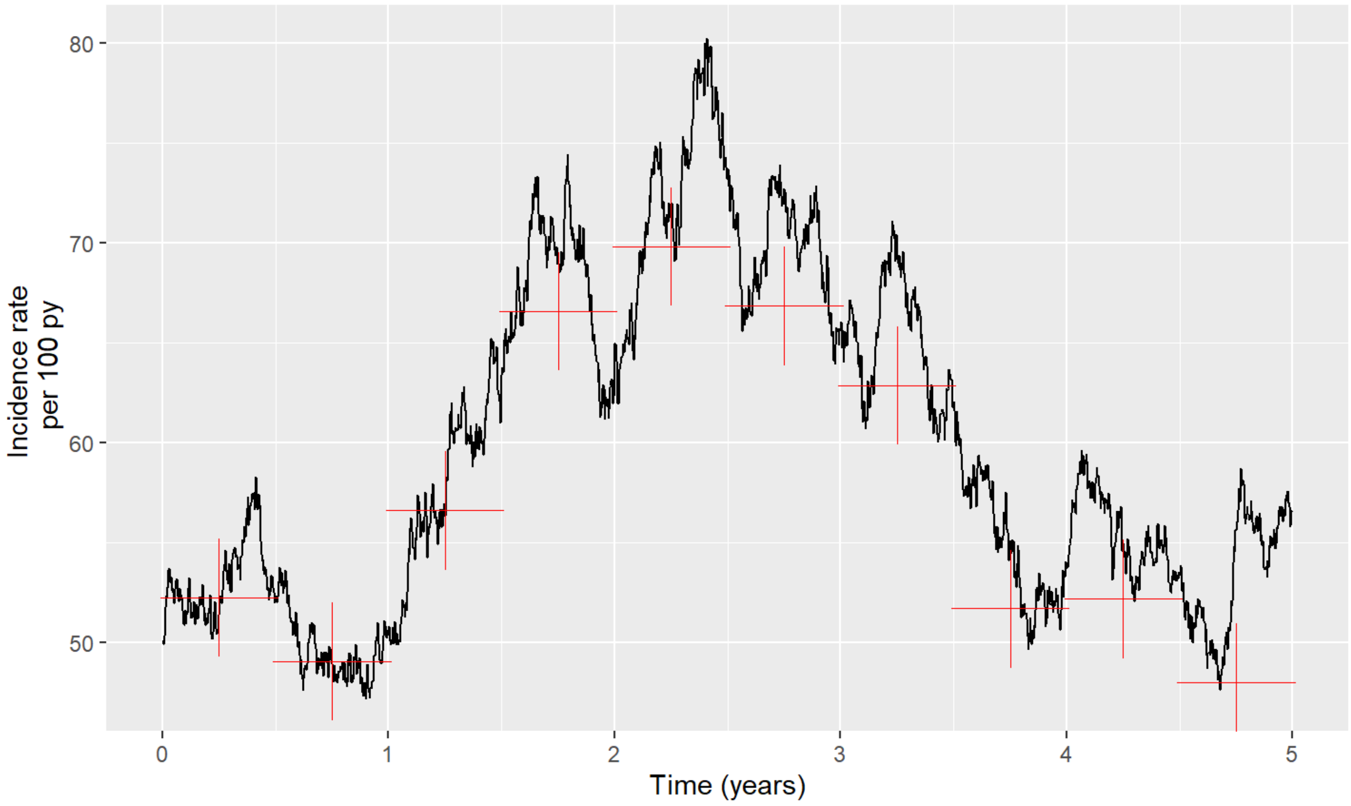
# Area under the curve



# Plot of varying rates and risk



# Example using incidence rate at discrete time periods



# Table for incidence rate at different time periods

| time_period | N_at_risk | events | person_time | rate |
|---|---|---|---|---|
| 1 | 1000 | 231 | 442 | 52 |
| 2 | 769 | 168 | 342 | 49 |
| 3 | 601 | 149 | 263 | 57 |
| 4 | 452 | 129 | 194 | 67 |
| 5 | 323 | 96 | 138 | 70 |
| 6 | 227 | 65 | 97 | 67 |
| 7 | 162 | 44 | 70 | 63 |
| 8 | 118 | 27 | 52 | 52 |
| 9 | 91 | 21 | 40 | 52 |

