

Competing Risks - What, Why, When and How?

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Survival Analysis for Junior Researchers

- Competing risks methodology is being increasingly applied to cause of death data as a way of obtaining “real world” probabilities of death broken down by specific causes.
- This kind of information could be vital not only for informing patients of the risks they face in certain situations but also for making decisions about which treatment regime to assign a patient, how best to allocate health resources and for understanding the longer term outcomes of chronic conditions.

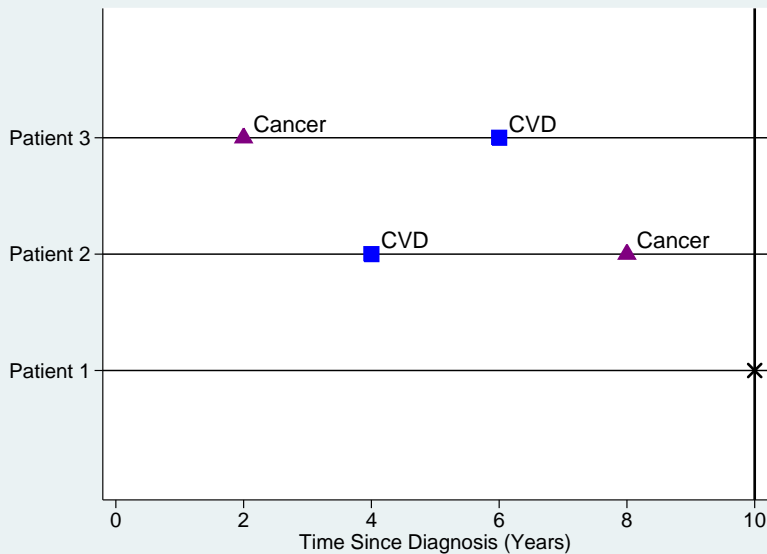
Illustrative Example

- SEER public use dataset on survival of breast cancer patients from 1992-2007 (n=61,050). *National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch (released April 2011)*
- Follow-up restricted to 10 years.
- Cause of death was categorised into the following:
 - ① Breast cancer (n=8,329)
 - ② Heart disease (n=2,818)
 - ③ Other causes (n=4,454)
- Age categorised into 18-59, 60-84 and 85+

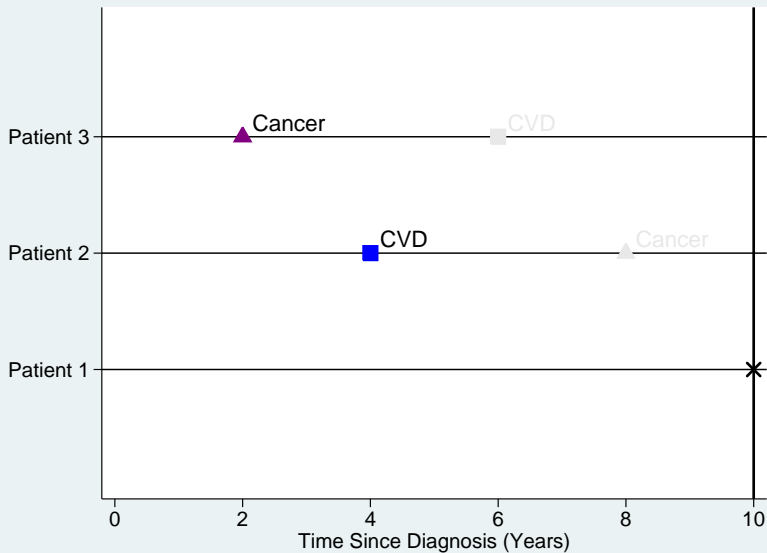
What are Competing Risks?

Competing risks are said to be present when a patient is at risk of more than one mutually exclusive event, such as death from different causes, and the occurrence of one of these will prevent any other event from ever happening. *Gichangi & Vach (2005)*

Example



Example



Key Concepts

- Survival function
- Cause-specific hazard
- Subdistribution hazard
- Cumulative incidence function (CIF)

Cause-specific Hazard Function

The cause-specific hazard, $h_k(t)$, is the instantaneous risk of dying from a particular cause k given that the subject is still alive at time t .
Prentice et al. (1978)

$$h_k(t) = \lim_{\delta t \rightarrow 0} \left\{ \frac{P(t \leq T < t + \delta t, K = k \mid T \geq t)}{\delta t} \right\}$$

