# Landmarks in the analysis of Competing risks

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# Definition

Competing risks type of event=

***the event whose occurrence either precludes the occurrence of another event under investigation* or *fundamentally alters the probability of occurrence of this other event*.**

Gooley, TA; Leisenring, W; Crowley, J; Storer, BE, "Estimation of failure probabilities in the presence of competing risks: new representations of old estimators" *Statistics in Medicine* 1999 pp. 695-706

# Definition, Examples

*the event whose occurrence either precludes the occurrence of another event under investigation*

- **Death: due to disease (MI) and due to other causes**
- **First relapse: local relapse and distant relapse**

*fundamentally alters the probability of occurrence of this other event*

# How to analyse?
# Ignore CR

**Censor CR event**
**Apply usual survival techniques**

- Event of interest: Death to MI →**1**
- CR event: Death of other causes → **0**
- Alive → **0**

**Anything wrong with this ?**

Kaplan-Meier

Log-rank test

Cox proportional hazards model

# Censoring the competing risk event (Applying KM, Cox model)

- The KM estimates are not probabilities
- The estimates for (1-KM) are larger than the probability of event

Because:

- It is assumed that those with CR will eventually experience the event if followed long enough.

# How to analyse?
# NOT ignoring CR

**Identify CR event**
**Apply proper techniques.**

- Event of interest: Death to MI →**1**
- CR event: Death of other causes → **2**
- Alive → **0**

Estimate cumulative incidence function (CIF)

Gray test (Modified log-rank test)

Fine and Gray model (Modified Cox PH)

# Estimation of the distribution function (no CR)
# Probability of event

$t_1 < t_2 < \ldots < t_r$ Ordered time points of the events

$d_j$ Number of events of interest at time $t_j$

$n_j$ Number at risk just before $t_j$

$$\hat{S}(t) = \prod_{t_j \le t} \frac{n_j - d_j}{n_j}$$ Kaplan-Meier, product-limit estimator

$$\hat{F}(t) = 1 - \hat{S}(t) = \sum_{all\ j, t_j \le t} \frac{d_j}{n_j} \hat{S}(t_{j-1})$$ Estimates the probability of event

Consider that $d_j$ are not all the same. Some are of interest ($d_{ev\ j}$) and some are not of interest or competing risks ($d_{cr\ j}$). Thus at any point in time $d_j = d_{ev\ j} + d_{cr\ j}$

$$F_{all\ events}(t) = \sum_{all\ j\ t_j \le t} \frac{d_j}{n_j} \hat{S}(t_{j-1}) = \sum_{all\ j\ t_j \le t} \frac{d_{ev\ j} + d_{cr\ j}}{n_j} \hat{S}(t_{j-1}) =$$

$$= \sum_{all\ j\ t_j \le t} \frac{d_{ev\ j}}{n_j} \hat{S}(t_{j-1}) + \sum_{all\ j\ t_j \le t} \frac{d_{cr\ j}}{n_j} \hat{S}(t_{j-1}) = F_{ev}(t) + F_{cr}(t)$$

Probability of all events can be partitioned into probability for events of interest and probability for competing risks.

Kalbfleisch, JD; Prentice, RL, *The Statistical Analysis of Failure Time Data*, Wiley, New York, (1980)