# Table for incidence rate at different time periods, continued

| time_period | N_at_risk | events | person_time | rate | Risk |
|---|---|---|---|---|---|
| 1 | 1000 | 231 | 442 | 52 | 23.1% |
| 2 | 769 | 168 | 342 | 49 | 39.9% |
| 3 | 601 | 149 | 263 | 57 | 54.8% |
| 4 | 452 | 129 | 194 | 67 | 67.7% |
| 5 | 323 | 96 | 138 | 70 | 77.3% |
| 6 | 227 | 65 | 97 | 67 | 83.8% |
| 7 | 162 | 44 | 70 | 63 | 88.2% |
| 8 | 118 | 27 | 52 | 52 | 90.9% |

# What happens to risks and effect estimates for different rates

https://ihwph-hehta.shinyapps.io/competing_risks/

Set “Rate of target event per 100 person-years:” to 10, and the “Rate ratio for effect of treatment on target event:” to 0.78. Leave the other settings as they are. Examine the effect of increasing the “Rate of target event per 100 person-years:”. What impact do these changes have on the:-

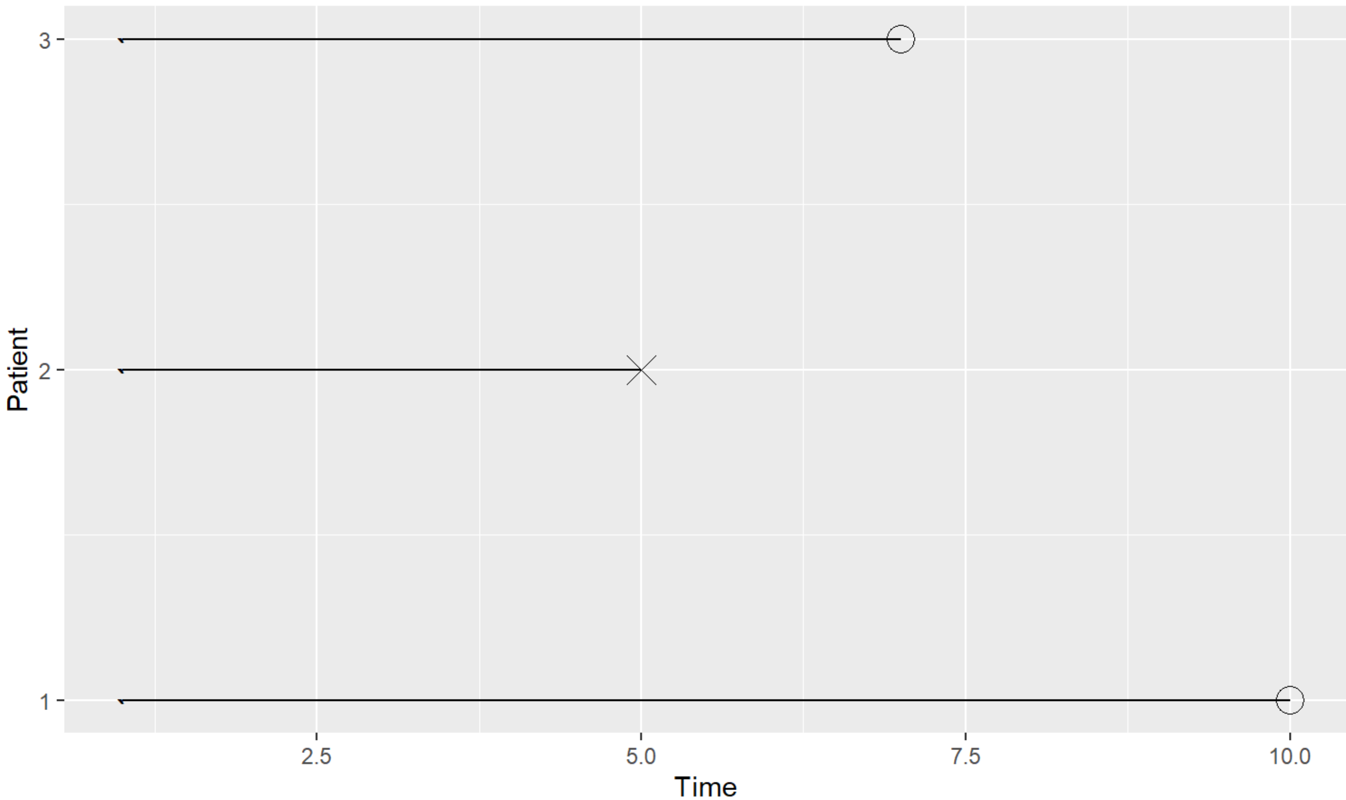
- Risk of target events
- Odds ratio
- Relative risk
- Absolute risk reduction