$$S_k(t) = \exp \left(- \int_0^t h_k(u) du \right)$$

Cause-specific Hazard Function

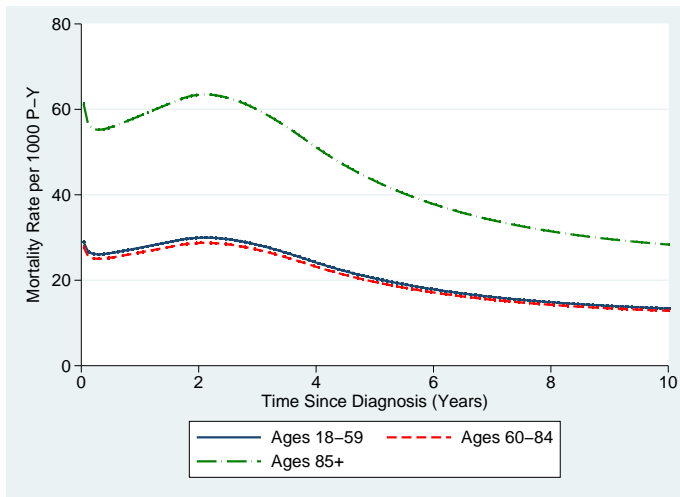


Figure: Hazard functions for breast cancer for each of 3 age groups - FPM proportional hazards model.

Cause-specific Survival Function

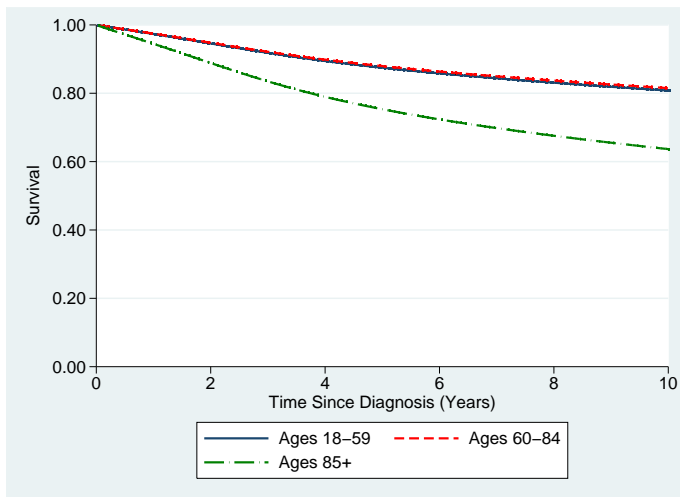


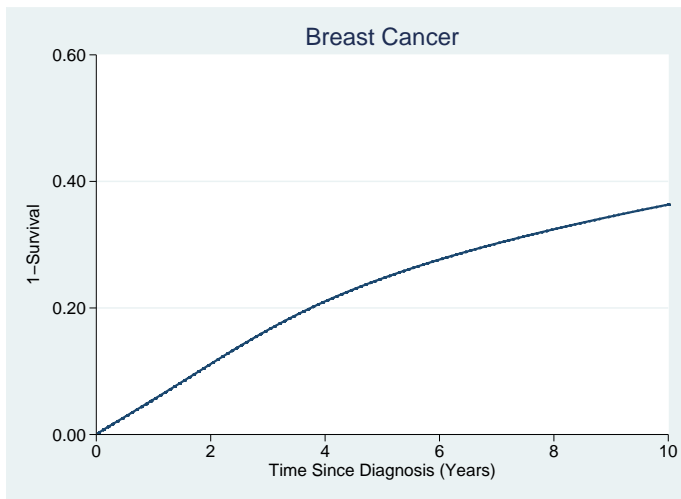
Figure: Survival functions for breast cancer for each of 3 age groups - FPM proportional hazards model.

Cause-specific Survival?

- When competing risks are present, cause-specific hazard is interpretable but corresponding survival function is difficult to describe as a probability.
- Consider deaths due to heart disease or other causes as “independent censoring” .
- Have to assume independence is reasonable - no way to test this.
- This forces us into the hypothetical world where patients can not die of anything but their cancer - net survival.

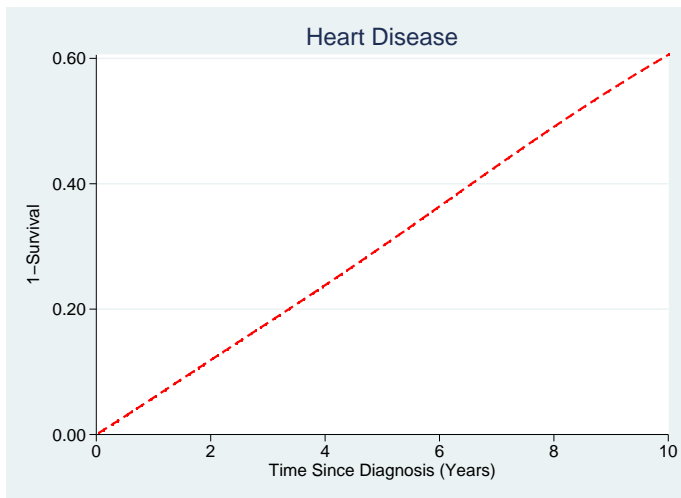
- Net survival is the probability of surviving your cancer in the hypothetical world where it is impossible to die from anything else. *Lambert et al. (2010)*
- Relative survival and cause-specific survival attempt to estimate this under certain assumptions.
- Little use to patients making decisions in the real world where death from other causes play a big role.

