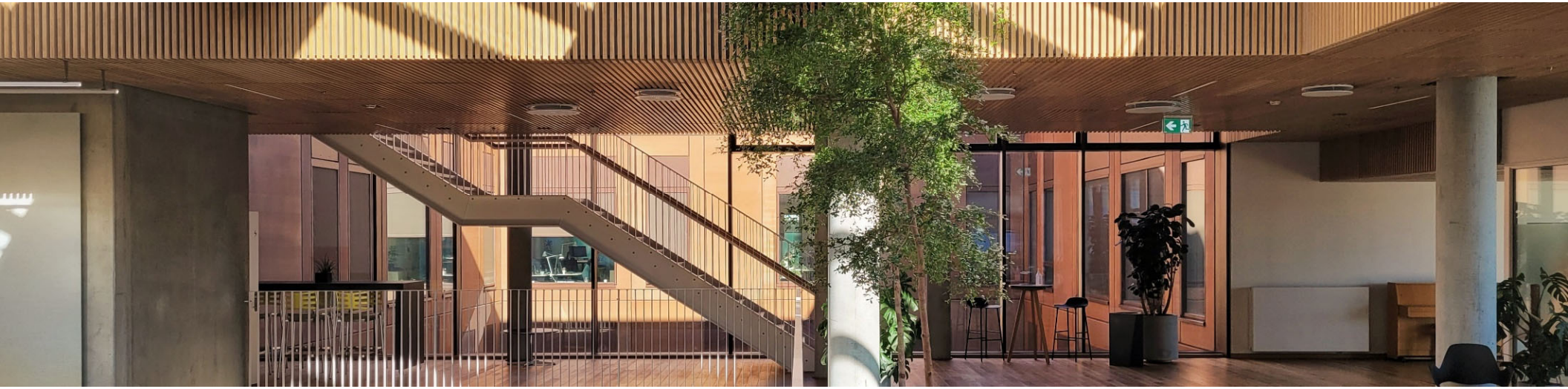

Fundamentals of Survival Analysis (aka Time-To-Event (TTE))

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Overview – intro for survival analysis

- Example of survival analysis
- Data on survival
- Lexis diagrams and study design
- Survival function, densities and hazard rates
- Kaplan-Meier estimate of survival curve
- Log-rank test
- Censoring vs competing risks

Example - Bevacizumab

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Bevacizumab plus Irinotecan, Fluorouracil, and Leucovorin for Metastatic Colorectal Cancer

Herbert Hurwitz, M.D., Louis Fehrenbacher, M.D., William Novotny, M.D., Thomas Cartwright, M.D., John Hainsworth, M.D., William Heim, M.D., Jordan Berlin, M.D., Ari Baron, M.D., Susan Griffing, B.S., Eric Holmgren, Ph.D., Napoleone Ferrara, M.D., Gwen Fyfe, M.D., Beth Rogers, B.S., Robert Ross, M.D., and Fairooz Kabbinavar, M.D.

ABSTRACT

BACKGROUND

Bevacizumab, a monoclonal antibody against vascular endothelial growth factor, has shown promising preclinical and clinical activity against metastatic colorectal cancer, particularly in combination with chemotherapy.

From Duke University, Durham, N.C. (H.H.); Kaiser Permanente, Vallejo, Calif. (L.F.); Genentech, South San Francisco, Calif. (W.N., S.G., E.H., N.F., G.F., B.R., R.R.); Ocala Oncology, Ocala, Fla. (T.C.);

Example - Bevacizumab

STATISTICAL ANALYSIS

The primary outcome measure was the duration of overall survival; survival was measured without regard to subsequent treatments. There was no crossover between groups, however. Secondary outcome measures were progression-free survival, objective response rates (complete and partial responses), the duration of responses, and the quality of life.

For patients who were alive at the time of analysis, data on survival were censored at the time of the last contact. Progression-free survival was defined as the time from randomization to progression or death during the study, with death during the study defined as any death that occurred within 30 days after the last dose of bevacizumab or chemotherapy. For patients without disease progression at the time of the final analysis, data on progression-free survival were censored at the last assessment of tumor status or on day 0 if no further assessment was performed after baseline. Patients without adequate follow-up data were categorized as having no response.

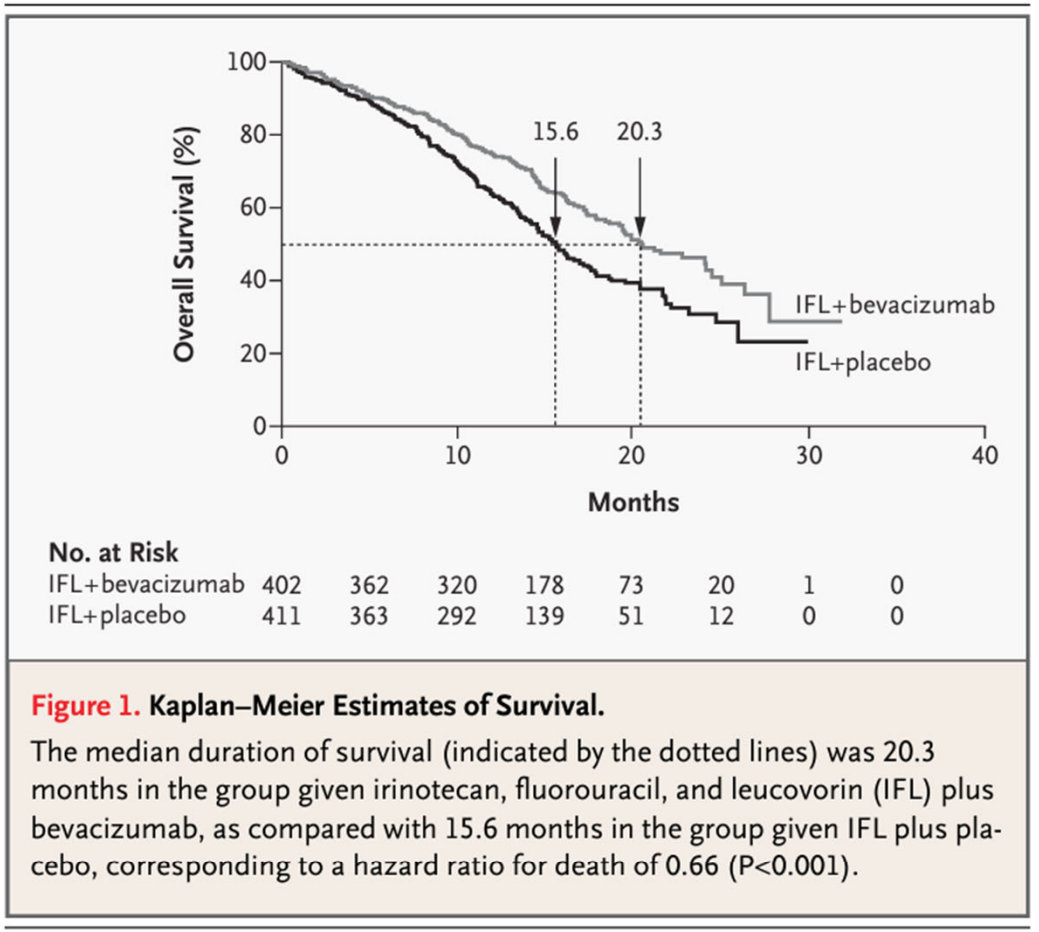


Figure 1. Kaplan–Meier Estimates of Survival.