# Estimation of the subdistribution (CR) Probability of the event of interest

$t_1 < t_2 < \ldots < t_r$ Ordered time points of **all types** of events

$d_{ev\ j}$ Number of events of interest at time $t_j$

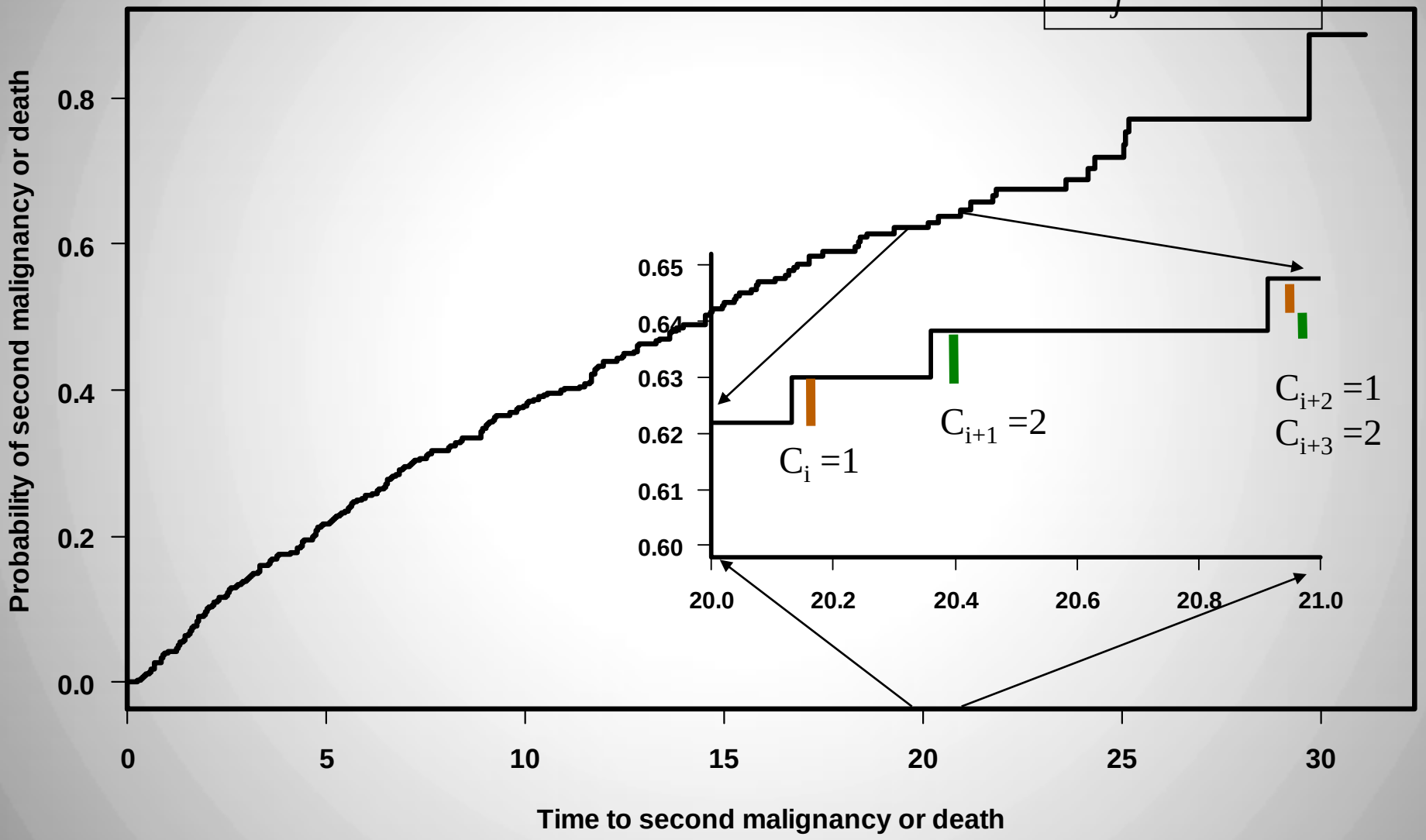
$n_j$ Number at risk just before $t_j$

$S(t_j)$ Probability of event free at time $t_j$

$$\hat{F}_{ev}(t) = \sum_{all\ j, t_j \le t} \frac{d_{ev\ j}}{n_j} \hat{S}(t_{j-1})$$

Kalbfleisch, JD; Prentice, RL, *The Statistical Analysis of Failure Time Data*, Wiley, New York, (1980)

$$\frac{d_{ev\,j}}{n_j}\hat{S}(t_{j-1})$$



# Cox proportional hazards model (no CR)

$$h(t \mid x) = h_0(t)\exp(\beta x)$$

$$PL(\beta) = \prod_{j=1}^{r}\left(\frac{\exp(\beta x_j)}{\sum_{i \in R_j}\exp(\beta x_i)}\right)$$

