# Statistical Practice in Epidemiology 2018

## Survival analysis with competing risks

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# Points to be covered

1. Survival or time to event data & censoring.
2. Competing risks: event-specific cumulative incidences & hazards.
3. Kaplan–Meier and Aalen–Johansen estimators.
4. Regression modelling of hazards: Cox model.
5. Packages `survival`, `mstate`, `cmprisk`.
6. Functions `Surv()`, `survfit()`, `plot.survfit()`, `coxph()`, `Cuminc()`.

# Survival time – time to event

**Time** spent (`lex.dur`) in a given **state** (`lex.Cst`) from its beginning till a certain *endpoint* or *outcome* **event** (`lex.Xst`) or *transition* occurs, changing the state to another.

Examples of such times and outcome events:

- lifetime: birth $\rightarrow$ death,
- duration of marriage: wedding $\rightarrow$ divorce,
- healthy exposure time:
  start of exposure $\rightarrow$ onset of disease,
- clinical survival time:
  diagnosis of a disease $\rightarrow$ death.

# Ex. Survival of 338 oral cancer patients

Important variables:

- `time` = duration of patientship from diagnosis (**entry**) till death (`death`) or censoring (`Alive`), (`lex.Cst` is (`Alive`))
- `event` = indicator for the outcome and its observation at the end of follow-up (**exit**):
  0 = censoring,
  1 = death from oral cancer
  2 = death from some other cause.

Special features:

- Two possible endpoints
- Censoring – incomplete observation of the survival time.

# Set-up of classical survival analysis

- **Two-state model**: only one type of event changes the initial state.
- Major applications: analysis of lifetimes since birth and of survival times since diagnosis of a disease until death from any cause.


- **Censoring**: Death and final lifetime not observed for some subjects due to emigration or closing the follow-up while they are still alive

# Distribution concepts: hazard function

The **hazard rate** or **intensity** function $\lambda(t)$

$$\lambda(t) = P(t < T \leq t + \Delta | T > t)/\Delta, \ \mathit{forsmall}\Delta$$

$\approx$ the conditional probability that the event occurs in a short interval $(t, t + \Delta]$, given that it does not occur before $t$, divided by interval length.

In other words, during a short interval

$$\text{risk of event} \approx \text{hazard} \times \text{interval length}$$

# Distribution concepts: survival and cumulative hazard functions

**Survival function**

$$S(t) = P(T > t),$$

$=$ probability of avoiding the event at least up to $t$
(the event occurs only after $t$).
The **cumulative hazard** (or integrated intensity):

$$\Lambda(t) = \int_0^t \lambda(u)du$$

Connections between the functions:

$$S(t) \quad = \quad \exp\{-\Lambda(t)\}$$

# Observed data on survival times

For individuals $i = 1, \ldots, n$ let

$T_i$ = time to outcome event,

$U_i$ = time to censoring.

Censoring is assumed **noninformative**, *i.e.* independent from occurrence of events.

We observe

$y_i = \min\{T_i, U_i\}$, *i.e.* the exit time, and

$\delta_i = 1_{\{T_i < U_i\}}$, indicator (1/0) for the outcome event occurring first, before censoring.

Censoring must properly be taken into account in the statistical analysis.

# Approaches for analysing survival time

- **Parametric model** (like Weibull, gamma, etc.) on hazard rate $\lambda(t) \rightarrow$ Likelihood:

$$L = \prod_{i=1}^{n} \lambda(y_i)^{\delta_i} S(y_i)$$

- **Piecewise constant rate** model on $\lambda(t)$
  – see Bendix's lecture on time-splitting (Poisson likelihood).

- **Non-parametric** methods, like
  Kaplan–Meier (KM) estimator of survival curve $S(t)$ and Cox proportional hazards model on $\lambda(t)$.