What happens to the relationship between the rate ratio and risk ratio as you increase the target event rate?

What implications does this have for interpreting hazard ratios?


Censoring

# Example of censoring



# Calculating cumulative incidence (risk)

- Statistical methods to cope with censoring
  - Kaplan-Meier

$$S_t = \prod_{i:t_i \leq t} (1 - \frac{d_i}{n_i})$$

  - Nelson-Aalen

$$\tilde{H}_{(t)} = \sum_{i:t_i \leq t} (\frac{d_i}{n_i})$$

with $d_i$ the number of events at $t_i$ and $n_i$ the total individuals at risk at $t_i$

- Nelson Aalen - $risk = 1 - e^{-H_{(t)}}$

# Worked example

see Excel spreadsheet “competing_risk_calculation.xlsx”

# Summary: without competing risks

- Rates lie between 0 and infinity
- Risks lie between zero and 1
- Risks can be estimated from rates (and vice versa)
- doubling rate and doubling time have the same effect on the risk
- The relationship between rates and risk is non-linear
- The relationship between time and risk is non-linear
- If the rate ratio is constant over time, the risk ratio will attenuate over time
- Rate ratios are **NOT** risk ratios

# Competing risks

# What happens to risk of event if there is a competing event

https://ihwph-hehta.shinyapps.io/competing_risks/

Set “Rate of target event per 100 person-years:” to 10 and “Rate ratio for effect of treatment on target event:” to 0.78. Leaving the other settings as they are, gradually increase the event rate for competing events. NOTE THAT IN THIS SCENARIO THE TREATMENT IS NOT RELATED TO THE COMPETING EVENT. What impact do these changes have on the:-

- Risk of target events
- Odds ratio
- Relative risk
- Absolute risk reduction

Repeat the exercise varying the target event rate too.

# Estimating risk if there are competing events

# If no censoring

| Relapse | Death | Either | Relapse_Cum | Death_Cum | Either_Cum | Relapse_Risk | Death_Risk | Either_Risk |
|---|---|---|---|---|---|---|---|---|
| **17** | 10 | 27 | 17 | 10 | 27 | 0.017 | 0.010 | 0.027 |
| **19** | 7 | 26 | 36 | 17 | 53 | 0.036 | 0.017 | 0.053 |
| **24** | 8 | 32 | 60 | 25 | 85 | 0.060 | 0.025 | 0.085 |
| **11** | 10 | 21 | 71 | 35 | 106 | 0.071 | 0.035 | 0.106 |
| **20** | 11 | 31 | 91 | 46 | 137 | 0.091 | 0.046 | 0.137 |
| **18** | 10 | 28 | 109 | 56 | 165 | 0.109 | 0.056 | 0.165 |
| **21** | 11 | 32 | 130 | 67 | 197 | 0.130 | 0.067 | 0.197 |
| **27** | 7 | 34 | 157 | 74 | 231 | 0.157 | 0.074 | 0.231 |

