SESSION 2: COMPETING RISKS, CAUSE-SPECIFIC HAZARDS, CUMULATIVE INCIDENCE AND FINE-GRAY MODELS

Module 13: Survival Analysis for Observational Data

Summer Institute in Statistics for Clinical Research
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OUTLINE

- Definition of competing risks
- Identifiability issues
- Estimating cumulative incidence
- Interpretation under independent competing risks
  – Cumulative incidence
  – Fine-Gray regression
  – Cox regression
  – Cause-specific hazards
- Interpretation under dependent competing risks
  – Cox regression and cause-specific hazards
  – Cumulative incidence and Fine-Gray regression
- Composite outcomes
- Examples

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COMPETING RISKS

- When there is more than one cause of failure:
  - Cancer recurrence or death before recurrence
  - MI, stroke, PE or death from other causes
- The different types of failure are called "competing risks".
  - They "compete" to be the first to make subjects experience an event

MONOCLONAL GAMMOPATHY

- 241 Mayo Clinic Patients (Monoclonal Gammopathy of Undetermined Significance)

- 20-40 years of follow-up after diagnosis

- 64 developed plasma cell malignancy (PCM), 163 died without it.

- PCM and death without PCM are competing risks

R Kyle, Benign monoclonal gammopathy – after 20 to 35 years of follow-up, Mayo Clinic Proc 1993; 68:26-36

DATA

- In the monoclonal gammopathy data, there are k = 2 competing risks

- Data for the ith subject are T_i and c_i, where
  - T_i = time to first of PCM or death
  - c_i = 1 if PCM; c_i = 2 if death

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CENSORING?

- Let c = k, k = 1, ..., K indicate the "cause" of failure out of K competing risks. Here K = 2 (PCM and death no PCM).

- Suppose we are interested in risk factors for the development of PCM

- How do we treat the subjects who die without having experienced PCM? Can we treat them as censored?

  – Censoring assumptions:

  – Are they met?

IDENTIFIABILITY AND COMPETING RISKS

- Tsiatis (1975) showed that we cannot identify from ($T, c = k$) data whether subjects who fail from one cause would have been more or less susceptible later to failure from another cause, had they survived.
  - Cannot tell whether those who die from heart disease would have been more or less likely to develop cancer had they lived.
  - Cannot tell whether those who die w/o PCM would have been more or less likely to develop PCM had they lived.
- Dependence between the competing risks is not identifiable from (T, c) data.

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TREATING DEATHS AS CENSORING

- What could be the effect on the KM estimate of S(t)?

- What could be the effect on Cox regression for the association of risk factors with PCM?

KAPLAN MEIER

- In situations like this, it was once common practice to apply the KM method to estimate "survival" functions:
  - Probability of avoiding PCM over time
  - Probability of avoiding death w/o PCM
- For PCM curve, treat deaths w/o PCM as censored
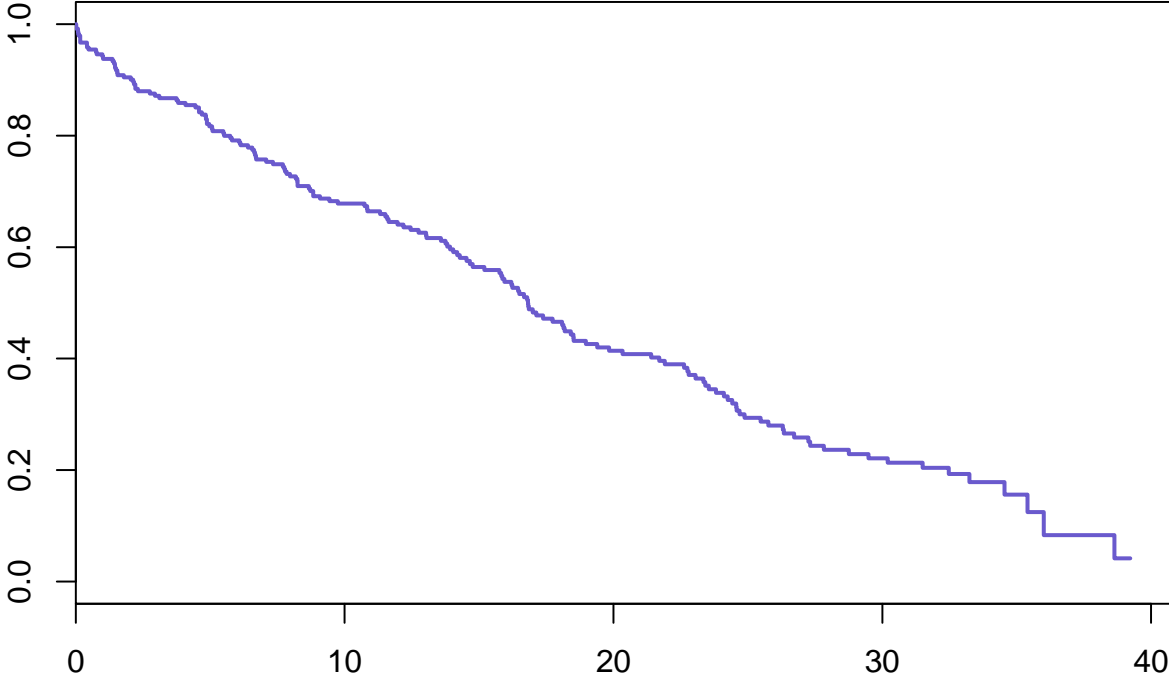- For death w/o PCM, treat PCMs as censored
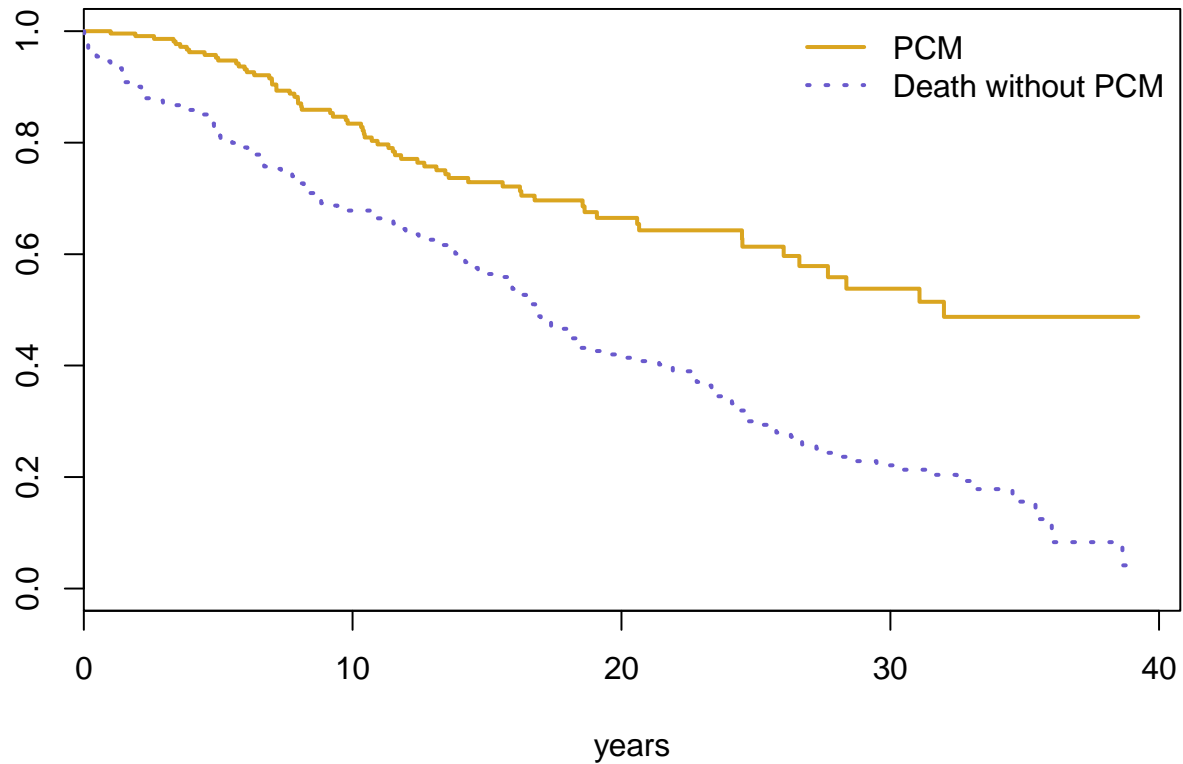
KM FOR NO PCM