$$R_j = \{i; t_i \geq t_j\}$$

$r$ = number of events

$x$ = the covariate

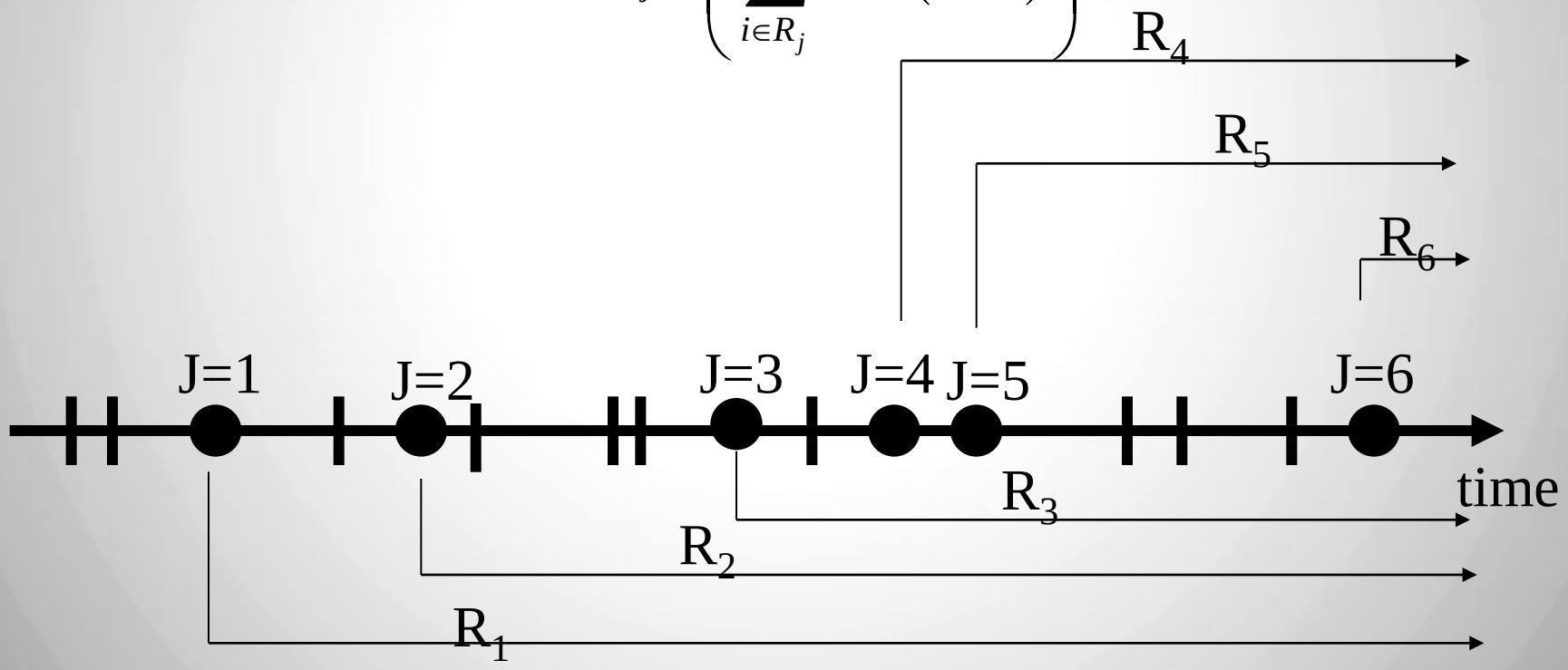
$R_j$ = the risk set at time $t_j$

$$\exp(\beta) = hazard\ ratio = HR$$

Fold increase of the hazard due to one unit increase of the covariate x

# Cox proportional hazards model (no CR)

$$PL(\beta) = \prod_{j=1}^{r} \left( \frac{\exp\left(\beta x_j\right)}{\sum_{i \in R_j} \exp\left(\beta x_i\right)} \right)$$