The median duration of survival (indicated by the dotted lines) was 20.3 months in the group given irinotecan, fluorouracil, and leucovorin (IFL) plus bevacizumab, as compared with 15.6 months in the group given IFL plus placebo, corresponding to a hazard ratio for death of 0.66 ($P<0.001$).

Survival data

- Most generic form

ID	t0	t1	status at t1
1	0	35	1
2	0	156	0
3	0	57	1
…	…	…	…

- Person is observed from t_0 to t_1
- Status at t_1 is 1 for event, 0 for censoring

Survival data

Caerphilly study – description:

Follow-up study focusing on risk factors for cardiovascular diseases.

Inclusion period: July 1979 to October 1983.

Study population: Men aged 43-61 at the start.

Primary outcomes: Myocardial infarction (MI) or death.

End of study: February 1999.

Survival data - example

- Caerphilly study

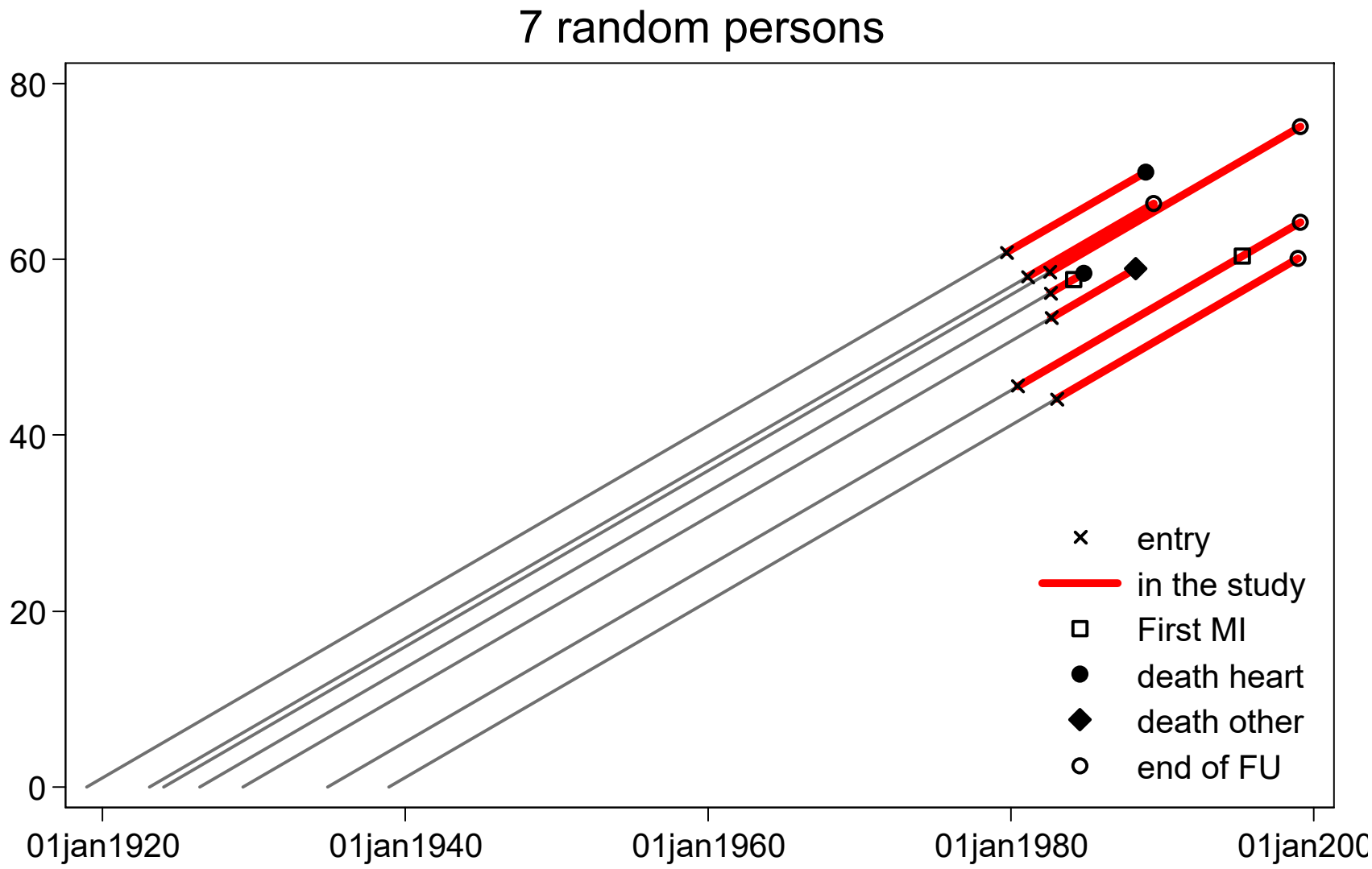
Survival_I - RStudio Source Editor

caerphilly_dat

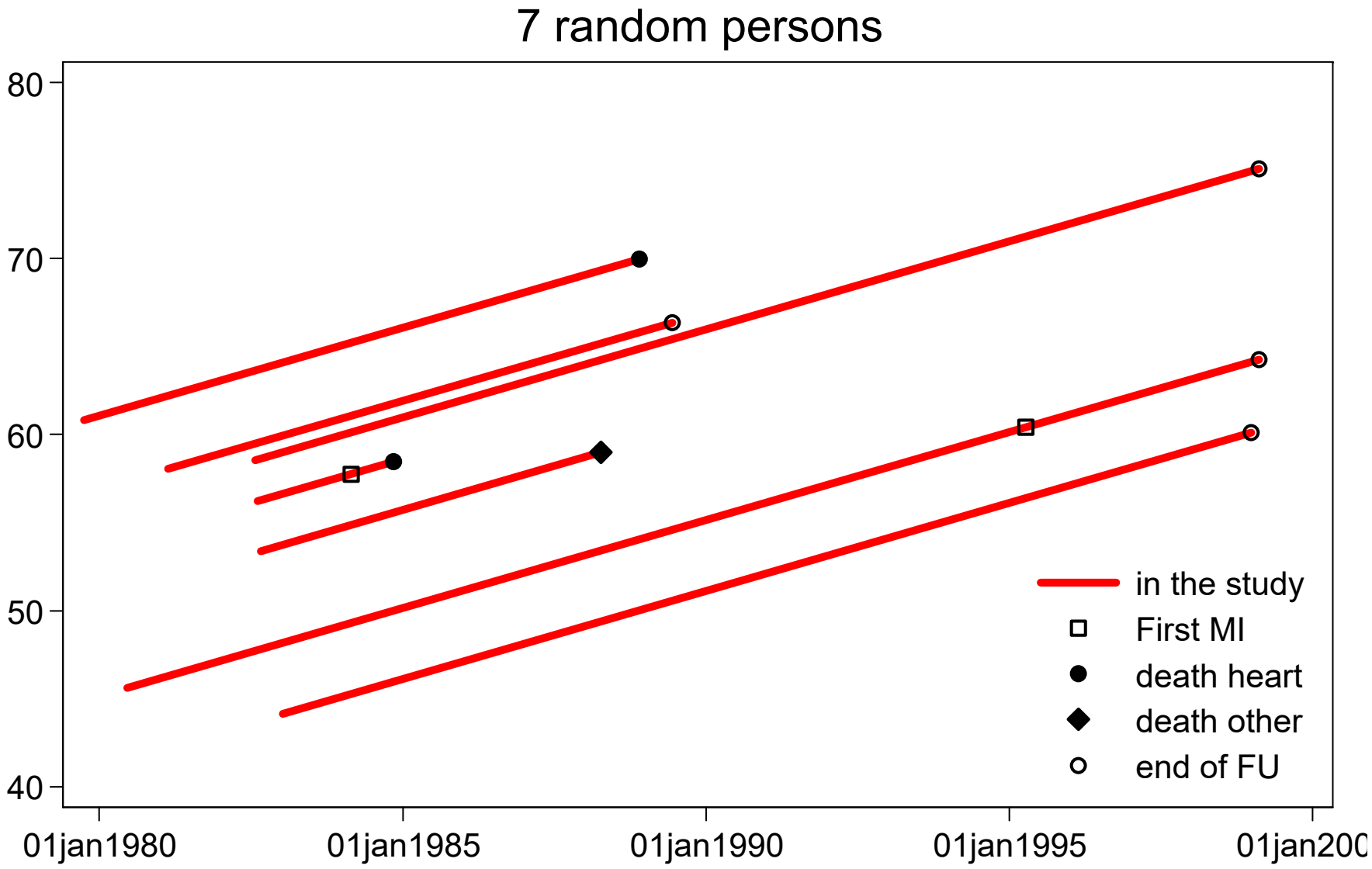
Filter

	id	birthdate Date of birth	examdate Date of first examination	dthdate Date of death	midate Date of first MI	emdate Date of emigration	eosdate End of study	socclass Social class	diabetes Diabetes at baseline	smokir Smoking