Cause-specific Survival?



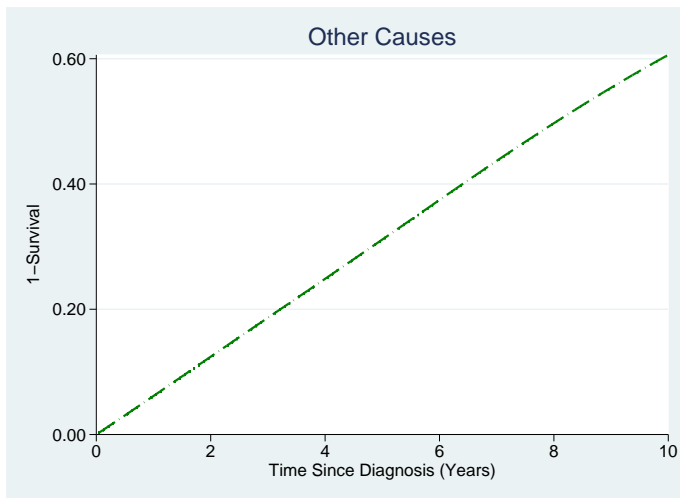
Probability of death from breast cancer, heart disease and other causes for ages 85+.

Cause-specific Survival?



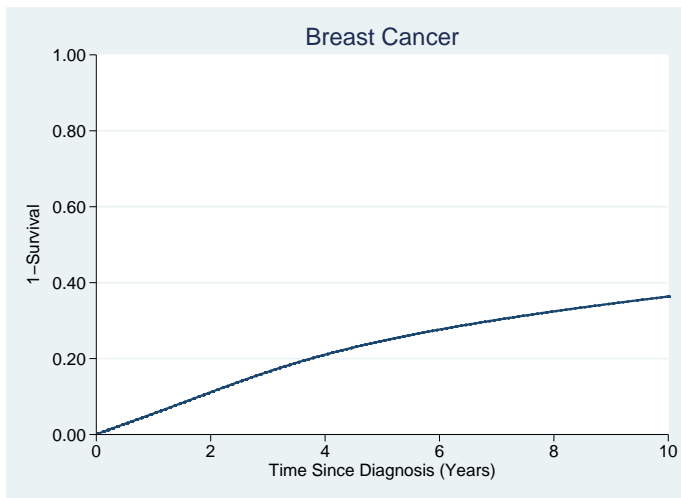
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Cause-specific Survival?



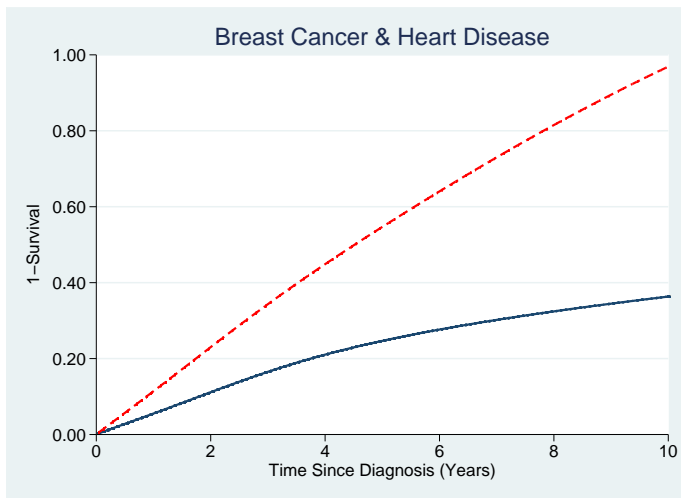
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Cause-specific Survival?



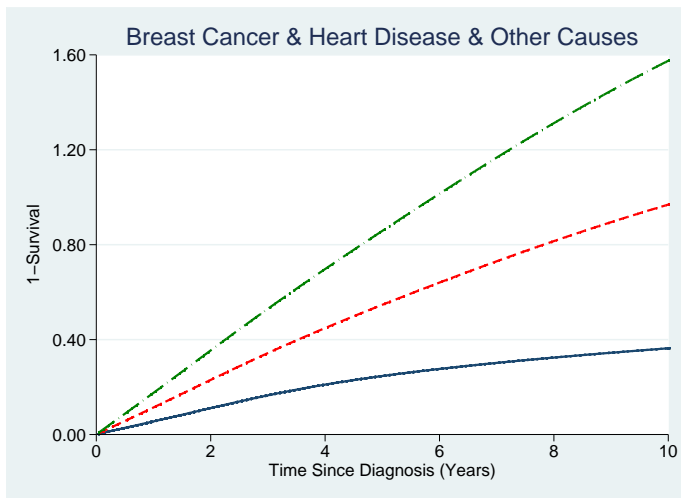
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Cause-specific Survival?



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Cause-specific Survival?



Probability of death from breast cancer, heart disease and other causes for ages 85+.