# Fine and Gray - modelling the hazard of the subdistribution

$$\gamma(t \mid x) = \gamma_0(t)\exp(\beta x)$$

$$PL(\beta) = \prod_{j=1}^{r}\left(\frac{\exp(\beta x_j)}{\sum_{i \in R_j} w_{ji}\exp(\beta x_i)}\right) \qquad w_{ji} = \frac{\hat{G}(t_j)}{\hat{G}(\min(t_j, t_i))}$$

$$R_j(t) = \{i; T_i \geq t \quad or \quad T_i \leq t \text{ and the subject had a CR event}\}$$

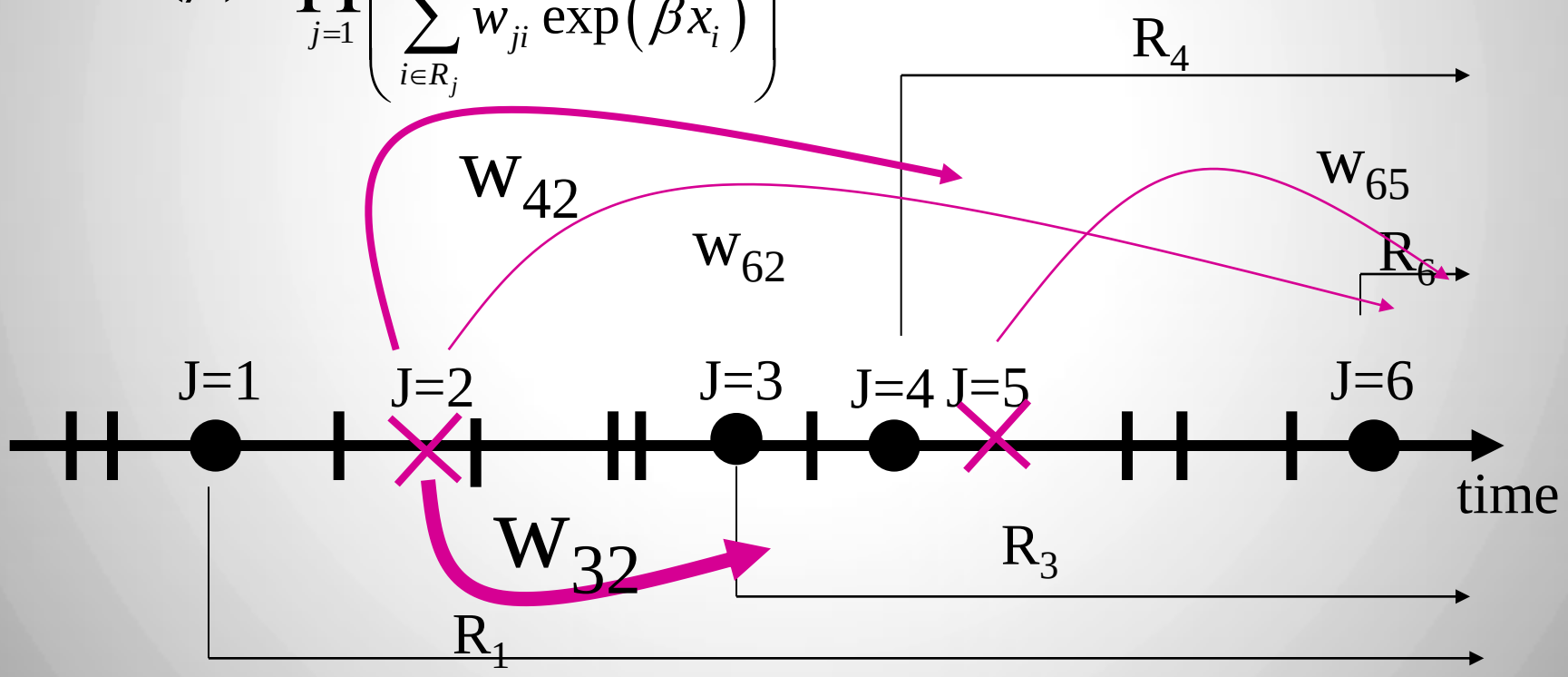
$$\hat{G}(t_j) = probability\ of\ censoring$$

Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk . **JASA** 94 (446): 496-509 JUN 1999

# Fine and Gray - modelling the hazard of the subdistribution

$$PL(\beta) = \prod_{j=1}^{r} \left( \frac{\exp(\beta x_j)}{\sum_{i \in R_j} w_{ji} \exp(\beta x_i)} \right)^{\delta_j}$$