1	1	1929-05-20	1982-06-17	*NA*	*NA*	*NA*	1998-12-31	3	0	3
2	2	1930-07-09	1983-01-10	*NA*	*NA*	*NA*	1998-12-24	3	0	0
3	3	1929-02-06	1982-12-23	*NA*	*NA*	*NA*	1998-11-26	3	0	3
4	4	1931-05-24	1983-07-07	1984-11-22	1984-11-22	*NA*	*NA*	3	0	1
5	5	1934-02-09	1980-09-03	*NA*	*NA*	*NA*	1998-12-19	3	0	1
6	6	1930-03-14	1981-11-17	*NA*	*NA*	*NA*	1998-12-31	3	0	2
7	7	1933-05-13	1980-10-30	*NA*	*NA*	*NA*	1998-12-27	3	0	3
8	8	1924-05-23	1980-04-24	1986-01-24	1986-01-24	*NA*	*NA*	3	1	4
9	9	1931-06-20	1980-06-11	*NA*	*NA*	*NA*	1998-12-12	2	0	4
10	10	1929-05-12	1979-11-17	1995-01-20	1995-01-20	*NA*	*NA*	4	0	1
11	11	1924-02-22	1981-08-29	*NA*	*NA*	*NA*	1998-12-01	3	0	4
12	12	1937-11-25	1982-07-13	*NA*	*NA*	*NA*	1998-12-31	5	0	1
13	13	1921-02-25	1980-05-02	*NA*	*NA*	*NA*	1998-12-31	2	0	0
14	14	1926-03-24	1980-12-18	1994-12-26	1994-12-26	*NA*	*NA*	4	0	0
15	15	1928-04-20	1980-07-15	*NA*	*NA*	*NA*	1998-12-15	2	0	1
16	16	1923-10-30	1980-02-10	*NA*	*NA*	*NA*	1998-12-31	5	0	4
17	17	1923-01-31	1983-04-24	*NA*	*NA*	*NA*	1998-12-31	2	0	1
18	18	1924-01-15	1980-09-11	*NA*	1993-08-04	*NA*	1999-02-14	2	0	1