Cox proportional hazards model

- makes no assumptions about the baseline hazard function
- assumes proportional hazards

Flexible parametric model

- models baseline hazard function using restricted cubic splines
- easily incorporate time-dependent effects

Hazard Ratio

Age group	Cause-specific HR	P-value	95% CI
18-59	1.00	-	-
60-84	0.96	0.073	0.92 to 1.01
85+	2.11	<0.001	1.93 to 2.32

Table: Cause-specific hazard ratios for breast cancer.

Standard Survival Analysis Methods

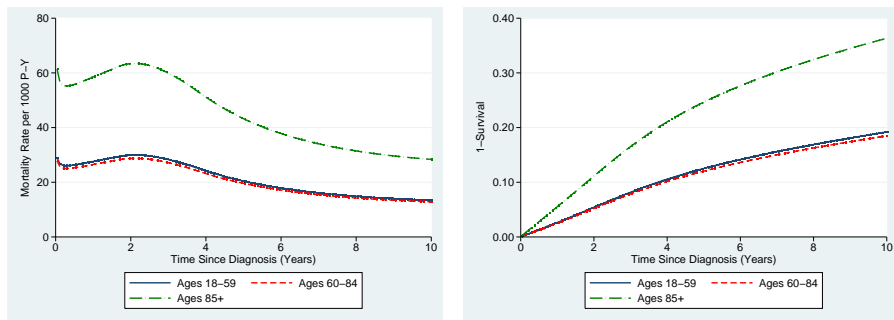


Figure: Cause-specific hazard and survival curves for breast cancer for each of 3 age groups.

- Direct relationship between cause-specific hazard rate and the probability of death (1-survival).

Competing Risks Analysis

- Better approach is to acknowledge that patients may die from something else other than cancer.
- Competing risks theory allows us to calculate “real world” probabilities where a patient is not only at risk of dying from their cancer but also from any other cause of death.
- The methods also provide a way of breaking down probabilities of death to give patients a clearer indication of the risks that they face with each decision that they make.

Cumulative Incidence Function (CIF)

The cumulative incidence function, $C_k(t)$, gives the proportion of patients at time t who have died from cause k accounting for the fact that patients can die from other causes.

$$C_k(t) = \int_0^t h_k(u | X) S(u) du$$

Notation

t - time

h_k - cause-specific hazard

X - vector of covariates

S - overall survival function

Cause-specific vs. Cumulative Incidence Function

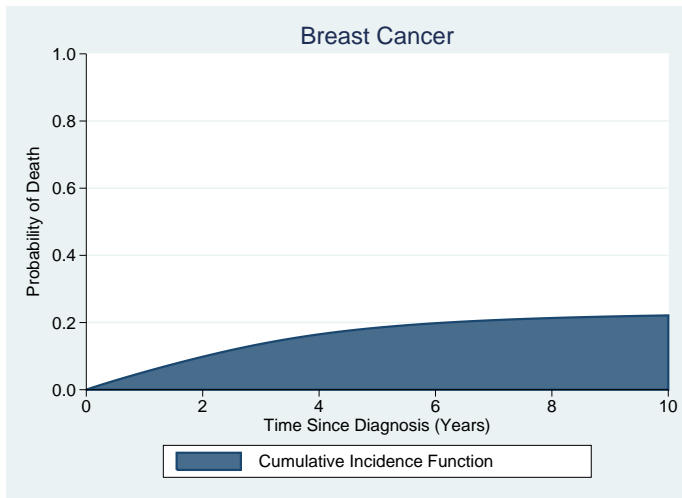


Figure: Cause-specific vs. cumulative incidence function for 85+ age group - FPM proportional hazards model.

Cause-specific vs. Cumulative Incidence Function

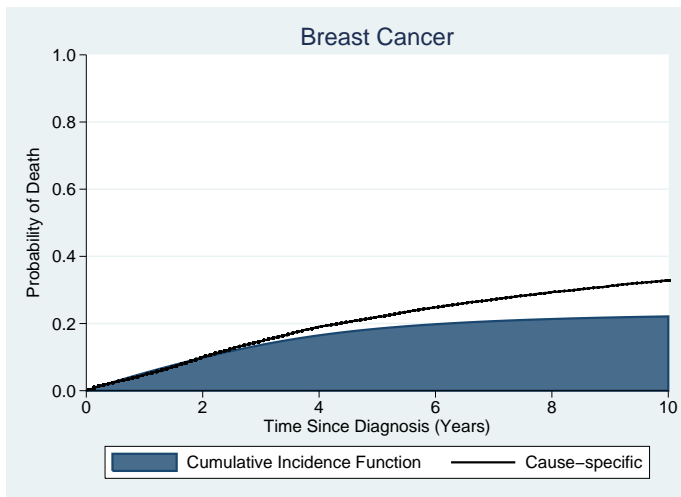


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Stacking the Cumulative Incidence Function