**$w_{32} > w_{42} > w_{62}$**



# A look of the 2 approaches: censoring the CR and accounting for CR

| | Censoring the CR | Accounting for CR |
|---|---|---|
| Estimation | 1. 1-KM is not a probability<br>2. 1-KM > probability of event | CIF estimates the probability of event |
| Modelling | 1. If the 2 types of events are INDEPENDENT it can be interpreted as effect in the absence of CR<br>2. I the INDEPENDENCE does not hold, it is not interpretable. | Models the effect on the observed probabilities. |

# How to analyse?

Package *cmprsk* in R:

- Estimate the probability of event (*cuminc*)
- Apply a modified test of the logrank test introduces by Gray (*cuminc*)
- Plot the probabilities (*plot.cuminc*)
- Modelling with the posibility of tome varying coefficients (*crr*)
- Check the proportionality of subdistribution hazards ($ res within *crr*)
- Plot the predicted probabilities (*plot.predict.crr*)

# For the SAS lovers

- Use mstate package in R to create a dataset which has the weights incorporated
- In SAS merge this with the rest of covariates
- Use PHREG to model the data
  - Patient id as cluster
  - weight.cens as weights
  - Use Tstart and Tstop and (status ==1) as time and censor variable

# Example:

| ptnum | time | cens |
|---|---|---|
| P1 | 1 | 0 |
| P2 | 2 | 1 |
| P3 | 3 | 1 |
| P4 | 4 | 0 |
| **P5** | **5** | **2** |

a=crprep(time,cens,data=d1,id='ptnum')

| ptnum | time | cens | | ptnum | time | cens | | ptnum | time | cens |
|---|---|---|---|---|---|---|---|---|---|---|
| P2 | 2 | 1 | | P13 | 13 | 1 | | P33 | 33 | 1 |
| P3 | 3 | 1 | | P16 | 16 | 1 | | P34 | 34 | 1 |
| P8 | 8 | 1 | | P21 | 21 | 1 | | P35 | 35 | 1 |
| P10 | 10 | 1 | | P23 | 23 | 1 | | P36 | 36 | 1 |
| P11 | 11 | 1 | | P26 | 26 | 1 | | P37 | 37 | 1 |

| id | Tstart | Tstop | status | weight.cens | count | failcode |
|---|---|---|---|---|---|---|
| P1 | 0 | 1 | 0 | 1 | 1 | 1 |
| P2 | 0 | 2 | 1 | 1 | 1 | 1 |
| P3 | 0 | 3 | 1 | 1 | 1 | 1 |
| P4 | 0 | 4 | 0 | 1 | 1 | 1 |
| P5 | 0 | 5 | 2 | 1 | 1 | 1 |
| P5 | 5 | 8 | 2 | 0.9948 | 2 | 1 |
| P5 | 8 | 11 | 2 | 0.9897 | 3 | 1 |
| P5 | 11 | 13 | 2 | 0.9844 | 4 | 1 |
| P5 | 13 | 16 | 2 | 0.9739 | 5 | 1 |
| P5 | 16 | 21 | 2 | 0.9579 | 6 | 1 |
| P5 | 21 | 23 | 2 | 0.9526 | 7 | 1 |
| P5 | 23 | 26 | 2 | 0.9418 | 8 | 1 |
| P5 | 26 | 37 | 2 | 0.9147 | 9 | 1 |

# Sample size calculation

- α, Type I error = probability to find a significance when none exists
- β, Type II error = probability of not finding an existing difference
- power=1- β , probability to detect a specific effect