Lexis diagram for Caerphilly study

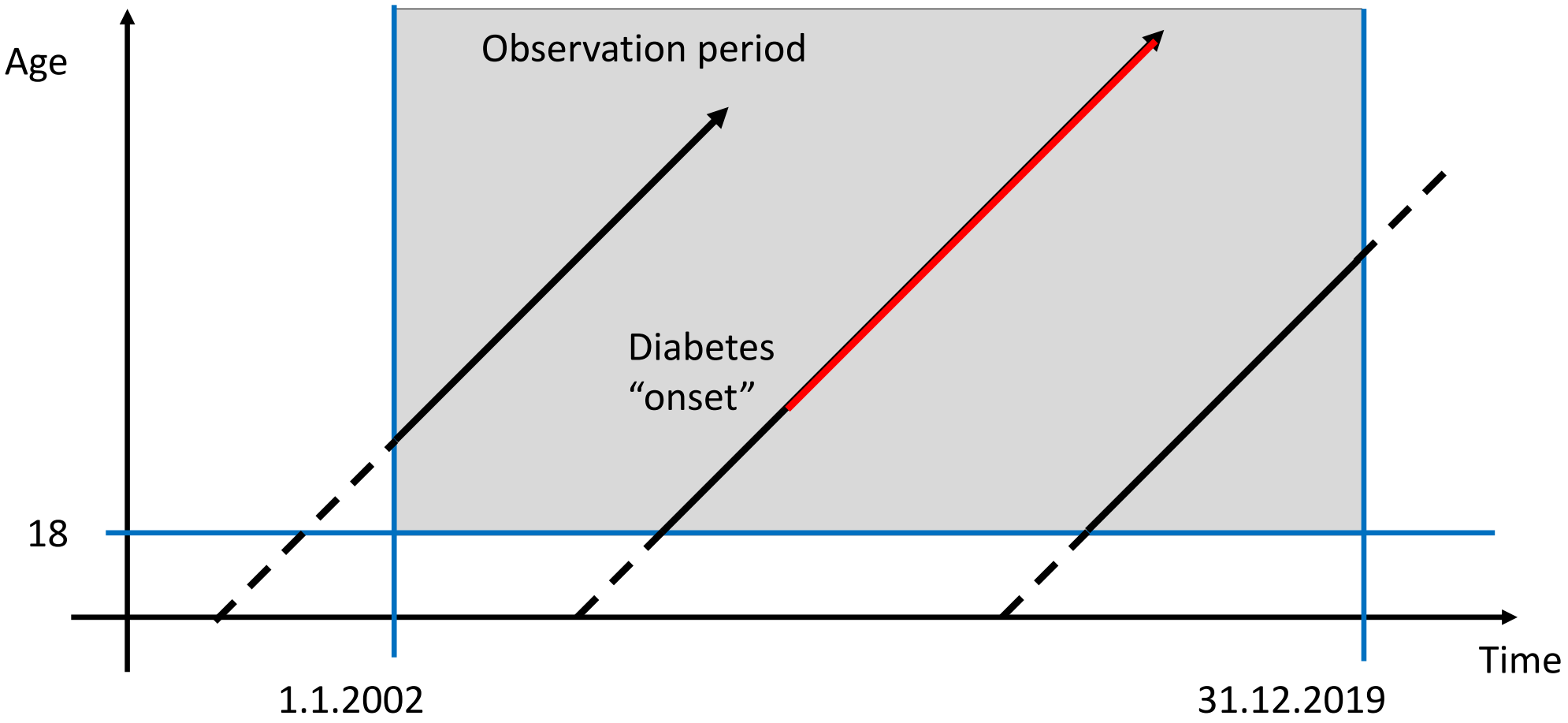


Lexis diagram for Caerphilly study (zoomed)



Lexis diagram for study design

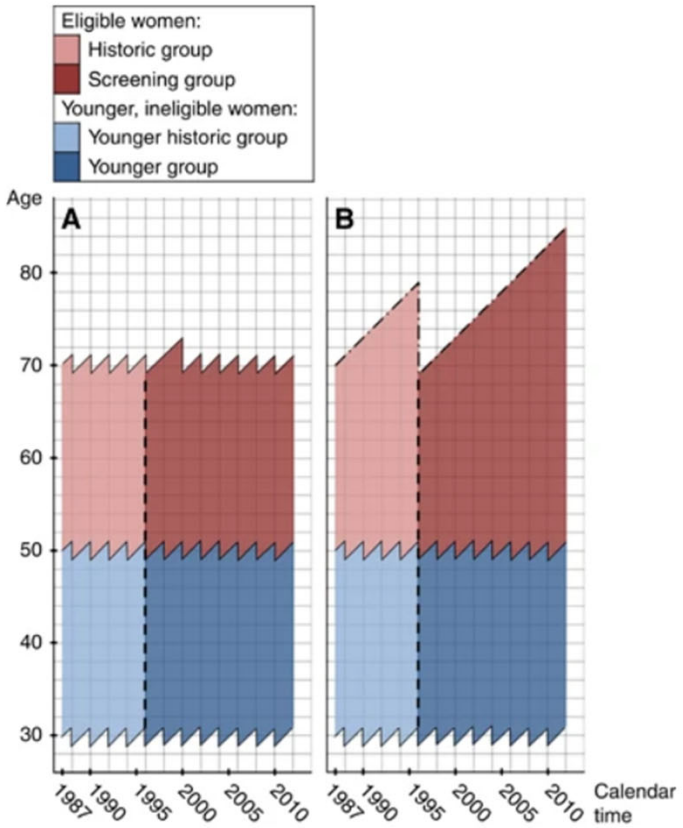
- Discuss: Which birth cohorts aged 70+ can be compared?



Schematic use of Lexis diagram to present study design

Figure 1

From: Effect of organised mammography screening on stage-specific incidence in Norway: population study



Study design illustrated for the county of Oslo, where screening was introduced on 8 January 1996. Women are eligible for screening based on birth cohorts and programme start. Younger, ineligible women are below the age of screening. (**A**) Follow-up ends at the upper age limit for screening. (**B**) Follow-up of birth cohorts is continued to include the compensatory drop.

Time scales

- Any time scale is defined by its origin:
  - Birth -> age
  - Diagnosis -> duration as patient
  - Inclusion -> time in study
  - 1 January, 0 -> calendar time
  - Last menstrual date -> gestational age
- First thing to determine for any survival analysis:

  Which time scale do we want to use?

Survival data

- Caerphilly study

Survival_I - RStudio Source Editor

caerphilly_dat

Filter

	id	birthdate Date of birth	examdate Date of first examination	dthdate Date of death	midate Date of first MI	emdate Date of emigration	eosdate End of study	socclass Social class	diabetes Diabetes at baseline	smokir Smoking
1	1	1929-05-20	1982-06-17	NA	NA	NA	1998-12-31	3	0	3
2	2	1930-07-09	1983-01-10	NA	NA	NA	1998-12-24	3	0	0
3	3	1929-02-06	1982-12-23	NA	NA	NA	1998-11-26	3	0	3
4	4	1931-05-24	1983-07-07	1984-11-22	1984-11-22	NA	NA	3	0	1
5	5	1934-02-09	1980-09-03	NA	NA	NA	1998-12-19	3	0	1
6	6	1930-03-14	1981-11-17	NA	NA	NA	1998-12-31	3	0	2
7	7	1933-05-13	1980-10-30	NA	NA	NA	1998-12-27	3	0	3
8	8	1924-05-23	1980-04-24	1986-01-24	1986-01-24	NA	NA	3	1	4
9	9	1931-06-20	1980-06-11	NA	NA	NA	1998-12-12	2	0	4
10	10	1929-05-12	1979-11-17	1995-01-20	1995-01-20	NA	NA	4	0	1
11	11	1924-02-22	1981-08-29	NA	NA	NA	1998-12-01	3	0	4
12	12	1937-11-25	1982-07-13	NA	NA	NA	1998-12-31	5	0	1
13	13	1921-02-25	1980-05-02	NA	NA	NA	1998-12-31	2	0	0
14	14	1926-03-24	1980-12-18	1994-12-26	1994-12-26	NA	NA	4	0	0
15	15	1928-04-20	1980-07-15	NA	NA	NA	1998-12-15	2	0	1
16	16	1923-10-30	1980-02-10	NA	NA	NA	1998-12-31	5	0	4
17	17	1923-01-31	1983-04-24	NA	NA	NA	1998-12-31	2	0	1
18	18	1924-01-15	1980-09-11	NA	1993-08-04	NA	1999-02-14	2	0	1

How to choose a time scale

- Who is it most reasonable to compare with respect to risk of event:
  - People of similar age?
  - Patients with same duration after inclusion?
  - Patients with similar duration of disease?
  - …

- Discuss: Which time scale(s) would be relevant in Caerphilly study? How many can you identify?
- BTW: what is the origin of the time scale underlying these?