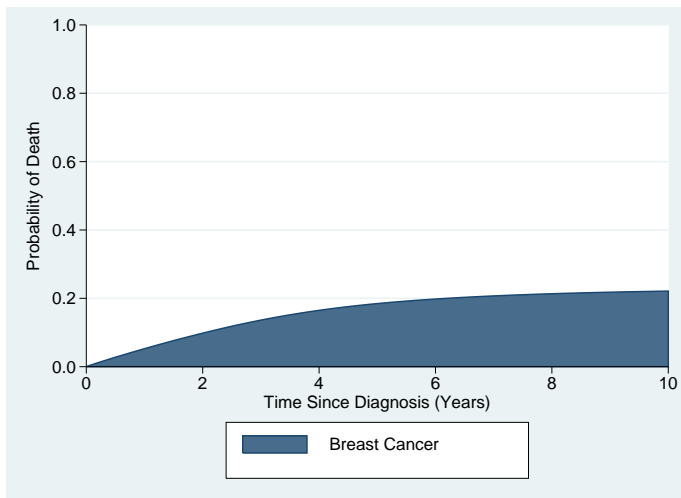


Figure: Stacked cumulative incidence functions for 85+ age group - FPM proportional hazards model.

Stacking the Cumulative Incidence Function

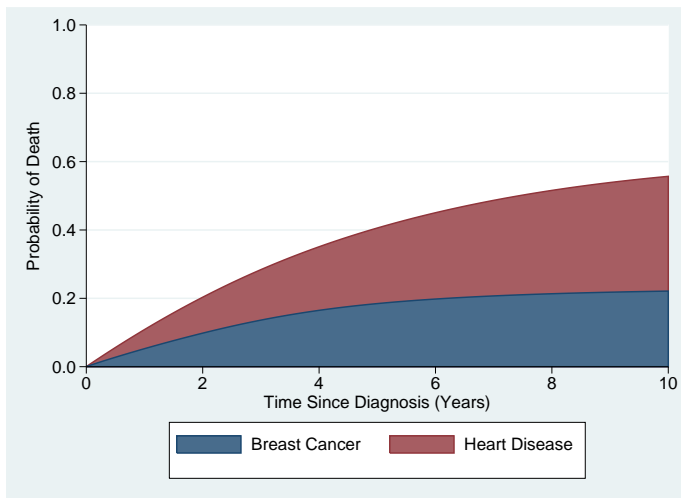


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Stacking the Cumulative Incidence Function

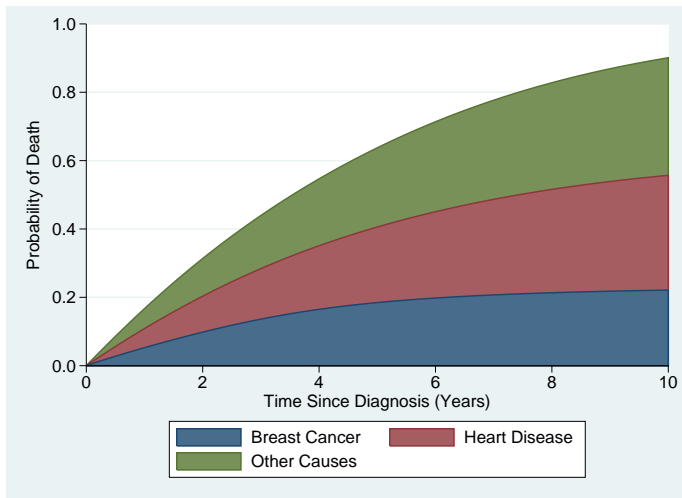


Figure: Stacked cumulative incidence functions for 85+ age group - FPM proportional hazards model.

Cumulative Incidence Function (CIF)

- The CIF for breast cancer will not only depend on the hazard for breast cancer but also on the hazards for heart disease and other causes.
- No longer a direct relationship between cause-specific hazard rate and the probability of death.
- Covariates may not be associated with the CIF in the same way that they associate with the cause-specific hazard.
- This property motivated models that directly link the cumulative incidence function to covariates - *Fine & Gray (1999)*

Fine and Gray Regression Model

- Modification of the Cox model that proposes direct transformation of CIF.
- Based on the relationship between the hazard and survival functions, they defined a subdistribution function. *Putter et al. (2007)*

Subdistribution Hazards

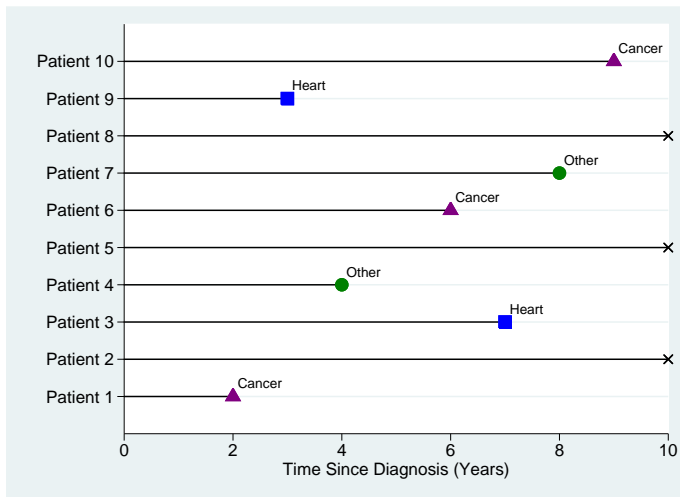
The subdistribution hazard, $h_{k_s}(t)$, is the instantaneous risk of dying from a particular cause k given that the subject has not died from cause k .