# R package `survival`

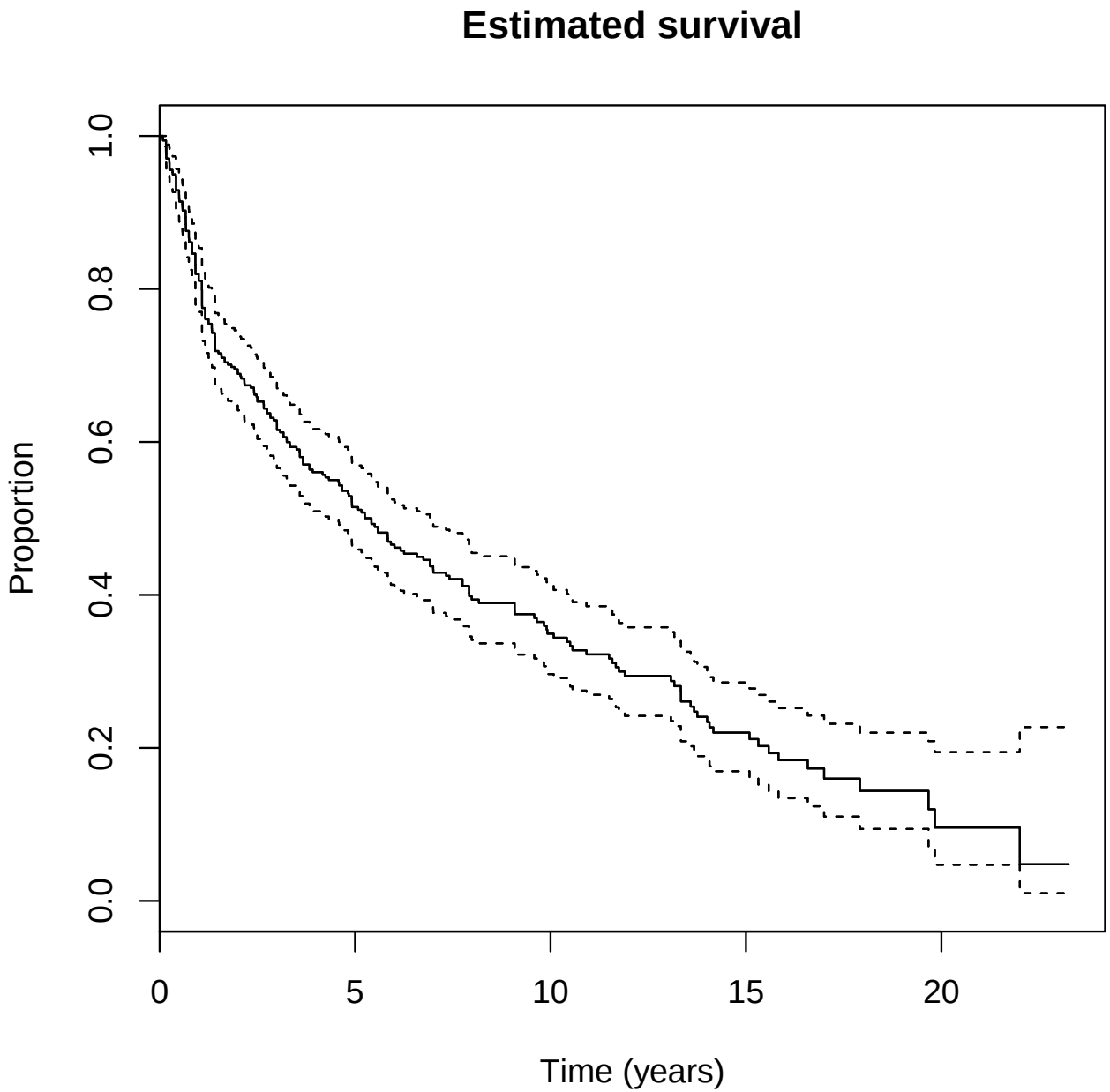
Tools for analysis with one outcome event.

- `Surv(time, event) -> sobj`
  creates a **survival object** `sobj` assuming that all start at 0, containing pairs $(y_i, \delta_i)$,
- `Surv(entry, exit, event) -> sobj2`
  creates a survival object from `entry` and `exit` times,
- `survfit(sobj ~ x) -> sfo`
  creates a **survfit** object `sfo` containing KM or other non-parametric estimates (also from a fitted Cox model),
- `plot(sfo)`
  plot method for survival curves and related graphs,
- `coxph(sobj ~ x1 + x2)`
  fits a Cox model with covariates `x1` and `x2`.
- `survreg()` – parametric survival models.