Probability no PCM

years
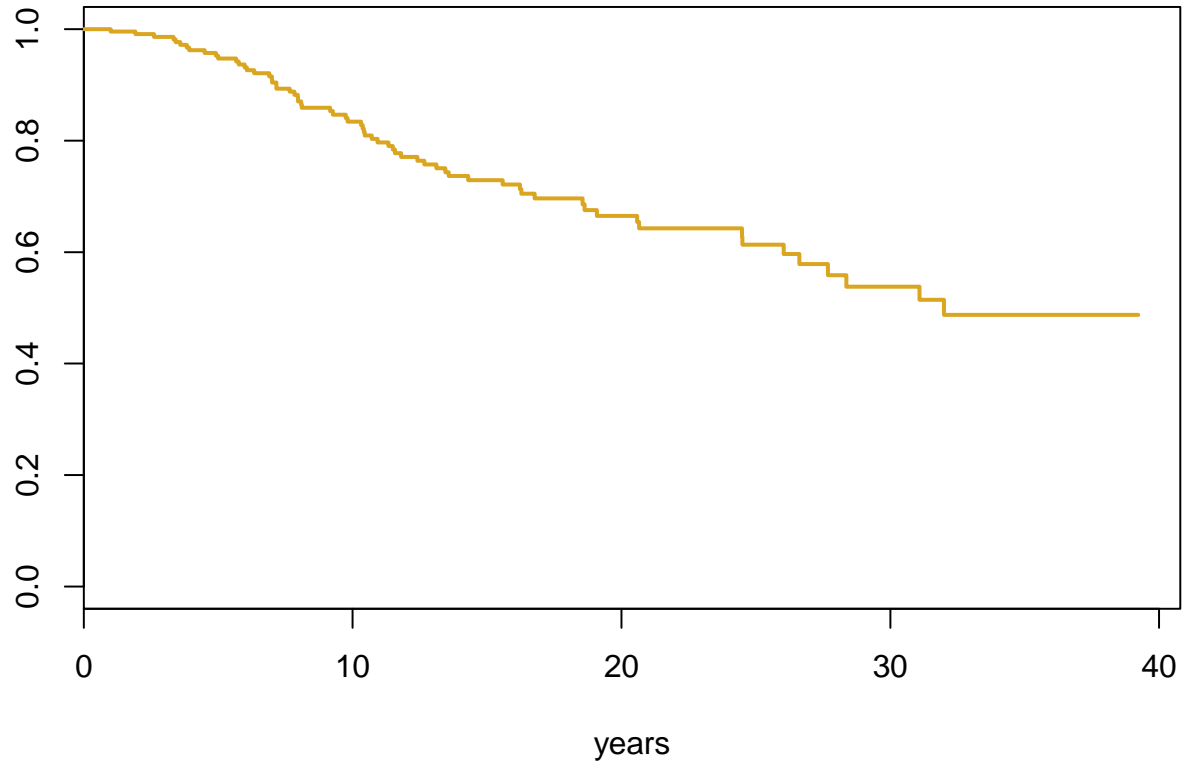
KM FOR DEATH NO PCM

Probability no Death without PCM

BOTH KM SURVIVAL FUNCTIONS

Probability of avoiding PCM or death w/o PCM

KM ESTIMATE OF S(t)

- Recall that the Kaplan-Meier estimate of the survival function S(t) = Pr[T > t] = the probability of surviving beyond time t is given by:

$$\hat{S}(t) = \prod_{j:t_{(j)} \leq t} \frac{S_{(j)}}{N_{(j)}}$$

- Where $t_{(j)}$ is the jth smallest failure time, $S_{(j)}$ is the number known to survive beyond $t_{(j)}$, and $N_{(j)}$ is the number at risk of being observed to fail at $t_{(j)}$.

ESTIMATING $1 - S(t)$ FOR K^{TH} TYPE

- We can write

$$1 - \hat{S}^{(k)}(t) = \sum_{j:t_{(j)} \leq t} \frac{D^{(k)}_{(j)}}{N_{(j)}} \hat{S}^{(k)}(t_{(j-1)})$$

- At the second failure time of type k,

$$1 - \hat{S}^{(k)}(t_{(2)}) = 1 - \frac{N_{(1)} - D^{(k)}_{(1)}}{N_{(1)}} \cdot \frac{N_{(2)} - D^{(k)}_{(2)}}{N_{(2)}} = \frac{D^{(k)}_{(1)}}{N_{(1)}} + \frac{D^{(k)}_{(2)}}{N_{(2)}} \cdot \frac{N_{(1)} - D^{(k)}_{(1)}}{N_{(1)}}$$

- If any failures of another type have occurred between $t_{(1)}$ and $t_{(2)}$, $the \frac{N_{(1)} - D^{(k)}_{(1)}}{N_{(1)}}$ term is too big.

- This bias will accumulate and get larger, as we move to larger and larger $t_{(j)}$.

ESTIMATING CUMULATIVE INCIDENCE

- Letting $D_{(j)}^{(\bar{k})}$ = the number of failures of types other than k at $t_{(j)}$, an <u>un</u>biased estimate of $F^{(k)}(t)$ is given by