$$h_{k_s}(t) = \lim_{\delta t \rightarrow 0} \left\{ \frac{P(t \leq T < t + \delta t, K = k | T > t \text{ or } (T \leq t \ \& \ K \neq k))}{\delta t} \right\}$$

Subdistribution Hazards

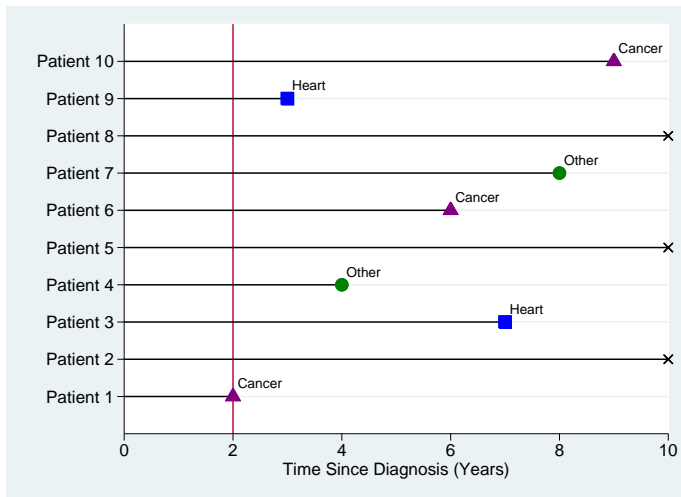
- The difference between cause-specific and subdistribution hazards is the risk set.
- For the cause-specific hazard the risk set decreases each time there is a death from another cause - censoring.
- With the subdistribution hazard subjects that die from another cause remain in the risk set and are given a censoring time that is larger than all event times.

Comparing Risks Sets



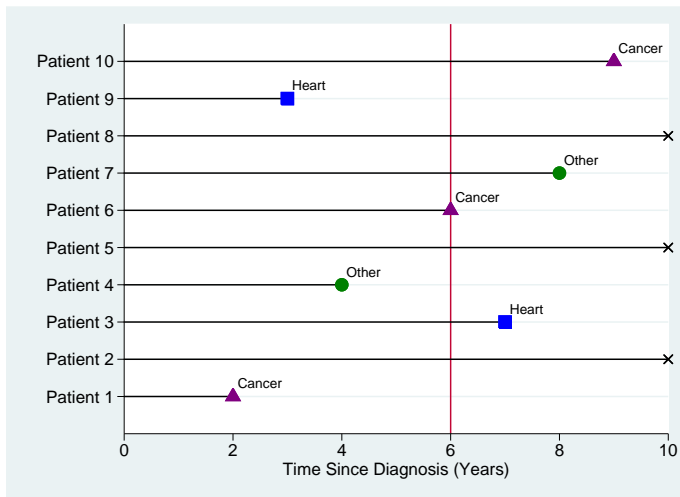
Risk sets for breast cancer when estimating cause-specific and subdistribution hazards.

Comparing Risks Sets



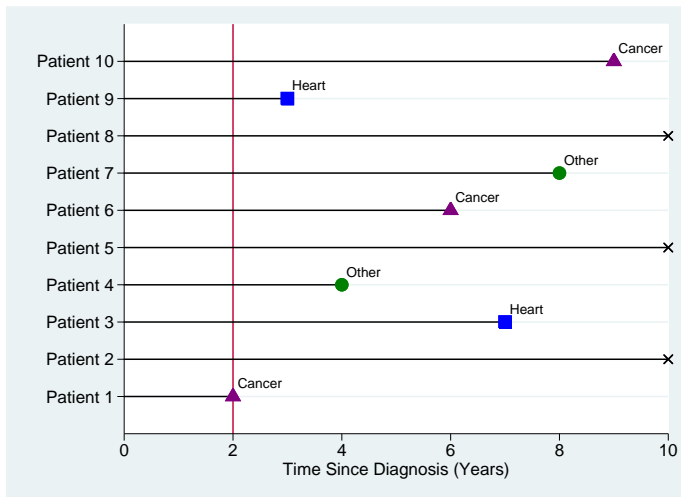
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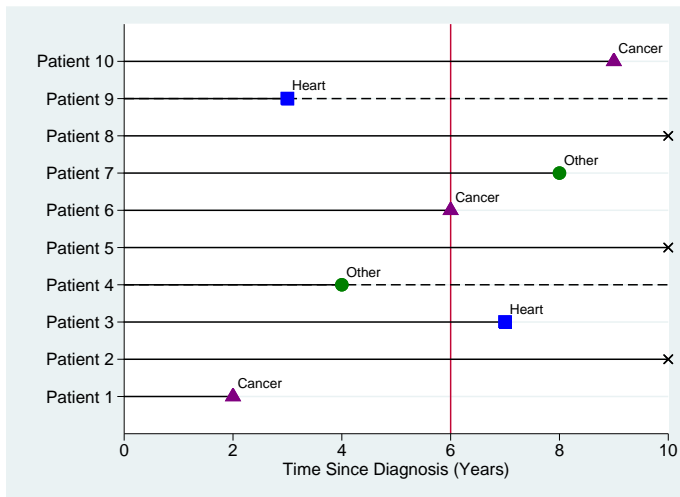
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Comparing Risks Sets