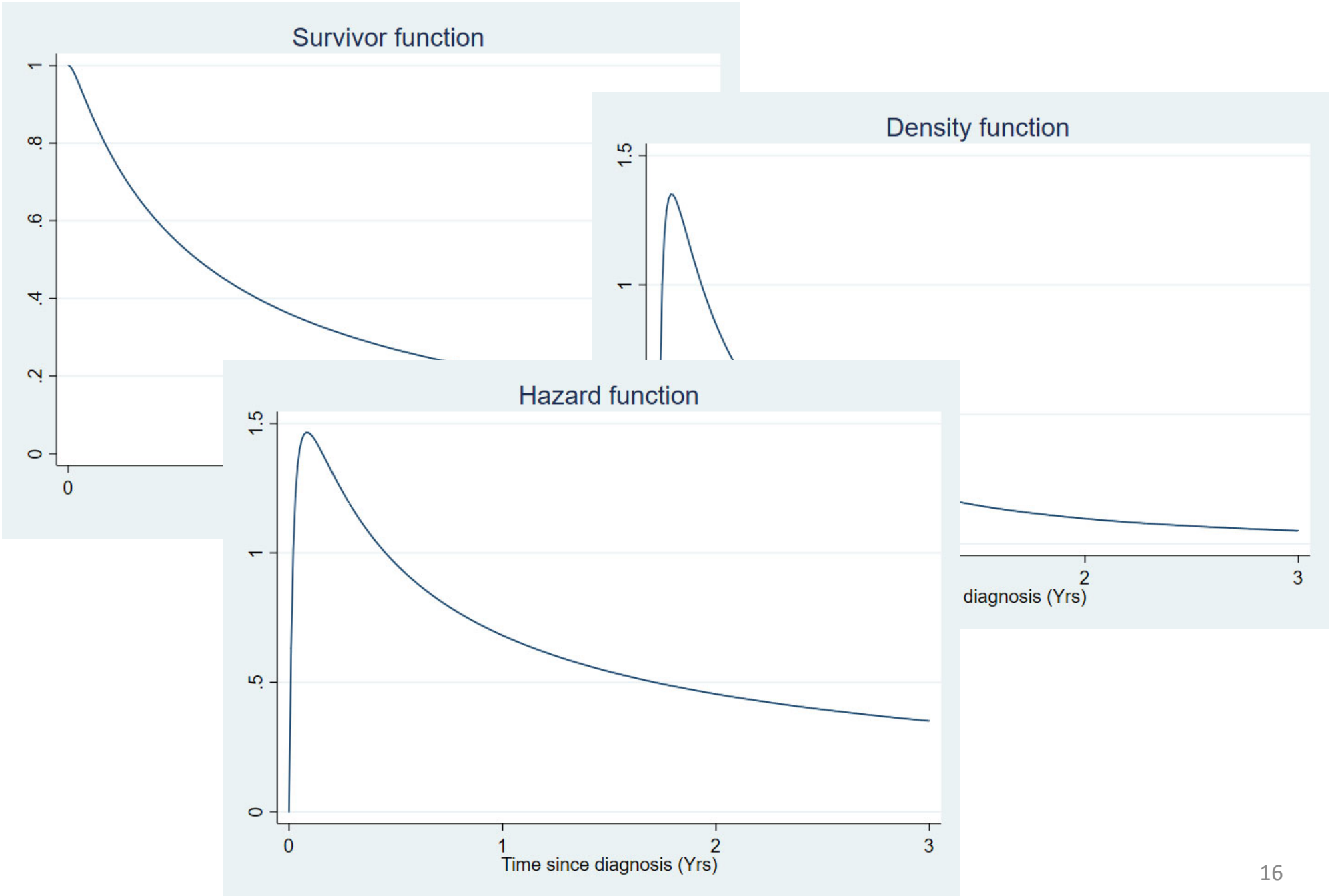
Functions in survival analysis

- The survivor function: $S(t)$
  Answers the question: What is chance of still being alive after time t among everyone included?

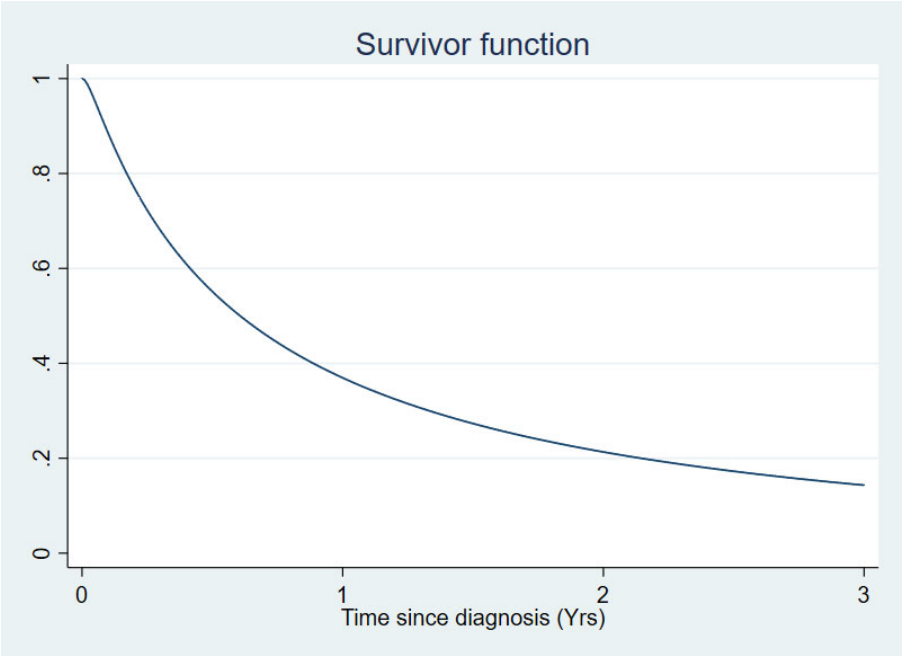
- The (probability) density function: $f(t)$
  Answers the question: What is the probability of dying approximately at time t among everyone included

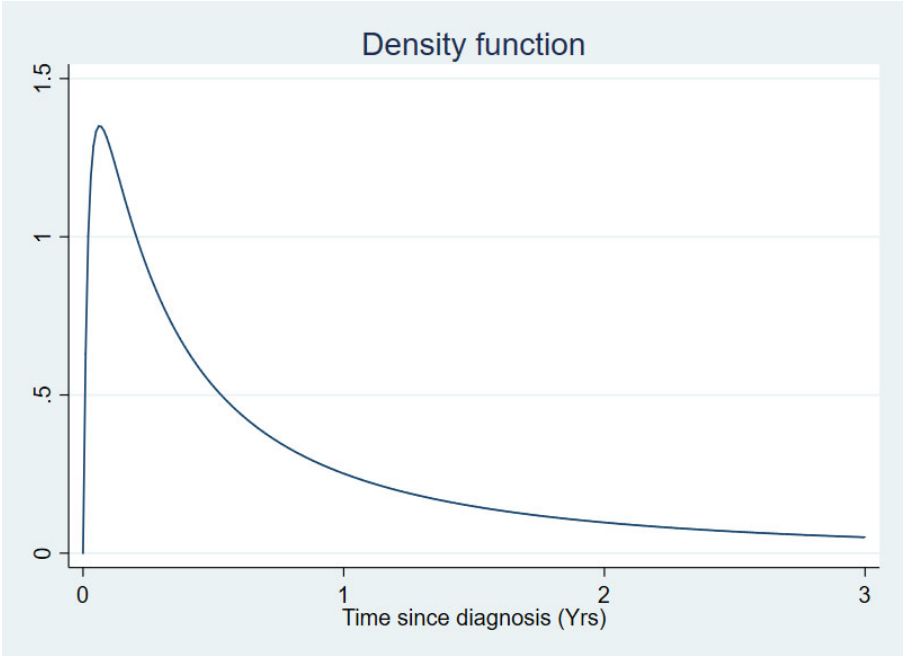
- The hazard function: $h(t)$
  Answers the question: What is the probability of dying in the next moment after time t among everyone, who survived until time t