$$\sum_{j:t_{(j)}\leq t} \frac{D_{(j)}^{(k)}}{N_{(j)}} \prod_{i=1}^{j-1} \frac{N_{(i)} - D_{(i)}^{(k)} - D_{(i)}^{(\bar{k})}}{N_{(i)}} = \sum_{j:t_{(j)}\leq t} \frac{D_{(j)}^{(k)}}{N_{(j)}} \prod_{i=1}^{j-1} \frac{N_{(i)} - D_{(i)}^{(k)}}{N_{(i)}} \cdot \frac{N_{(i)} - D_{(i)}^{(\bar{k})}}{N_{(i)}}$$
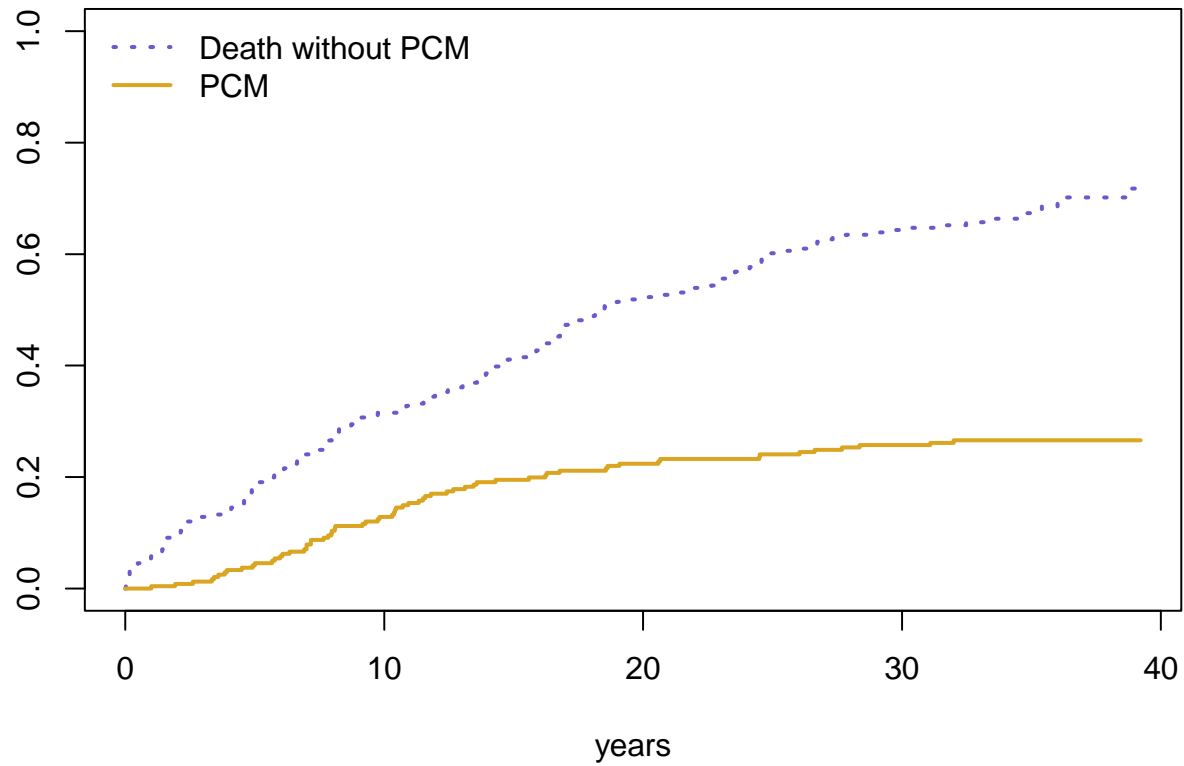
<div align="center">↑
no ties between failures of different types</div>
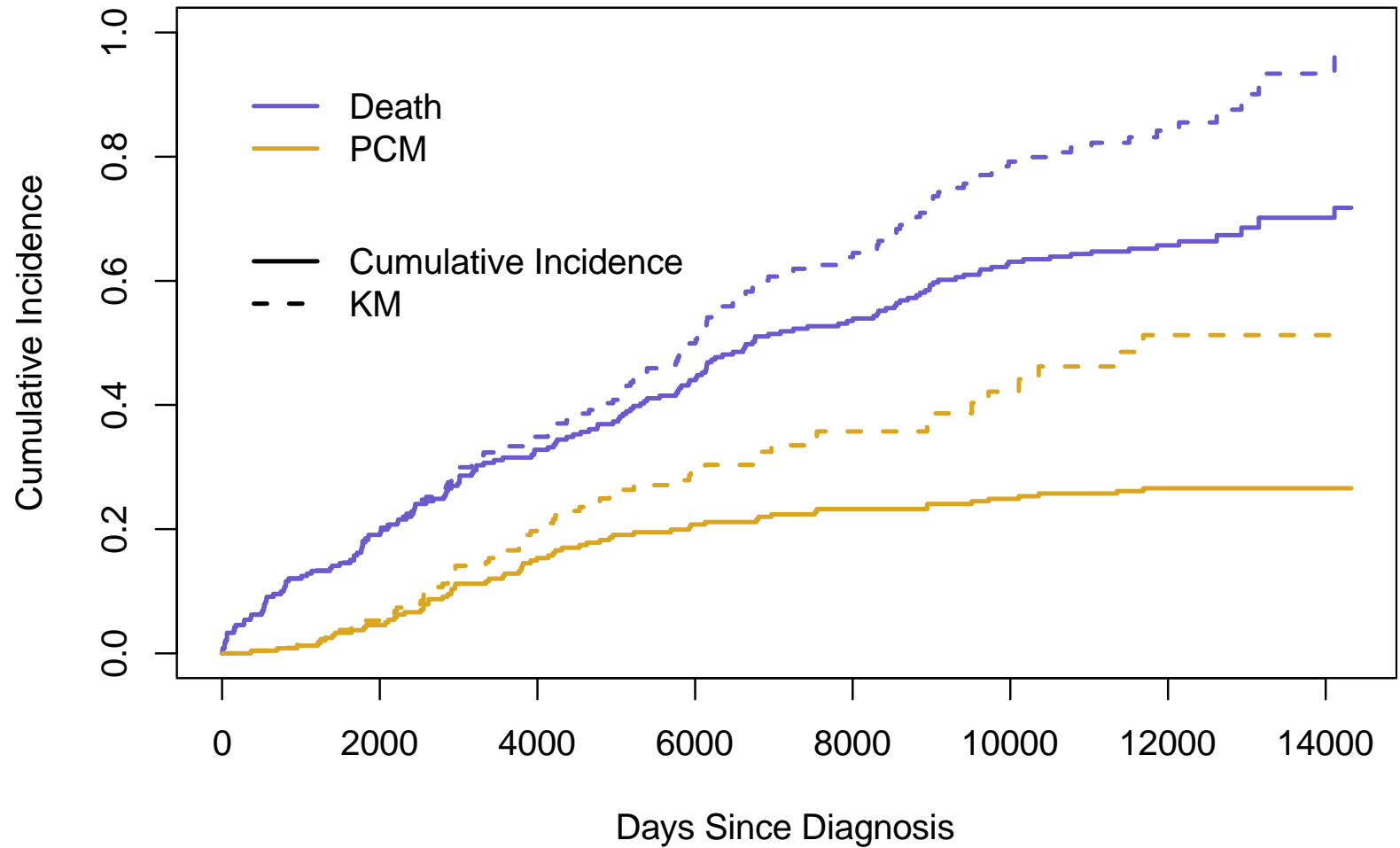
- Compare to biased upward

$$1 - \hat{S}^{(k)}(t) = \sum_{j:t_{(j)}\leq t} \frac{D_{(j)}^{(k)}}{N_{(j)}} \hat{S}^{(k)}(t_{(j-1)}) = \sum_{j:t_{(j)}\leq t} = \frac{D_{(j)}^{(k)}}{N_{(j)}} \prod_{i=1}^{j-1} \frac{N_{(i)} - D_{(i)}^{(k)}}{N_{(i)}}$$
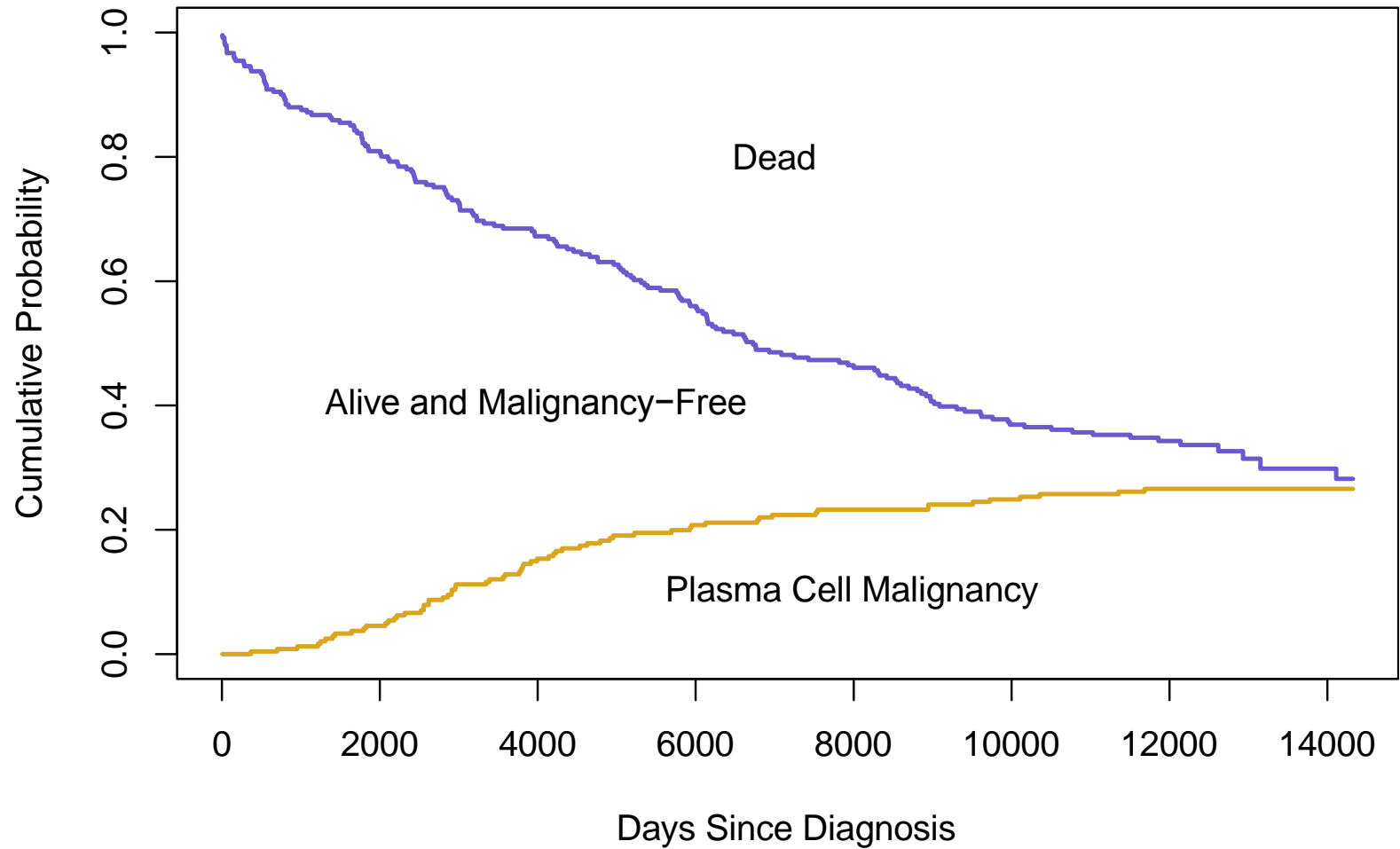
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CUMULATIVE INCIDENCE

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PREFERRED: TOGETHER

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START BY ASSUMING INDEPENDENCE

- To understand the strengths and weaknesses of estimating cumulative incidence and various regression models for competing risks data, it is helpful to begin by assuming the two risks are independent (unverifiable assumption)
  - Subjects who fail of one cause at t would have the same risk as those who do not fail of going on to experience the other event
  - In example: participants who die without PCM at t would be just as likely as those who do not to go on to develop PCM after t.