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Comparing Risks Sets



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Fine and Gray Regression Model

- There is a direct link between subdistribution hazards and CIF.
- Can now assess covariate effects on the CIF.

$$h_{k_s}(t) = -\frac{d\log(1 - C_k(t))}{dt}$$

Subhazard Ratios

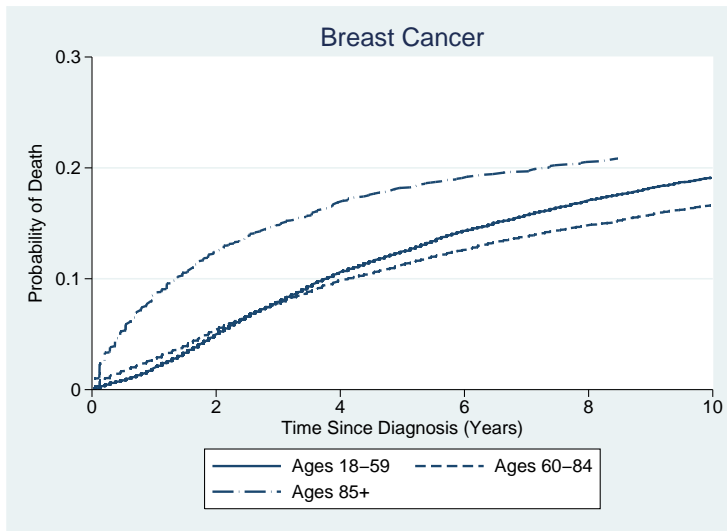
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85+	2.11	<0.001	1.93 to 2.32

Table: Cause-specific hazard ratios for breast cancer.

Age group	Subdistribution HR	P-value	95% CI
18-59	1.00	-	-
60-84	0.89	<0.001	0.85 to 0.93
85+	1.38	<0.001	1.25 to 1.52

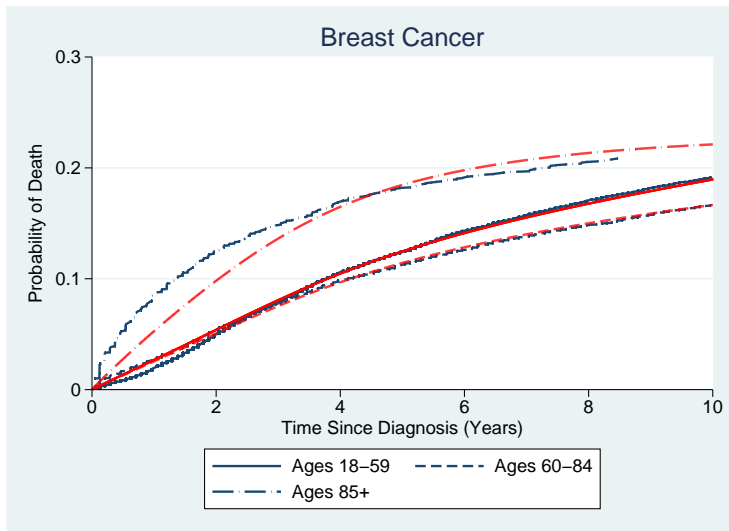
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Proportional (Sub)Hazards



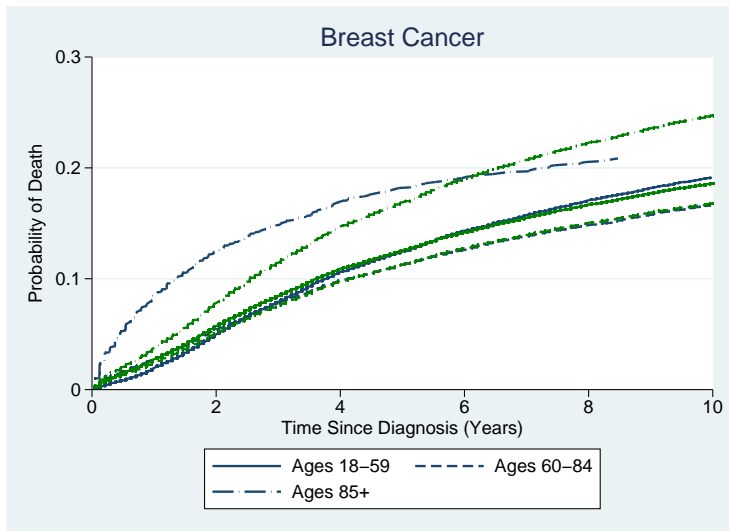
Non-parametric, FPM cause-specific, Fine and Gray subdistribution