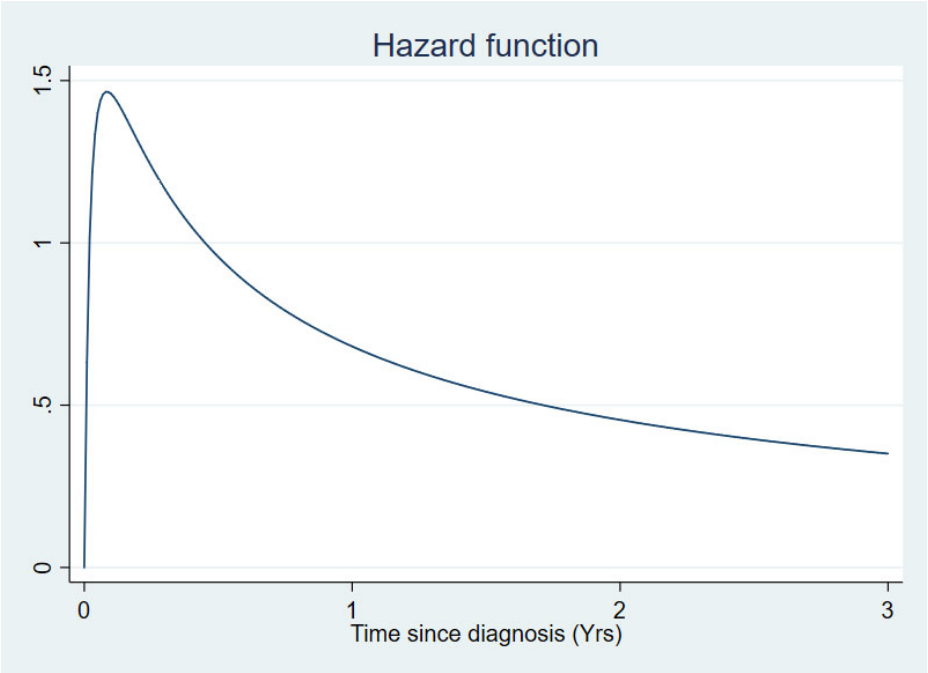
Functions in survival analysis – what they look like



Functions in survival analysis – what they look like







Functions in survival analysis - relationships

- Any one of the three uniquely determines the two other
- The hazard is often taken as the fundamental quantity, since

$$S(t) = \exp\left(-\int_0^t h(s)\,ds\right)$$

$$f(t) = h(t) \cdot \exp\left(-\int_0^t h(s)\,ds\right)$$

- Implications:

$$h(t) = \frac{f(t)}{S(t)}$$

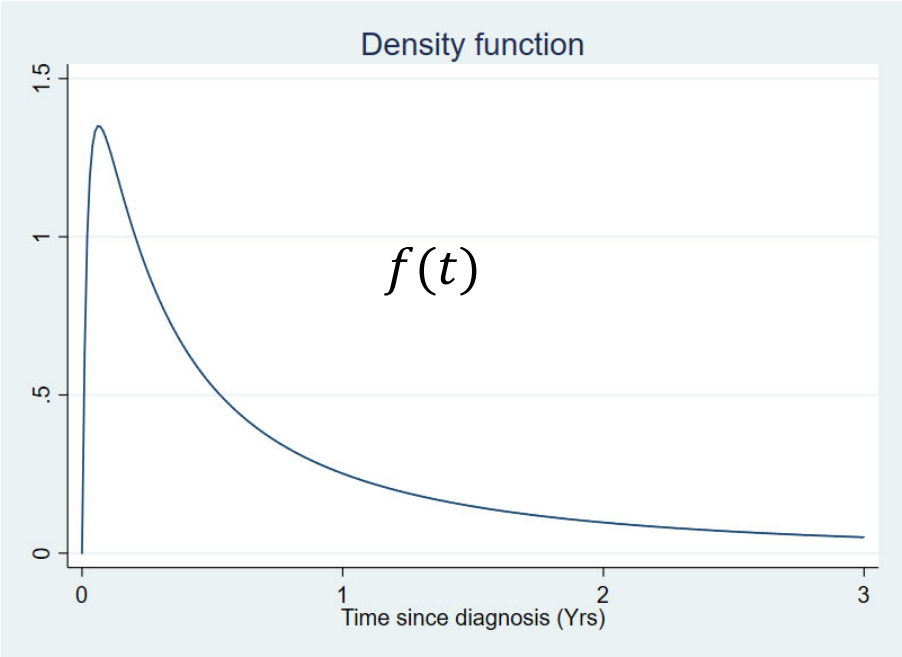
Or:

$$h(t) = \frac{d}{dt}\left(-\ln\left(S(t)\right)\right)$$

- Also you will often encounter *the integrated hazard* defined by

$$H(t) = \int_0^t h(s)\,ds$$

Functions in survival analysis – relationships



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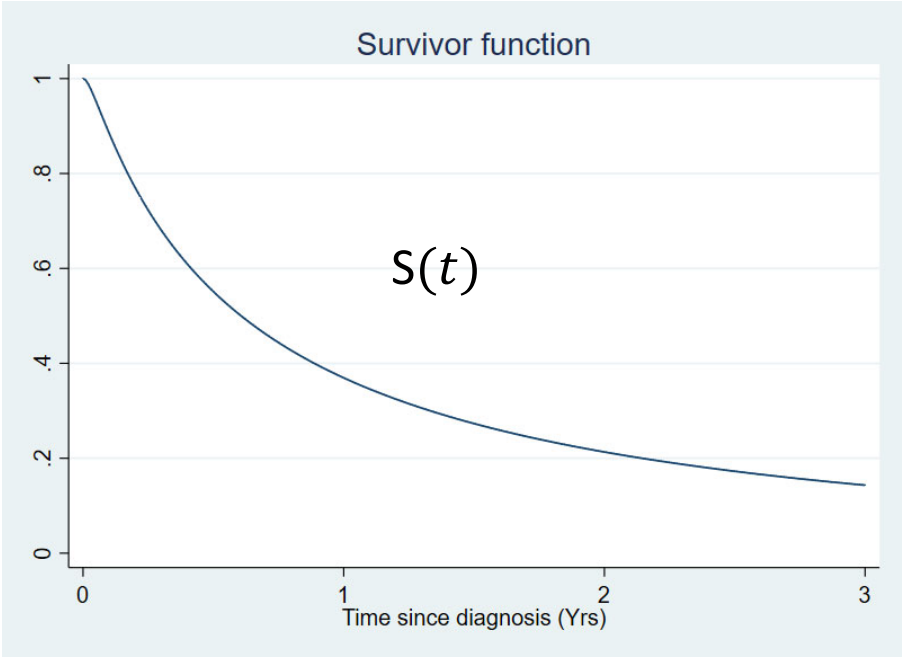