INDEPENDENT COMPETING RISKS AND CUMULATIVE INCIDENCE

- How might an intervention that increased the rate of the competing risk (death w/o PCM) influence the cumulative incidence of the event of interest (PCM)?

INDEPENDENT COMPETING RISKS AND CUMULATIVE INCIDENCE

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  - Higher death w/o PCM rate could mean fewer subjects develop PCM: ie. lower PCM incidence

SOME SUBTLETIES

- Cumulative incidence: the probability that an event of type k has occurred by time t:
  - Makes sense without requiring that a time to the kth type of event be defined for all subjects
  - Depends on the portion of the population still at risk at each time, so its value will depend not only on the risk of the event of interest, but also on the risk of all the other causes of failure.
  - Is a population-specific quantity that depends on what other risks are operating in the population and how they are related to the risk of the event of interest.

INDEPENDENT COMPETING RISKS AND CUMULATIVE INCIDENCE

- How might an intervention that increased the rate of the competing risk (death w/o PCM) influence the cumulative incidence of the event of interest (PCM)?
  - Higher death w/o PCM rate could mean fewer subjects develop PCM: ie. lower PCM incidence
  - Would we think this is wrong we were interested mainly in what influenced overall cost or prognosis?

INDEPENDENT COMPETING RISKS AND CUMULATIVE INCIDENCE

- How might an intervention that increased the rate of the competing risk (death w/o PCM) influence the cumulative incidence of the event of interest (PCM)?

  – Higher death w/o PCM rate could mean fewer subjects develop PCM: ie. lower PCM incidence

  – Would we think this is wrong we were interested mainly in what influenced cost or prognosis?

  – If <u>cost</u>, no. If <u>prognosis</u>, probably, though would want to look at association with all competing risks. This argues for a different (combined) definition of the event of interest. More on this later.

INDEPENDENT COMPETING RISKS AND CUMULATIVE INCIDENCE

- How might an intervention that increased the rate of the competing risk (death w/o PCM) influence the cumulative incidence of the event of interest (PCM)?

  - Higher death w/o PCM rate could mean fewer subjects develop PCM: ie. lower PCM incidence

- For understanding causal associations, how useful would it be to look at how risk factors are associated with the cumulative incidence?

INDEPENDENT COMPETING RISKS AND CUMULATIVE INCIDENCE

- How might an intervention that increased the rate of the competing risk (death w/o PCM) influence the cumulative incidence of the event of interest (PCM)?
  - Higher death w/o PCM rate could mean fewer subjects develop PCM: ie. lower PCM incidence
- For understanding causal associations, how useful would it be to look at how risk factors are associated with the cumulative incidence.
  - Not very. Apparent associations could be due to causal association only with the competing risk.

CUMULATIVE INCIDENCE: WHEN TO USE

- Q: For what types of questions would we be interested in cumulative incidence, and determining what variables associated with cumulative incidence?

- A:

CUMULATIVE INCIDENCE: WHEN TO USE

- Q: For what types of questions would we be interested in cumulative incidence, and variables associated with cumulative incidence?

- A: In studying prognosis, and variables related to prognosis like total cost, population disease burden.

INDEPENDENCE: WHEN TO USE

Q: When would we want to estimate the cumulative incidence?

"Independent" competing risks		
	Prognosis/Cost	**Causality**
Estimating distribution of T	Cumulative Incidence (Not KM)	
Regression		

ASSOCIATIONS WITH PROGNOSIS

- To see if a risk factor is associated with prognosis/cost, best to see how it is related to cumulative incidence.

- Fine-Gray regression models are the analogue of Cox regression for the cumulative incidence function.

FINE-GRAY HAZARD

$$\lambda^{FG(k)}(t) = \lim_{\Delta t \to 0} \Pr[T \in [t, t+\Delta t), c = k | T \geq t \text{ or both } T < t \text{ and } c \neq k]/\Delta t$$

- The risk of failure of type k among those still event free at t and those who have experienced any event other than a type k event by time t. (Note if type k is not death, this would include subjects who had already died.)

- The hazard function associated with the sub-distribution function which is the cumulative incidence of a type-k failure.

FINE-GRAY MODEL

- Fine-Gray hazard

$$\lambda^{FG(k)}(t) = \lim_{\Delta t \to 0} \Pr[T \in [t, t+\Delta t), c = k | T \geq t \text{ or both } T < t \text{ and } c \neq k]/\Delta t$$

- Fine-Gray regression model

$$\lambda^{FG(k)}(t|\mathbf{x}) = \lambda^{FG(k)}(t|\mathbf{0})e^{\beta \mathbf{x}}$$

INTERPRETATION

- When is Fine-Gray model appropriate?

- When concern is about associations with population burden of Type k events (ie PCM), total cost of type k events, or patient prognosis

FINE-GRAY RISK SETS

- All those who have not yet failed of any cause <u>PLUS</u> all those who have previously failed of all causes other than the cause of interest

- In monoclonal gammopathy example, assuming interest is in association with PCM, at time t, the risk sets is composed of:

  – All those alive and at risk of developing PCM <u>AND</u>
  – All those who died earlier without PCM

INDEPENDENCE: WHEN TO USE

Q: What regression model to use when interested in prognosis or total cost?

"Independent" competing risks		
	Prognosis/Cost	**Causality**
Estimating distribution of T	Cumulative Incidence (Not KM)	
Regression	Fine/Gray regression	

CAUSALITY AND INDEPENDENT COMPETING RISKS

- Q: So if we are interested in what is causally related to one of our competing risks and we think the different risks are independent, what can we do?

- A:

CAUSALITY AND INDEPENDENT COMPETING RISKS

- Q: So if we are interested in what is causally related to one of our competing risks and we think the different risks are independent, what can we do?

- A: Cox regression.

  – When we treat failures of the other types like we treat censoring, we are estimating the association with the "cause-specific hazard function" (Prentice et al., 1978)

$$\lambda^{(k)}(t) = \lim_{\Delta t \to 0} \Pr[T \in [t, t + \Delta t), c = k | T \geq t]/\Delta t$$

PROPERTIES

T =   time to first "failure" of any type

$$\lambda^{(k)}(t) = \lim_{\Delta t \to 0} \Pr[T \in [t, t + \Delta t), c = k | T \geq t]/\Delta t$$

• The different events defined by c must be mutually exclusive

• The different events defined by c must be exhaustive

• The hazard function for the distribution of T is given by :

$$\lambda(t) = \sum_{k=1}^{K} \lambda^{(k)}(t)$$

COX MODEL RISK SETS

- All those who have not yet failed of any cause
- In monoclonal gammopathy example, assuming interest is in association with PCM, at time t, the risk sets is composed of:
  - All those alive, PCM free, and at risk of developing PCM
- Under independent competing risks, this will not be affected by variables that cause differences in the risk of failure due to other causes (death no PCM).
  - If more people die sooner without PCM, there are fewer PCM events in the population, but there are also fewer subjects in the risk set (denominator).
  - If the risks are independent, the cause-specific hazard function should be unaffected.