# What if there is censoring

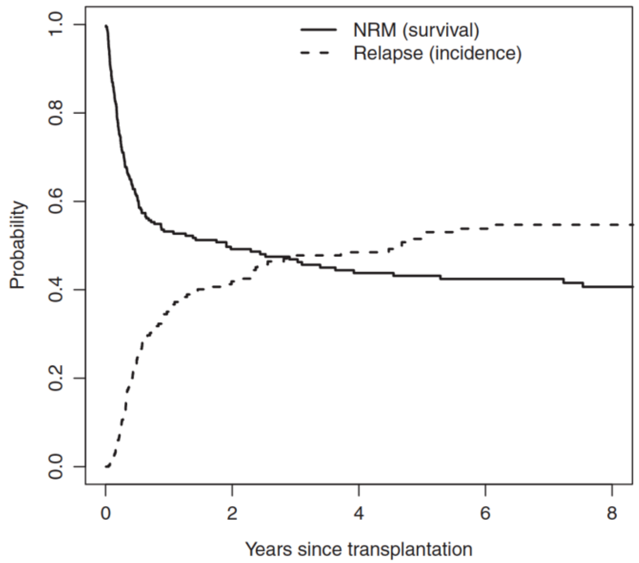



**Figure 2** Naïve Kaplan–Meier estimates of relapse and NRM, shown as incidence and survival curves, respectively

# Why

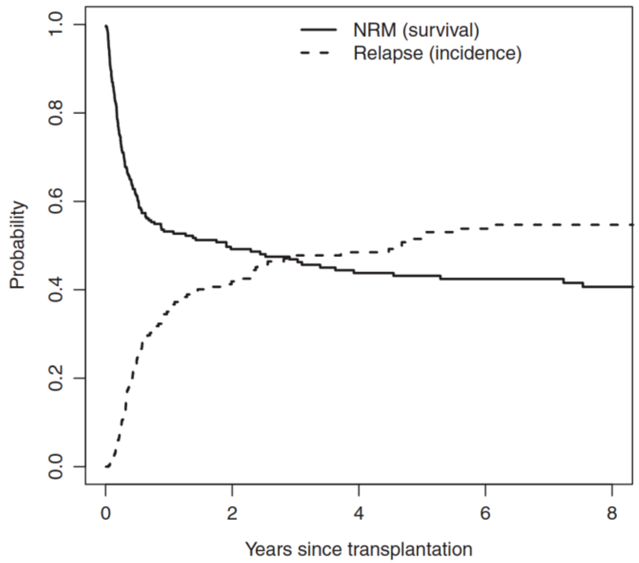



**Figure 2** Naïve Kaplan–Meier estimates of relapse and NRM, shown as incidence and survival curves, respectively

- Dashed line shows KM estimate treating non-relapse death as censoring
- Solid line shows KM estimate treating non-relapse death as censoring
- Double counting censoring if sum these

# Why is it different from censoring due to loss to follow-up

- We assume that such censoring is non-informative
- KM estimates the survival if those who died of a competing risk had had same underlying rates as those who did not die from a competing risk