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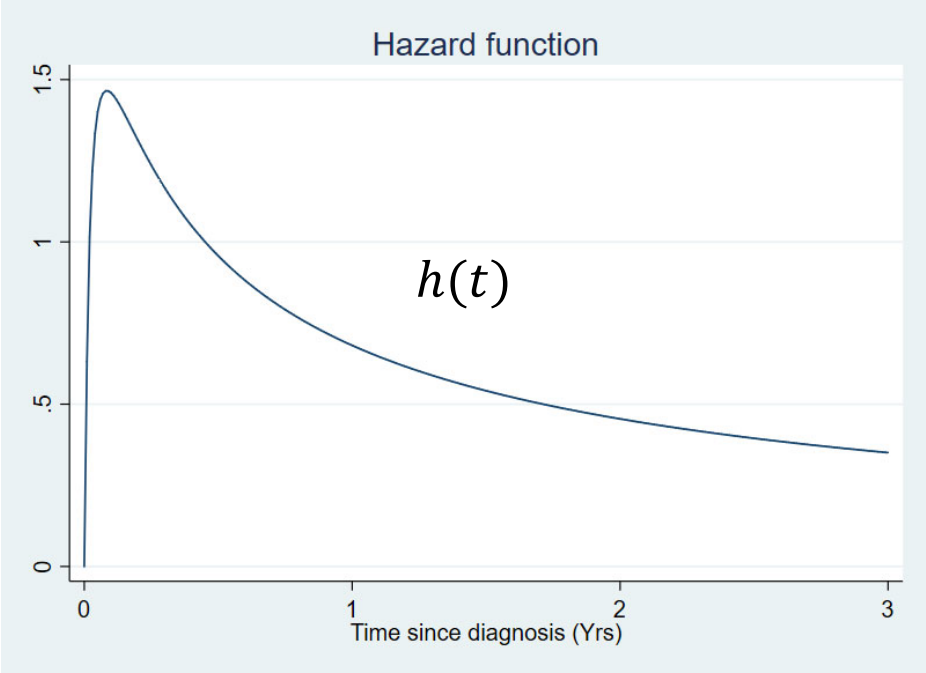
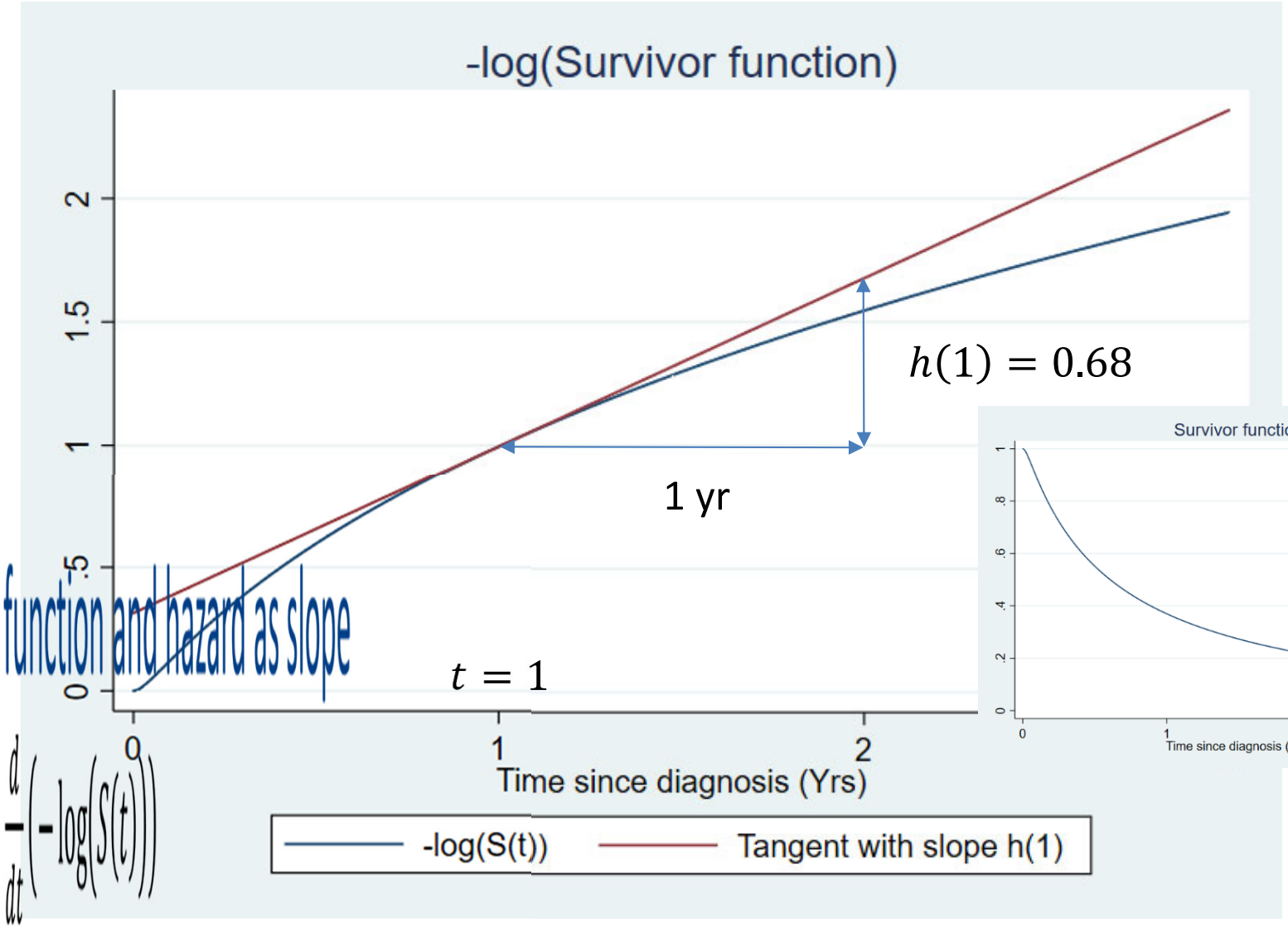