COX MODEL

- Cause-specific hazard

$$\lambda^{(k)}(t) = \lim_{\Delta t \to 0} \Pr[T \in [t, t + \Delta t), c = k | T \geq t]/\Delta t$$

- Cox model

$$\lambda^{(k)}(t|\mathbf{x}) = \lambda^{(k)}(t|\mathbf{0})e^{\beta \mathbf{x}}$$
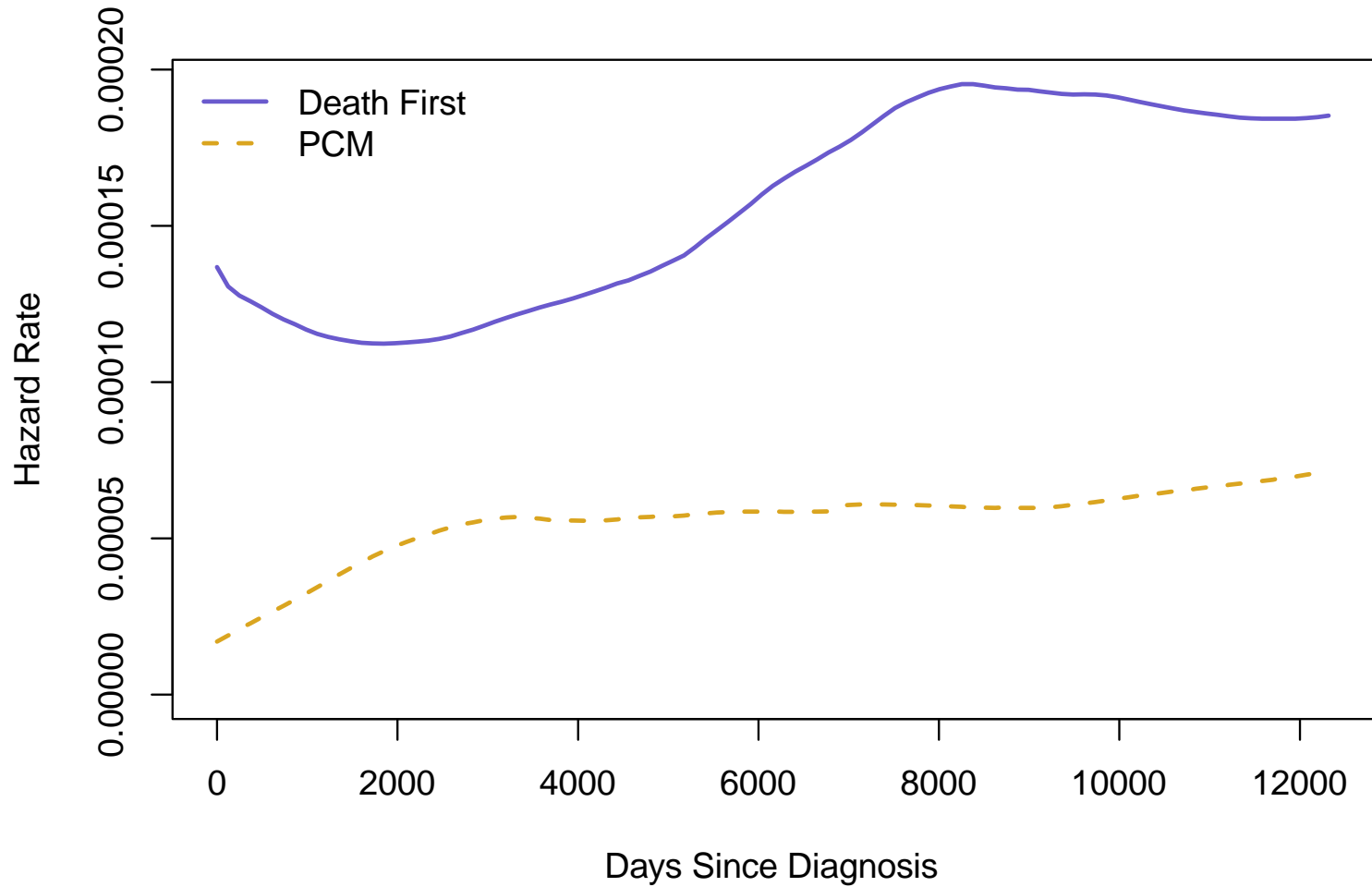
INDEPENDENCE: WHEN TO USE

Q: What to plot when interested in causality?

"Independent" competing risks		
	Prognosis/Cost	**Causality**
Estimating distribution of T	Cumulative Incidence (Not KM)	
Regression	Fine/Gray regression	Cox regression

INDEPENDENCE: DISTRIBUTION ESTIMATION FOR CAUSALITY

- Can estimate the cause-specific hazard function for a subgroup (or the whole sample) using kernel – smoothing methods (not covered).

- Allows visual comparison of the cause-specific hazard functions

MG DATA : HAZARDS

INDEPENDENCE: WHEN TO USE

Q: What to plot when interested in causality?

"Independent" competing risks		
	Prognosis/Cost	**Causality**
Estimating distribution of T	Cumulative Incidence (Not KM)	Kernel-smoothed cause-specific hazards
Regression	Fine/Gray regression	Cox regression

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DEPENDENT COMPETING RISKS

- How do these interpretations and recommendations change when we think the competing risks might be dependent?

  - As <u>one</u> example: What if subjects who died with without PCM were also less likely to go on to develop PCM, had they lived? (ie. Pretend population is a mix of susceptibles to PCM and susceptibles to death from other causes.) How would this affect interpretation of:

    - Cumulative incidence?
    - Cause-specific hazard?

DEPENDENT COMPETING RISKS

- In addition, suppose there is a potential risk factor that raises the risk of death with no PCM among susceptibles (and that susceptibles who die without PCM would be unlikely to go on to develop PCM)

- How might this risk factor affect the <u>cause-specific hazard function</u> for PCM?

DEPENDENT COMPETING RISKS

- In addition, suppose there is a potential risk factor that raises the risk of death with no PCM among susceptibles (and that susceptibles who die without PCM would be unlikely to go on to develop PCM)

- How might this risk factor affect the cause-specific hazard function for PCM?

  - It could raise it (fewer alive and at risk at any time, but a higher proportion of them develop PCM)

- Do we care?

DEPENDENT COMPETING RISKS

- In addition, suppose there is a potential risk factor that raises the risk of death with no PCM among susceptibles (and that susceptibles who die without PCM would be unlikely to go on to develop PCM)
- How might this risk factor affect the cause-specific hazard function for PCM?
  - It could raise it (fewer alive and at risk at any time, but a higher proportion of them develop PCM)
- Do we care?
  - Yes if interested in causality for PCM. Risk factor associated with PCM cause-specific hazard, but not biologically/causally related to the PCM disease process.
  - Perhaps not if interested in predicting annual per-person cost.

INTERPRETATION

- Prentice et al (1978) argued that the cause-specific hazard function (Cox model) was the best basis for causal inference in the population as it is constituted, but cannot extend interpretation to another population where competing risks are not operating.
  - Cannot say how x might be related to cancer risk in a population where there are no deaths from MI

DEPENDENT COMPETING RISKS

- Still suppose there is a potential risk factor that raises the risk of death with no PCM among susceptibles (and that susceptibles who die without PCM would be unlikely to go on to develop PCM)

- How might this risk factor affect the <u>cumulative incidence</u> of PCM?

DEPENDENT COMPETING RISKS

- Still suppose there is a potential risk factor that raises the risk of death with no PCM among susceptibles (and that susceptibles who die without PCM would be unlikely to go on to develop PCM)

- How might this risk factor affect the <u>cumulative incidence</u> of PCM?
  - Might not affect it much if the two sub-populations of susceptibles are entirely distinct.

- Do we care?

DEPENDENT COMPETING RISKS

- Still suppose there is a potential risk factor that raises the risk of death with no PCM among susceptibles (and that susceptibles who die without PCM would be unlikely to go on to develop PCM)
- How might this risk factor affect the <u>cumulative incidence</u> of PCM?
  - Might not affect it much if the two sub-populations of susceptibles are entirely distinct.
- Do we care?
  - No. Fine-Gray regression gives valid estimate of association with prognosis and total cost in population as currently constituted.

DEPENDENT COMPETING RISKS

- As <u>another</u> example: What if subjects who died with without PCM were <u>more</u> likely to go on to develop PCM, had they lived? (ie. Pretend some members of the population are frail and susceptible to both PCM and other causes of death.) How would this affect interpretation of:

  - Cumulative incidence?
  - Cause-specific hazard?

DEPENDENT COMPETING RISKS

- Pretend some members of the population are frail and susceptible to both PCM and other causes of death, so those who die without PCM would have been <u>more</u> likely to develop it, had they lived.