Proportional (Sub)Hazards



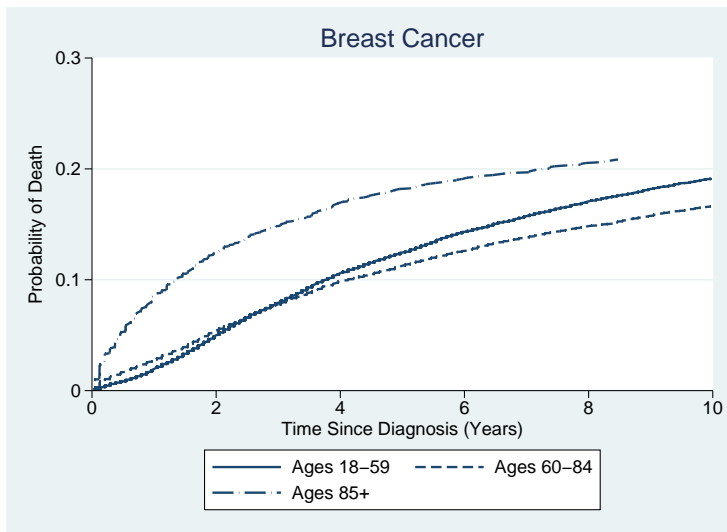
Non-parametric, **FPM** cause-specific, **Fine and Gray** subdistribution

Proportional (Sub)Hazards



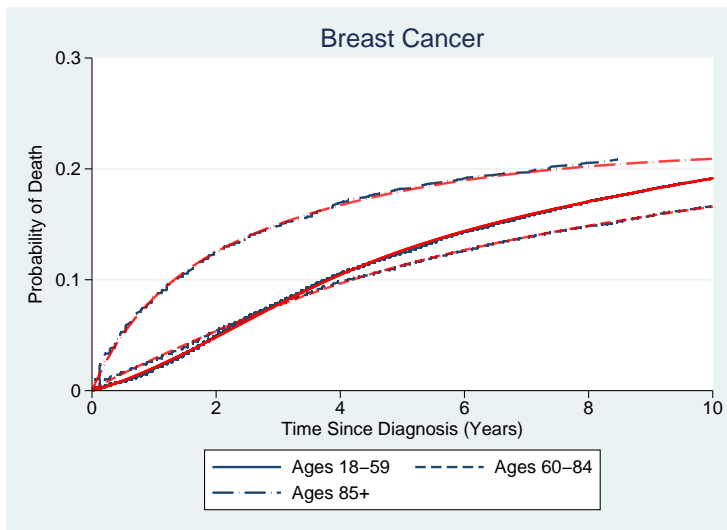
Non-parametric, **FPM** cause-specific, **Fine** and **Gray** subdistribution

Introducing Time-Dependent Effects



Non-parametric, FPM cause-specific, Fine and Gray subdistribution

Introducing Time-Dependent Effects



Non-parametric, FPM cause-specific, Fine and Gray subdistribution

Cause-specific

- Gives us relative measure - cause-specific hazard ratios.
- Can use any standard survival analysis method to obtain CIF.
- Covariates may not be associated with the CIF in the same way that they associate with the cause-specific hazard.

Subdistribution

- Subdistribution hazards account for competing events by altering risk set.
- Direct link between subdistribution hazard and CIF so can examine covariate effects.
- Subdistribution hazard has no resemblance to an epidemiological rate as individuals that die from other causes remain in the risk set. *Andersen et al. (2012)*

Stata

- `stcompet` - Non-parametric CIF calculation, based on Kaplan-Meier estimator.
- `stcompadj` - Cox model approach to computing CIF.
- `stpm2cif` - Flexible parametric model approach to computing CIF.
- `stcrreg` - Fine and Gray subdistribution approach to computing CIF.

Conclusion

What?

- Competing risks occur when a patient is at risk of more than one mutually exclusive event such as death from different causes.

Why and when?

- If we want real world probabilities of death then competing risks methodology should be used as opposed to standard survival analysis methods.
- Allows us to separate the probability of death into different causes.
- Stacked plots could be useful in explaining absolute risks to patients that have to choose between two treatment options.

How?

- Cause-specific approach can give use cause-specific hazards and CIFs both of which are useful interpretable quantities. However, we can not examine covariate effects on the CIF.
- Subdistribution approach allows us to test covariate effects on the CIF but subdistribution hazards are difficult to interpret and so should be used with caution.

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