Survival function and hazard as slope

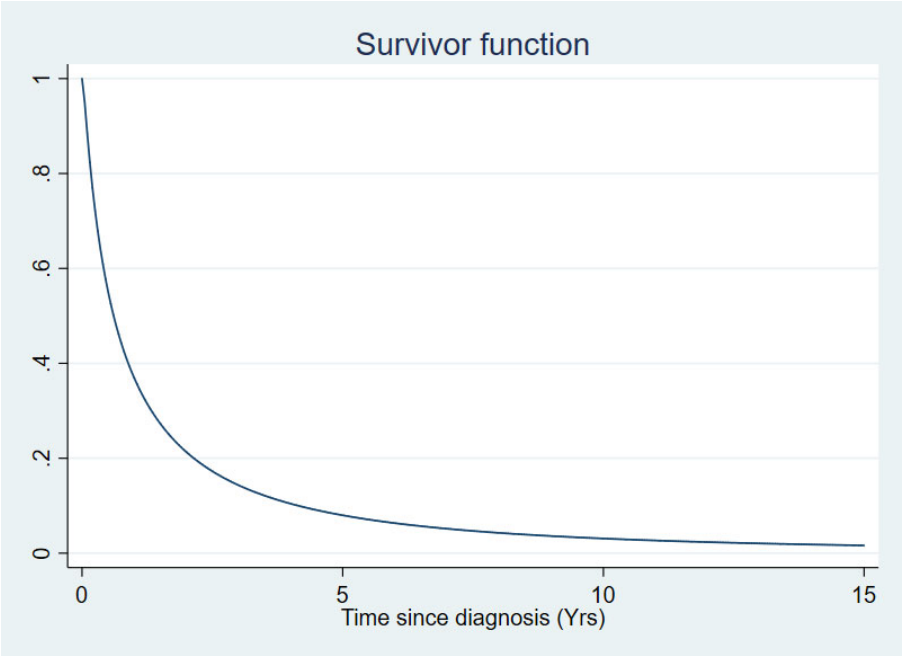
- $h(t) = \frac{d}{dt}\left(-\log\left(S(t)\right)\right)$

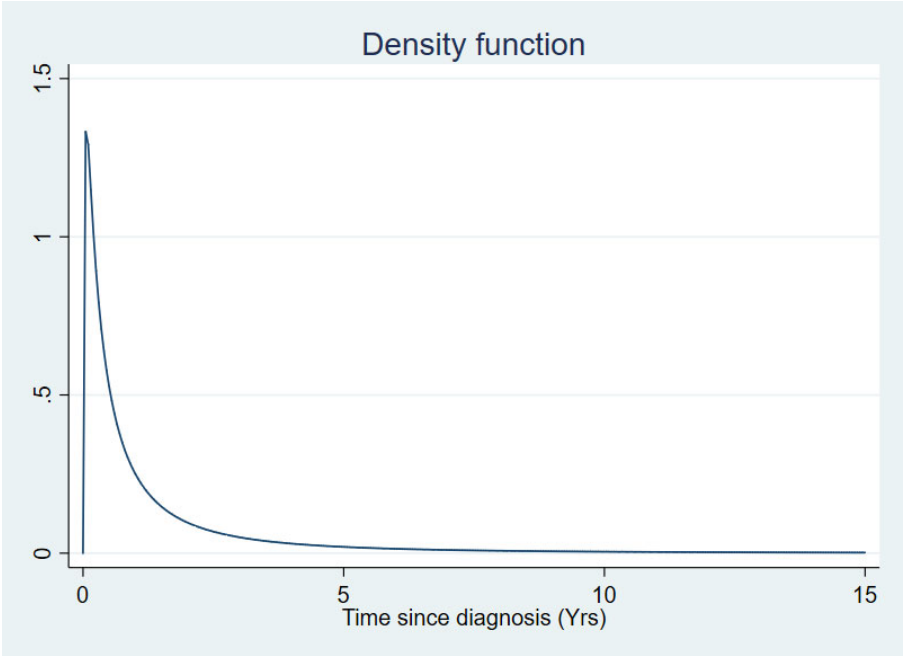


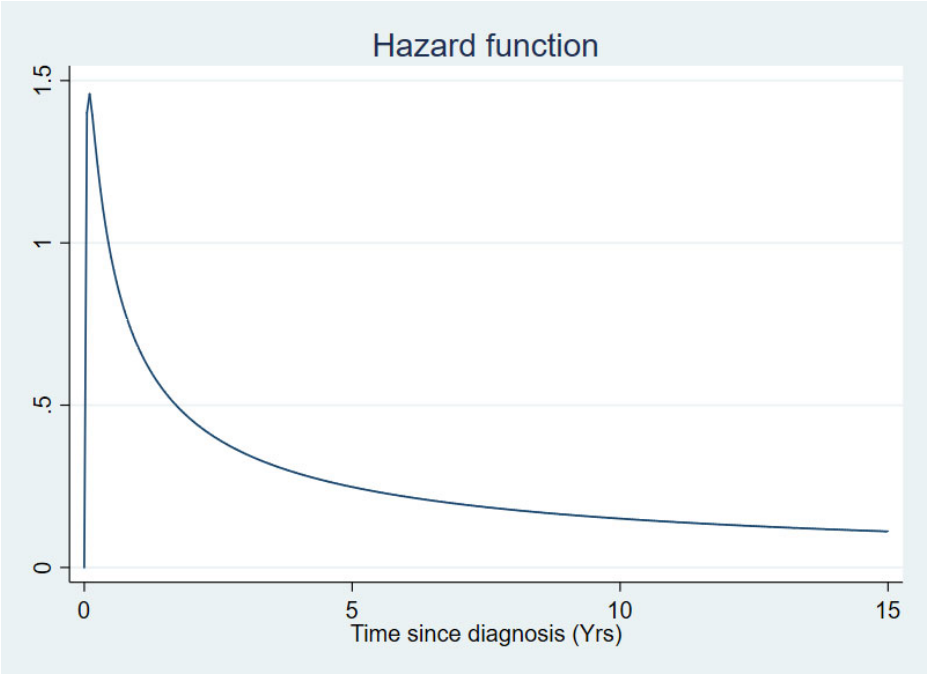
Survival function and hazard as slope

- $h(t) = \frac{d}{dt}\left(-\log\left(S(t)\right)\right)$

Functions in survival analysis – “full range”







Kaplan-Meier (KM) estimate of survivor function

- Usually, risk is estimated by proportions
- ... But we have censoring
- KM assumes censored individuals have the same future risk as those remaining in the study
- Thus, we can compute KM estimate as

$$S_{est}(t) = \sum_{t_j<t} \left(1 - \frac{m_j}{R_j}\right)$$

- Where

  m_j is number of deaths at event time t_j

  R_j is number at risk at time t_j
- See R-file *surv_example.R* for code

Log-rank test – comparing survival in groups

- Consider two groups, A and B
- Idea:

  If there is the same mortality in the two groups, then at any event time where there are R_A and R_B at risk in the two groups, we would expect that the probability of a death coming from group A is

$$\frac{R_A}{R_A + R_B}$$

- And one minus this for B
- We can sum this up in the two groups and compare with actual number of deaths
- Yields a p-value for the null-hypothesis of no difference
- See R-file *surv_example.R* for code

Censoring vs competing risk wrt Kaplan-Meier

- Key assumption:
  Censored individuals have the same future risk as those remaining in the study
- This is called non-informative (right) censoring
- Can typically not be checked in the observed data

- What happens if we study time to CVD diagnosis?
- People may die before diagnosis – is this censoring?
- **No -** people who died are no longer at risk of getting a CVD diagnosis
- Here death is a competing risk (but CVD is **not** a competing risk for death!)

Main problem with competing risk

- Cumulative risk is over-estimated
- Equivalently: Survival probability is under-estimated

Thanks for your attention – questions welcome!

(Djursland, July 2015 – H Støvring)