- How might a risk factor that increases the risk of death without PCM affect the <u>cause-specific hazard function</u> for PCM?

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DEPENDENT COMPETING RISKS

- Pretend some members of the population are frail and susceptible to both PCM and other causes of death, so those who die without PCM would have been <u>more</u> likely to develop it, had they lived.

- How might a risk factor that increases the risk of death without PCM affect the <u>cause-specific hazard function</u> for PCM?

  – It could lower it (presence of risk factor is depleting the population of susceptibles)

- Do we care?

DEPENDENT COMPETING RISKS

- Pretend some members of the population are frail and susceptible to both PCM and other causes of death, so those who die without PCM would have been <u>more</u> likely to develop it, had they lived.

- How might a risk factor that increases the risk of death without PCM affect the <u>cause-specific hazard function</u> for PCM?
  - It could lower it (presence of risk factor is depleting the population of susceptibles)

- Do we care?
  - Perhaps, if interested in biologic causality for PCM.
  - Perhaps not, if interested in predicting annual per-person cost.

DEPENDENT COMPETING RISKS

- Pretend some members of the population are frail and susceptible to both PCM and other causes of death, so those who die without PCM would have been <u>more</u> likely to develop it, had they lived.

- How might this risk factor affect the <u>cumulative incidence</u> of PCM?
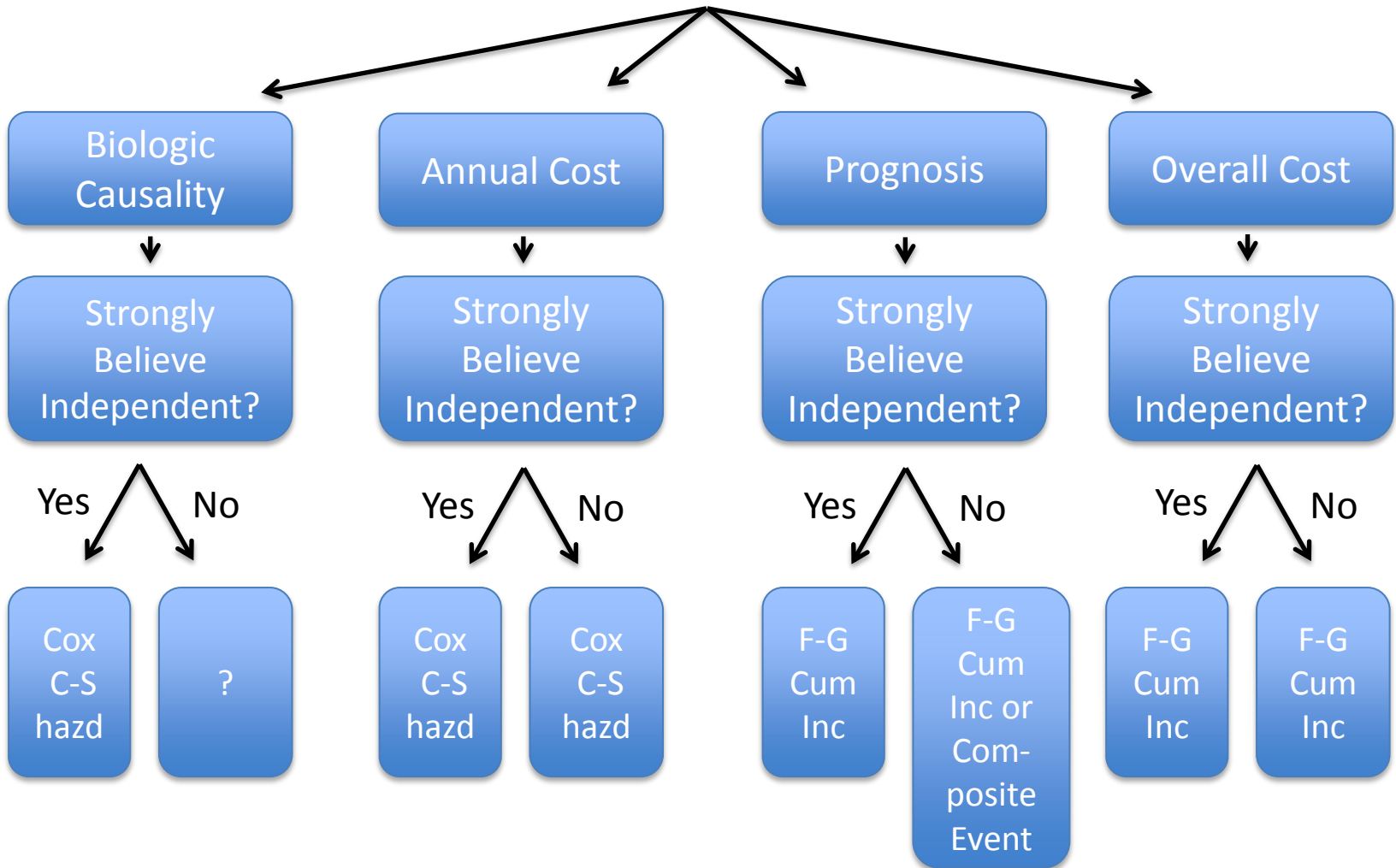
DEPENDENT COMPETING RISKS

- Pretend some members of the population are frail and susceptible to both PCM and other causes of death, so those who die without PCM would have been <u>more</u> likely to develop it, had they lived.

- How might this risk factor affect the <u>cumulative incidence</u> of PCM?

  - Might lower it. (presence of risk factor depletes the population of susceptibles)

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DEPENDENT COMPETING RISKS

- Pretend some members of the population are frail and susceptible to both PCM and other causes of death, so those who die without PCM would have been <u>more</u> likely to develop it, had they lived.

- How might this risk factor affect the <u>cumulative incidence</u> of PCM?

  – Might lower it. (presence of risk factor depletes the population of susceptibles)

- Do we care?

  – No. Accurate estimate of association with prognosis and total cost in population as currently constituted.

DEPENDENT COMPETING RISKS

"Dependent" competing risks		
	Prognosis/Cost	**Causality**
Estimating distribution of T	Cumulative Incidence (Not KM)	? Interpreting cause-specific hazard estimates may require knowledge/assumption about mechanism
Regression	Fine/Gray regression	? Interpreting Cox regression may require knowledge/assumption about mechanism

COMPETING RISKS: IMPORTANT POINTS

- Because we cannot tell whether competing risks are dependent, we cannot estimate hazard or incidence or anything else about the distribution of the event (time) of interest if there were no competing risks.

- All we can estimate and relate exposures to is the cumulative incidence and cause-specific hazard of the event of interest in the population as it is constituted (with potentially dependent competing risks).

COMPETING RISKS: IMPORTANT POINTS

- Biologic causality inferences from Cox regression must depend not only on the data, but also on biologic knowledge/assumptions that cannot be verified in the data.

- Cumulative incidence estimation and Fine-Gray regression are OK for inferences about prognosis or total cost even in the face of dependent competing risks, but these are not the same as inferences about biologic causality and may not be what we are interested in.

ADJUSTED FOR COMPETING RISKS

- Some people think of the results of Fine-Gray regression as <u>the</u> regression method that is "adjusted for competing risks"
- This is <u>incorrect</u>!
  - Fine-Gray regression gives us valid inferences about how variables are related to the cumulative incidence function.
  - It does not give us valid inferences about biologically causal associations between and exposure and the event of interest
  - Cox regression for cause-specific hazard functions can give valid inferences about biologically causal associations between exposure and the event of inference <u>if</u> the competing risks are independent, but we have no way of telling if they are.
  - If competing risks are not independent, all it tells us is how disease incidence rates in the population as it is constituted are related to exposure.

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PROGNOSIS

- If both competing risks are events we hope to avoid, Fine-Gray regression of risk factor's association with cumulative incidence of a single one of the risks may not be the most useful for estimating association with prognosis.