# Ex. Oral cancer data (cont'd)

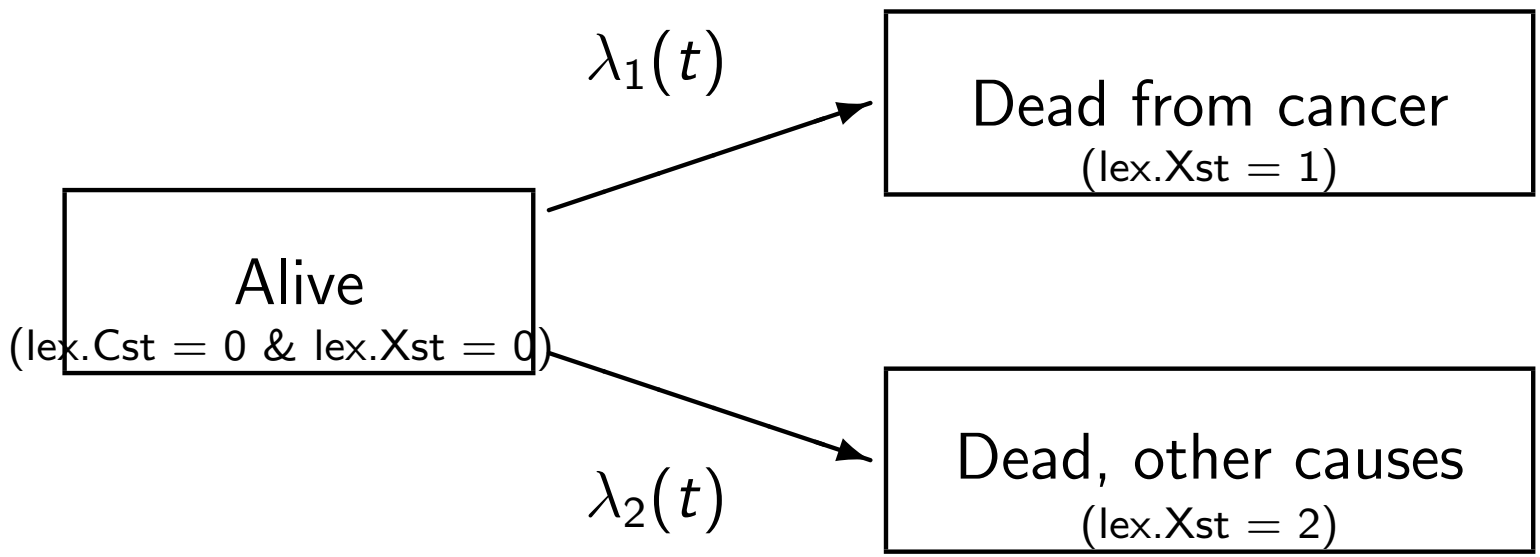
```
> orca$suob <- Surv(orca$time, 1*(orca$event > 0) )

> orca$suob[1:7]   #  + indicates censored observation
[1] 5.081+ 0.419  7.915  2.480  2.500  0.167  5.925+

> km1 <- survfit( suob ~ 1, data = orca)
> km1                  #  brief  summary
records   n.max n.start  events  median 0.95LCL 0.95UCL
 338.00  338.00  338.00  229.00    5.42    4.33    6.92

> summary(km1)      #  detailed KM-estimate
   time n.risk n.event survival std.err lower 95% CI upper 95% CI
  0.085    338       2   0.9941 0.00417       0.9859        1.000
  0.162    336       2   0.9882 0.00588       0.9767        1.000
  0.167    334       4   0.9763 0.00827       0.9603        0.993
  0.170    330       2   0.9704 0.00922       0.9525        0.989
  0.246    328       1   0.9675 0.00965       0.9487        0.987
   ...
```

# Ex. Oral cancer KM estimates



# Competing risks model: causes of death

- Often the interest is focused on the risk or hazard of dying from one specific cause.
- That cause may eventually not be realized, because a **competing cause** of death hits first.




- Generalizes to several competing causes.

# Competing events & competing risks

In many epidemiological and clinical contexts there are competing events that may occur before the target event and remove the person from the population at risk for the event, *e.g.*

- *target event*: occurrence of endometrial cancer,
  *competing events*: hysterectomy or death.
- *target event*: relapse of a disease
  (ending the state of remission),
  *competing event*: death while still in remission.
- *target event*: divorce,
  *competing event*: death of either spouse.

# Event-specific quantities

**Cumulative incidence function** (CIF) for event $c$:

$$F_c(t) = P(T \leq t \text{ and } C = c), \quad c = 1, 2,$$

From these one can recover

- $F(t) = \sum_c F_c(t)$, CDF of event-free survival time $T$, *i.e.* cumulative risk of any event by $t$.
- $S(t) = 1 - F(t)$, **event-free survival function**, *i.e.* probability of avoiding all events by $t$
- $1 - S(t) \neq F_1(t) + F_2(t)$

# Event-specific quantities (cont'd)

- CIF = risk of event $c$ over risk period $[0, t]$ in the presence of competing risks, also obtained

$$F_c(t) = \int_0^t \lambda_c(v) S(v) dv, \quad c = 1, 2,$$

- Survival depends on the sum of the hazards of the competing events, too, via

$$\begin{aligned} S(t) &= \exp\left\{ - \int_0^t [\lambda_1(v) + \lambda_2(v)] dv \right\} \\ &= \exp\left\{-\Lambda_1(t)\right\} \times \exp\left\{-\Lambda_2(t)\right\}. \end{aligned}$$

# Warning of "net risk" and "cause-specific survival"

- The "**net risk**" of outcome $c = 1$ by time $t$, assuming hypothetical elimination of competing risks, is often defined as

$$F_1^*(t) = 1 - S_1^*(t) = 1 - \exp\{-\Lambda_1(t)\} \neq S(t)$$

- In clinical survival studies, function $S_1^*(t)$ is often called "**cause-specific survival**", (estimated by KM) or net survival registry-based survival studies
- Yet, these *-functions, $F_1^*(t)$ and $S_1^*(t)$, lack proper probability interpretation when competing risks exist.
- Hence, their use should be viewed critically (Andersen & Keiding, *Stat Med*, 2012)

# Example: Risk of lung cancer by age $a$?

- Nordcan & Globocan give "**cumulative risk**" by 75 y of age, computed from $1 - \exp\{-\mathrm{CR}(75)\}$, as an estimate of the probability of getting cancer before age 75 y, assuming that death were avoided by that age. This is based on deriving "net risk" from cumulative hazard:

$$F_c^*(a) = 1 - \exp\{-\Lambda_c(a)\}.$$

- Yet, cancer occurs in a mortal population.
- As such CR(75) is a sound age-standardized summary measure for comparing cancer incidence across populations based on a neutral standard population.

# Example. Male lung cancer in Denmark

Event and age-specifc specific hazards for lung cancer ($\lambda_1(a)$) and death (($\lambda_2(a)$)) estimated by respective rates