# Sample size calculation (no CR)

$$\sqrt{n_{ev}} = \frac{(z_{1-\alpha/2} + z_{1-\beta})}{\sigma \ln(HR)}$$

$$P_{ev} = 1 - \frac{e^{-\lambda f} - e^{-\lambda(f+a)}}{\lambda a}$$

$$N = \frac{n_{ev}}{P_{ev}}$$

HR = hazard ratio to be detected

σ = standard deviation of the covariate

$z_{1-\alpha/2}$ = quantile of the standard normal

a = accrual time

f = follow-up time

λ = the hazard rate for the overall

**Assumption:** Exponential distribution

# Sample size calculation (CR)

$$\sqrt{n_{ev}} = \frac{(z_{1-\alpha/2} + z_{1-\beta})}{\sigma \ln(HR)}$$

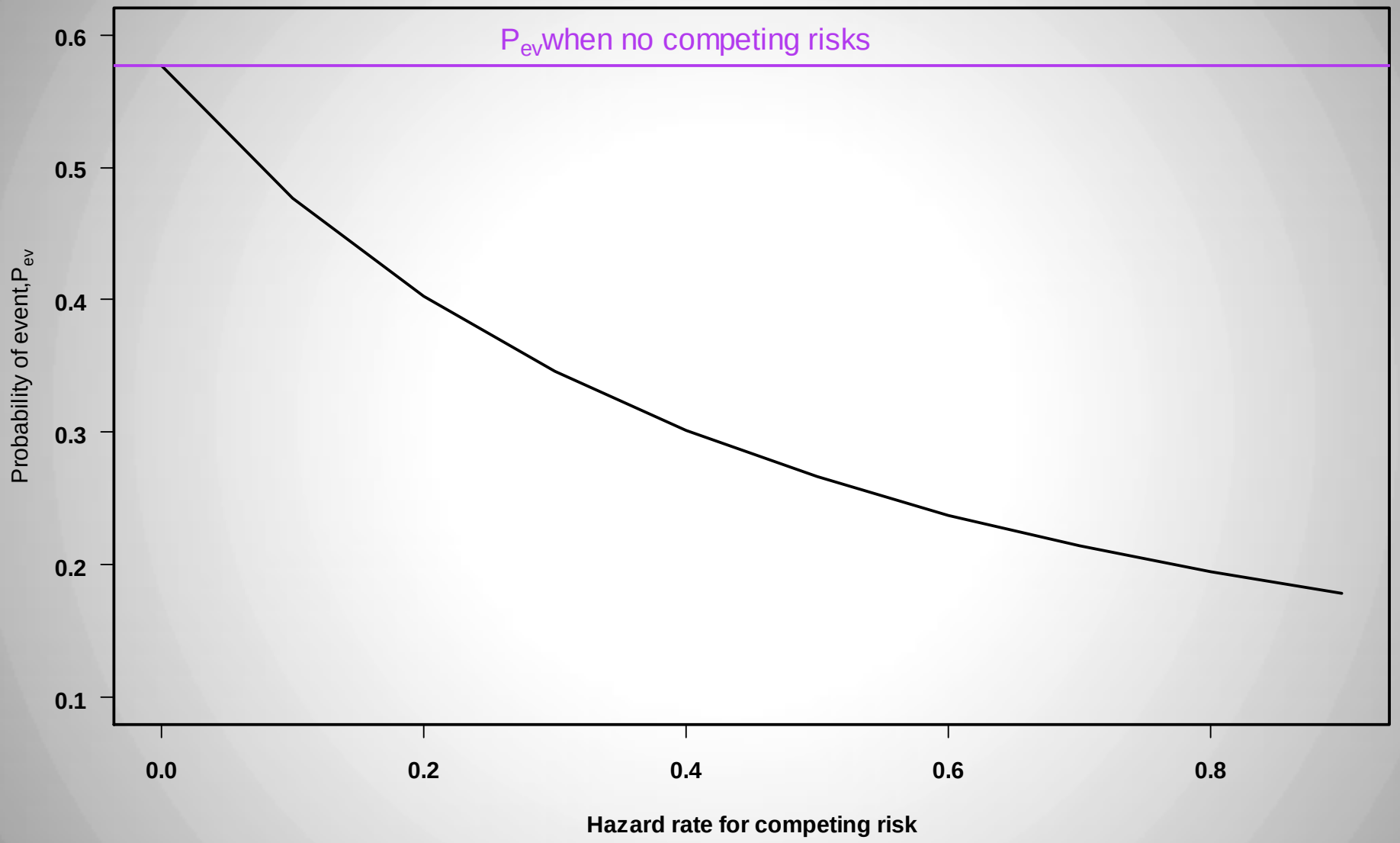
$$P_{ev} = \frac{\lambda_{ev}}{\lambda_{ev} + \lambda_{cr}} \times \left(1 - \frac{e^{-(\lambda_{ev}+\lambda_{cr})\times f} - e^{-(\lambda_{ev}+\lambda_{cr})\times(f+a)}}{(\lambda_{ev} + \lambda_{cr}) \times a}\right)$$