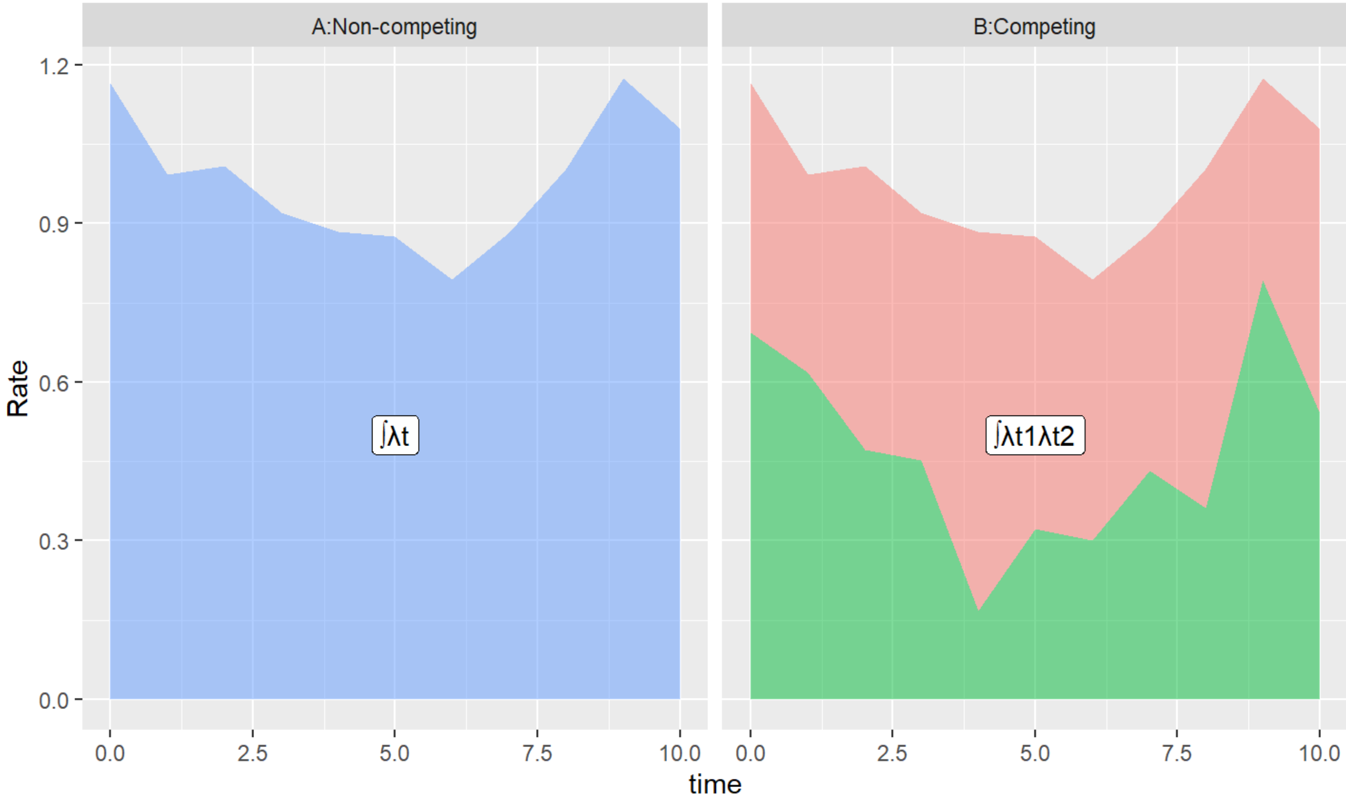
# Relationship between rates and risk

$$Risk_1(t) = \int_0^t S(t)\lambda_1(t)dt$$

$$S(t) = exp^{-\int_0^t \lambda_1(t)+\lambda_2(t)dt}$$

- At any time, survival plus Risk$_1$ plus Risk$_2$ always equals 1.
- Work through an example in excel