- Another option: composite events:

  - Death or PCM

  - Cancer relapse or death ("progression-free survival")

  - Death from any cause

- In clinical studies, combined event often of most interest to a patient

CUMULATIVE FUNCTIONS

Event-free Survival:

Estimating the probability a subject is alive and event-of-interest-free at time t is easy:
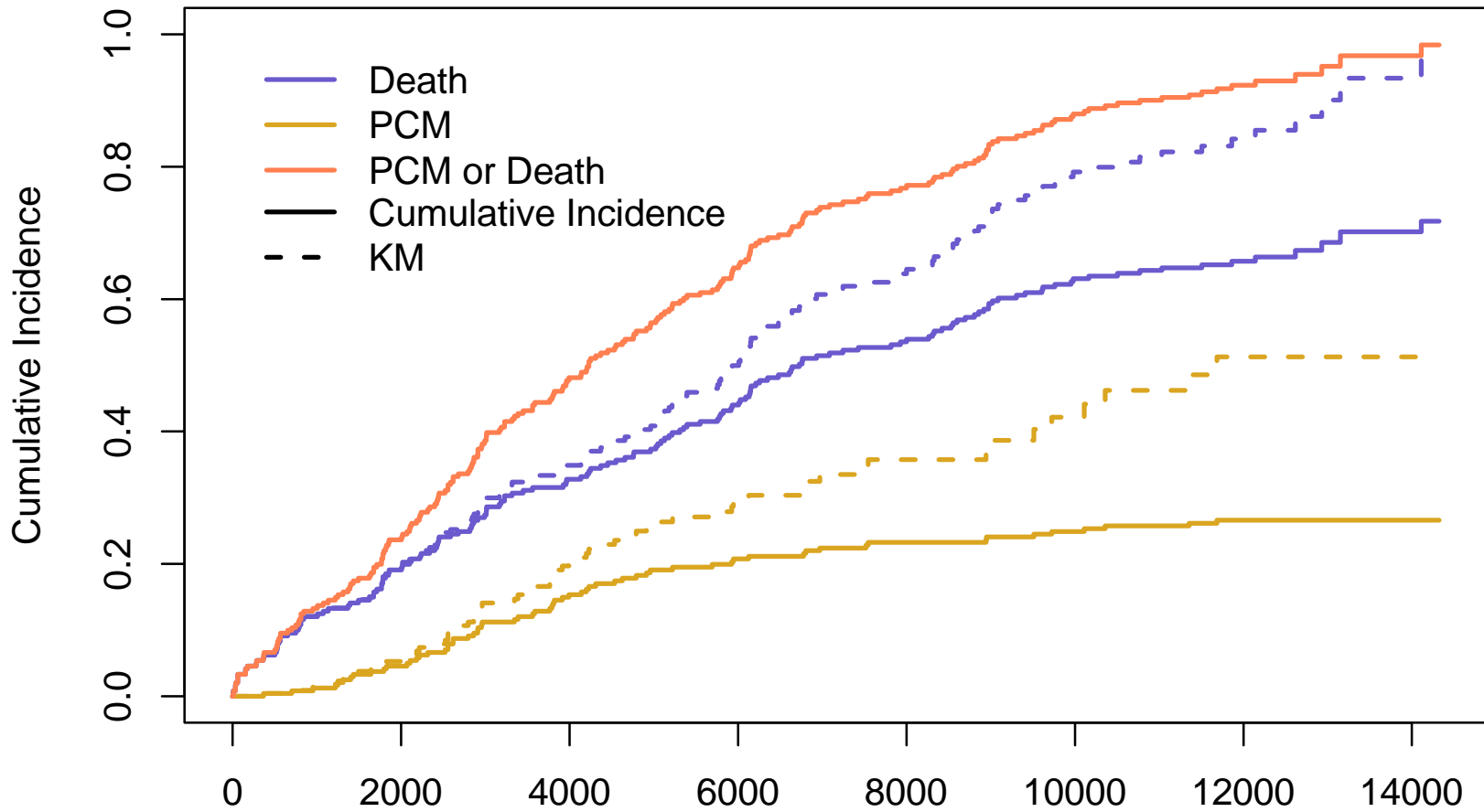
1. Redefine the event of interest to be either the original event of interest or death

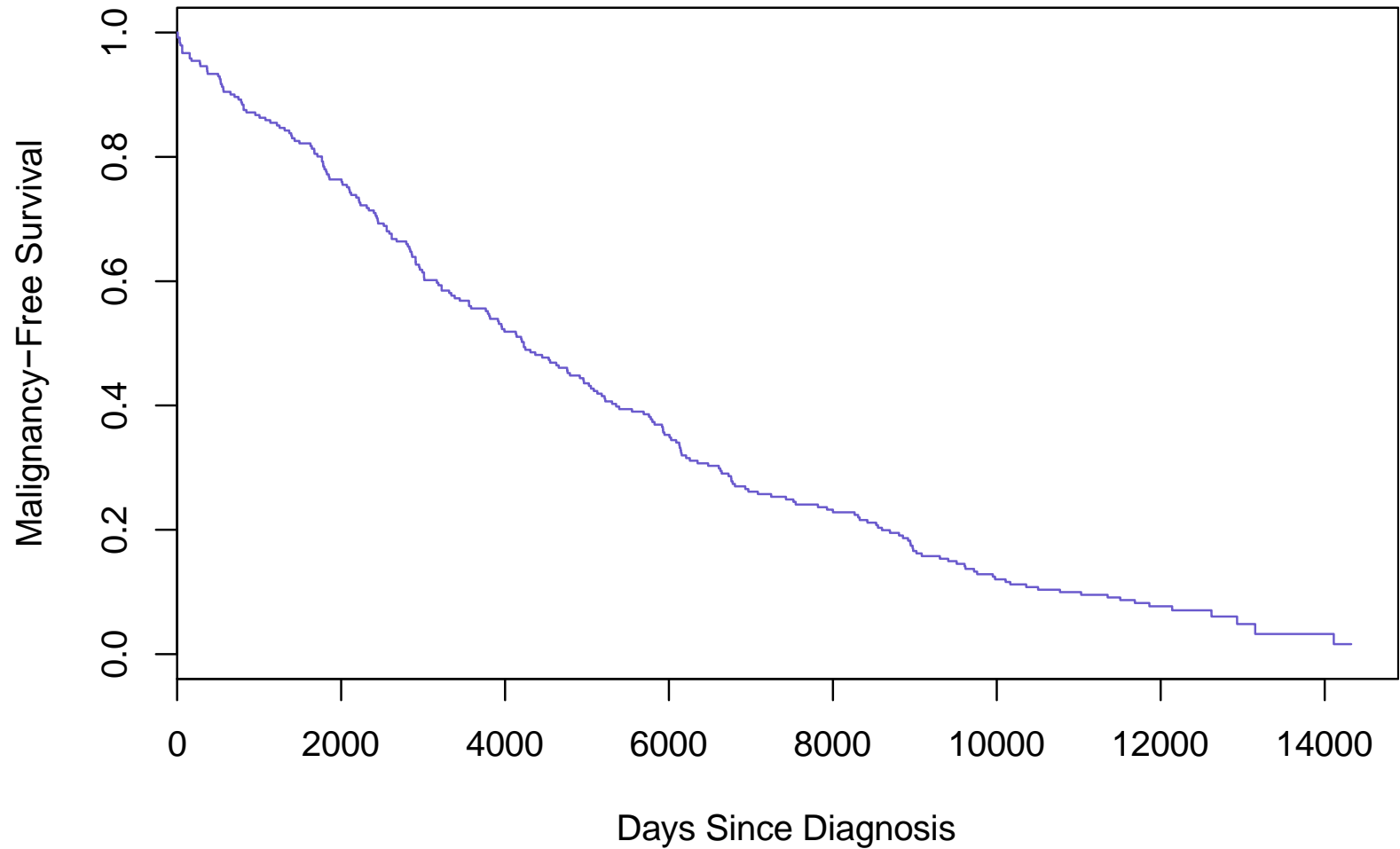$$\delta_i = \begin{cases} 1 & \text{event of interest or death from any cause} \\ 0 & \text{censored} \end{cases}$$