$$N = \frac{n_{ev}}{P_{ev}}$$

$$P_{ev} = 1 - \frac{e^{-\lambda_{ev} f} - e^{-\lambda_{ev}(f+a)}}{\lambda_{ev}\, a}$$

**Assumption:** Exponential distribution, independence

# Decrease of $P_{ev}$ as $\lambda_{cr}$ increases



# A very simple power calculation

If we know the number of events in the data set or the crude rate of events.

A randomized study accrued between 1992-2000. During the study, tumour tissue was collected and kept for future use.
Advantages:

- Uniform group of patients
- The allocation of treatment is based on randomization not on patient characteristics

Of interest is whether a specific marker (say expression of HIF1α gene) is prognostic for local control.

A genetic signature was developed for a group of patients with lung cancer. The treatment is fairly uniform for this disease.
It is desirable to validate the genetic signature.
Then, with similar follow-up, the Pev will be similar.

# A very simple power calculation

If we know the number of events in data set or the crude rate of events.

$$\sqrt{n_{ev}} = \frac{(z_{1-\alpha/2} + z_{1-\beta})}{\sigma \ln(HR)}$$

$$P_{ev} = \frac{n_{ev}}{N}$$

Essential to use the correct $P_{ev}$, crude rate of the events of interest.

# Sample size calculation (CR)

$$\sqrt{n_{ev}} = \frac{(z_{1-\alpha/2} + z_{1-\beta})}{\sigma \ln(HR)}$$

$$P_{ev} = \frac{\lambda_{ev}}{\lambda_{ev} + \lambda_{cr}} \times \left(1 - \frac{e^{-(\lambda_{ev}+\lambda_{cr})\times f} - e^{-(\lambda_{ev}+\lambda_{cr})\times(f+a)}}{(\lambda_{ev} + \lambda_{cr}) \times a}\right)$$

$$N = \frac{n_{ev}}{P_{ev}}$$

$$P_{ev} = 1 - \frac{e^{-\lambda_{ev} f} - e^{-\lambda_{ev}(f+a)}}{\lambda_{ev}\, a}$$

**Assumption:** Exponential distribution, independence

# Calculating the probability of the event of interest during the study period

The KM ($\hat{S}$) estimates for the event of interest and competing risks at a time point.

$$\lambda_{ev} = -\frac{\log\left(\hat{S}_{ev}\left(t_0\right)\right)}{t_0} \qquad \lambda_{cr} = -\frac{\log\left(\hat{S}_{cr}\left(t_0\right)\right)}{t_0}$$

# Calculating the probability of the event of interest during the study period

The CIF ($\hat{F}$) estimates for the event of interest and competing risks at a time point.

$$\lambda_{ev} = \hat{F}_{ev}\left(t_0\right) \times \frac{-\log\left(\hat{S}\left(t_0\right)\right)}{t_0\left(1-\hat{S}\left(t_0\right)\right)}$$

$$\hat{S}\left(t_0\right) = 1 - \hat{F}_{ev}\left(t_0\right) - \hat{F}_{cr}\left(t_0\right)$$

$$\lambda_{cr} = \hat{F}_{cr}\left(t_0\right) \times \frac{-\log\left(\hat{S}\left(t_0\right)\right)}{t_0\left(1-\hat{S}\left(t_0\right)\right)}$$

# Conclusions

- CIF for estimation of probability of event
- Modelling using Cox PH or F & G model. Each has its own interpretation.
- The interpretation of Cox PH is difficult when independence cannot be assumed.
- Proper power calculation needs to consider the competing risks regardless of which model is planned to be used.

# References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