# Area under the curve



# Impact of this graphically

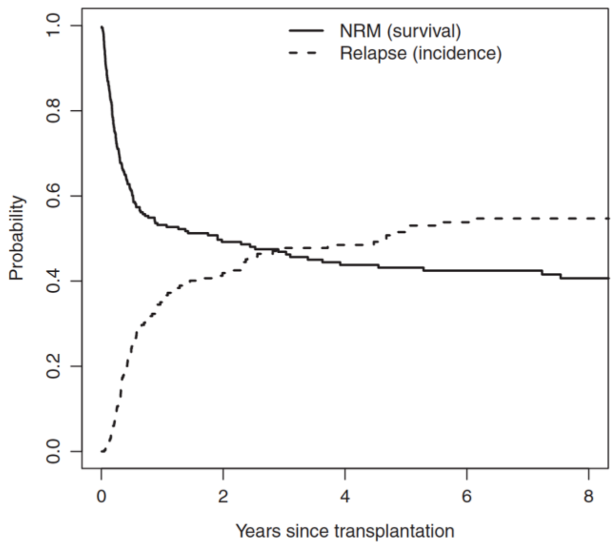



**Figure 2** Naïve Kaplan–Meier estimates of relapse and NRM, shown as incidence and survival curves, respectively

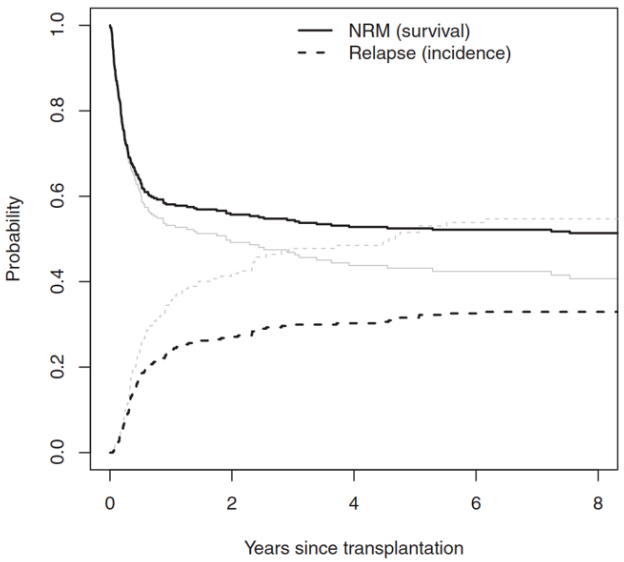



**Figure 3** Cumulative incidence estimates of relapse and NRM, shown as incidence and survival curves, respectively; naïve Kaplan–Meier estimates are shown in grey

# Cause-specific hazard ratios

- Can also use Cox regression to estimate the cause-specific hazard
- Same model, different interpretation
- Cannot directly translate to risk
- Instead combine the cause-specific hazards using the equation in previous slide to estimate the risk of each outcome
    - R packages such as mstate and msm allow combination of different models
    - Rely on simulation or bootstrapping to get 95 % confidence intervals

# Modelling cumulative incidence directly

- Can also estimate the cumulative incidence directly using Fine and Gray model
- Produces regression coefficients for effect of a predictor on the sub-distributional hazard rate
- Unlike the hazard rate from a Cox model this has no natural interpretation

# Direction of effect on cause-specific hazard rates

| Prognostic score | Relapse Cox | Death Cox |
| --- | --- | --- |
| **Very low** | 1 | 1 |
| **Low** | 1.01 (0.81-1.27) | 1.57 (1.25-1.97) |
| **Medium** | 1.28 (1.03-1.59) | 2.01 (1.61-2.52) |
| **High** | 1.57 (1.25-1.99) | 2.68 (2.12-3.37) |
| **Very high** | 2.67 (2.06-3.47) | 3.98 (3.09-5.13) |

# Direction of effect on cause-specific hazard rates and risk

| Prognostic score | Relapse Cox | Relapse Fine and Gray | Death Cox | Death Fine and Gray |
|---|---|---|---|---|
| **Very low** | 1 | 1 | 1 | 1 |
| **Low** | 1.01 (0.81-1.27) | 0.93 (0.75-1.16) | 1.57 (1.25-1.97) | 1.56 (1.24-1.96) |
| **Medium** | 1.28 (1.03-1.59) | 1.07 (0.87-1.33) | 2.01 (1.61-2.52) | 1.94 (1.55-2.42) |
| **High** | 1.57 (1.25-1.99) | 1.17 (0.93-1.48) | 2.68 (2.12-3.37) | 2.48 (1.96-3.12) |
| **Very high** | 2.67 (2.06-3.47) | 1.55 (1.19-2.02) | 3.98 (3.09-5.13) | 3.27 (2.5; .1.22) |

# What happens to risks and effect estimates if the treatment also affects the competing event

https://ihwph-hehta.shinyapps.io/competing_risks/

Set “Rate of target event per 100 person-years:” to 10, “Rate ratio for effect of treatment on target event:” to 0.78, “Rate of competing event per 100 person-years:” to 0.10 and “Rate ratio for effect of treatment on competing event:” to 1. Examine the effect of changing the “Rate ratio for effect of treatment on competing event:”. What impact do these changes have on the:-

- Risk of target events
- Odds ratio
- Relative risk
- Absolute risk reduction

Specifically, what happens to the effect of the treatment on the target event when the treatment also increases the competing risk. Do you think that this is generally a good thing?

# Additional references

see
https://docs.google.com/document/d/1eqVzqYM6ozlrt5I_4aqqe6OIR6OV6EJ8G6Tg1lBa
usp=sharing

You will also find the link to this on the front-page of
https://github.com/dmcalli2/Advanced_epidemiology_course