$$T_i = \text{ time to event of interest, death or censoring}$$

2. Compute the KM estimate of $S(t)$ in the usual way with (T_i, δ_i) data.
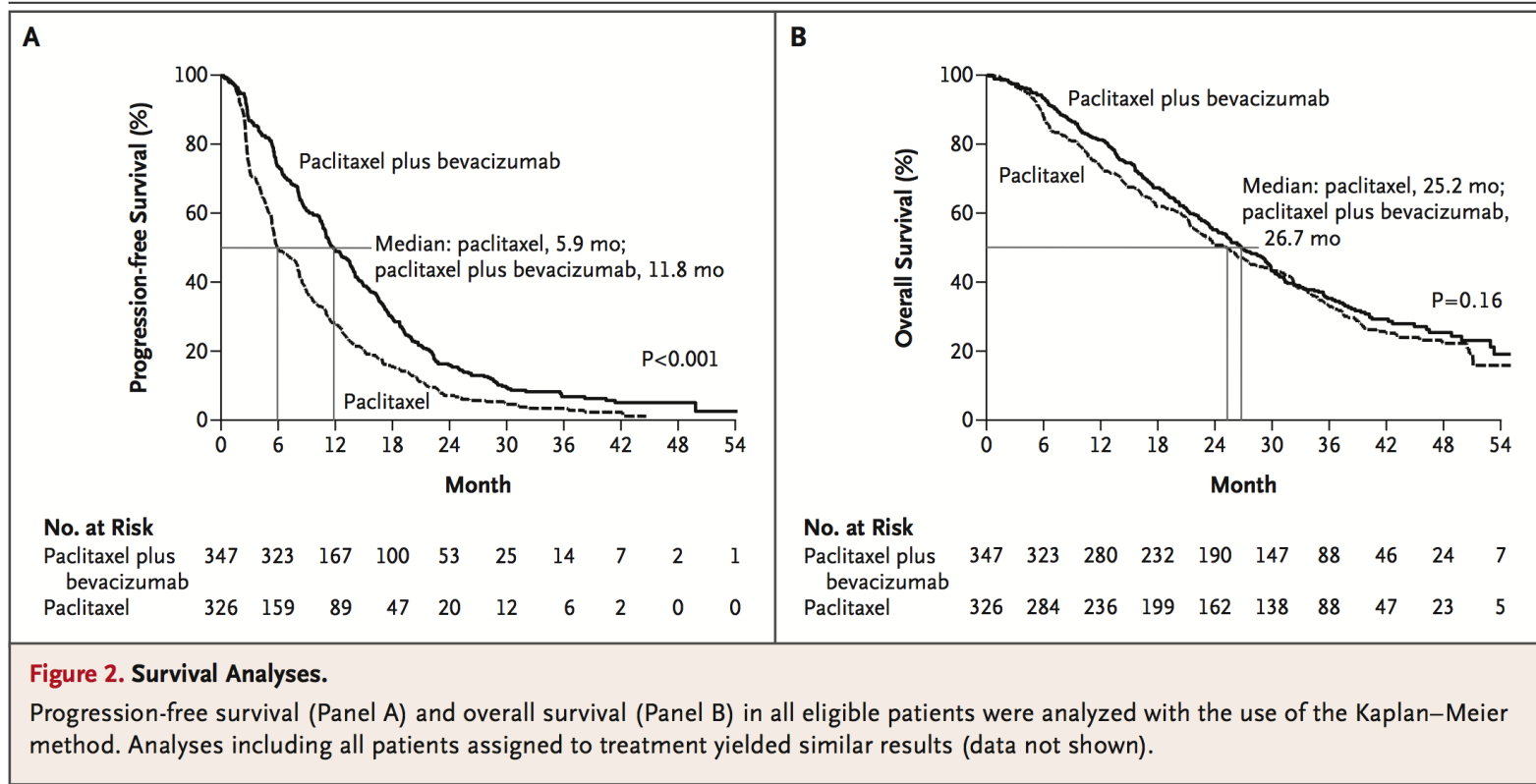
CUMULATIVE INCIDENCE

MALIGNANCY-FREE SURVIVAL

EXAMPLE

Miller K, Wang M, Gralow J, Dickler M, Cobleigh M, Perez EA, Shenkier T, Cella D, Davidson NE. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. New England Journal of Medicine. 2007;357(26):2666–2676.

Figure 2. Survival Analyses.

Progression-free survival (Panel A) and overall survival (Panel B) in all eligible patients were analyzed with the use of the Kaplan–Meier method. Analyses including all patients assigned to treatment yielded similar results (data not shown).

FINE POINT

- When there are competing risks, functions that describe the probability distribution of the time to one of the events do not make sense.

- Cannot talk about $P[T > t]$ or $P[T \leq t]$ for a time to PCM T, since T does not exist for everyone

- Instead, need to interpret these functions as "Event has happened by time t" (cumulative incidence at t) and "Event has not happened by time t" (1 – cumulative incidence at t).

OUTLINE

- Definition of competing risks
- Identifiability issues
- Estimating cumulative incidence
- Interpretation under independent competing risks
  – Cumulative incidence
  – Fine-Gray regression
  – Cox regression
  – Cause-specific hazards
- Interpretation under dependent competing risks
  – Cox regression and cause-specific hazards
  – Cumulative incidence and Fine-Gray regression
- Composite outcomes
- **Examples**

MGUS REGRESSION EXAMPLE

- Cox and Fine-Gray models for the association of sex with PCM and Death before PCM in the Monoclonal Gammopathy data.

- Will show

  – Cause-specific hazard functions by sex and cause

  – Cumulative incidence functions by sex and cause

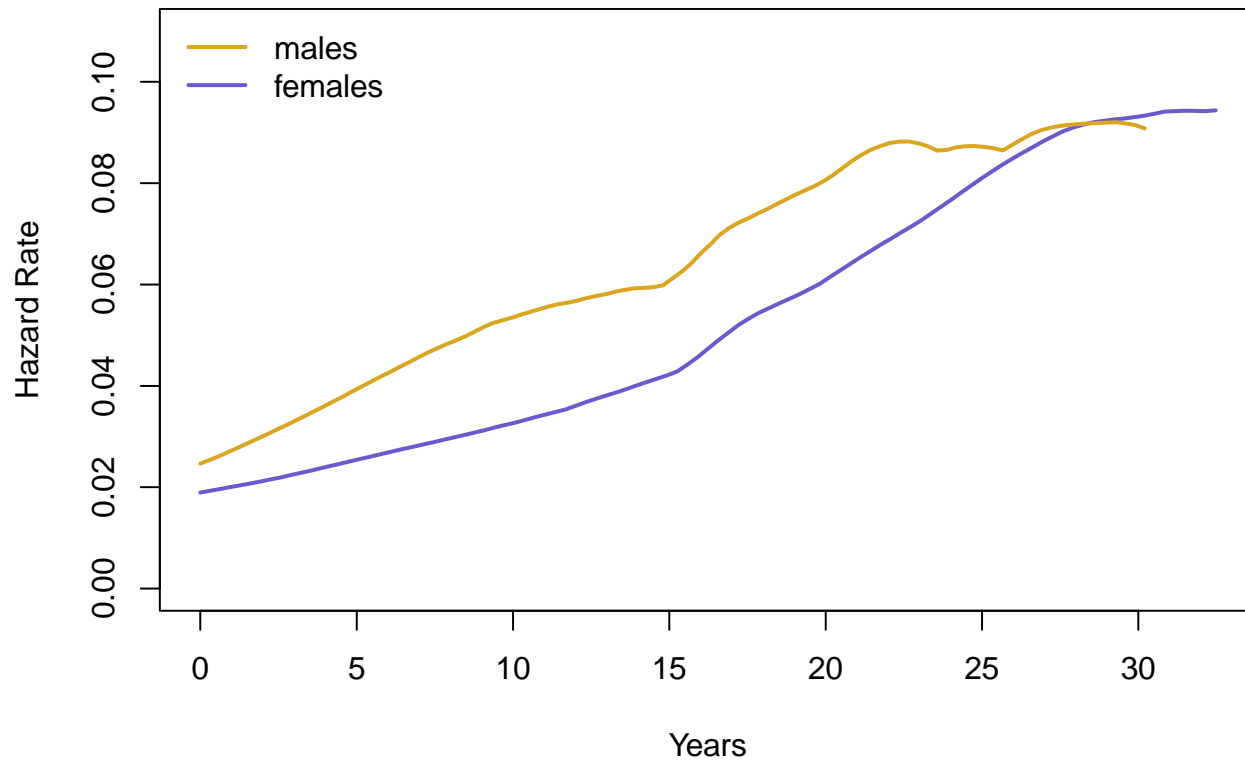 – Estimated Hazard ratios (male to female) by cause under both models

CAUSE-SPECIFIC HAZARD ESTIMATES

Plasma Cell Malignancy
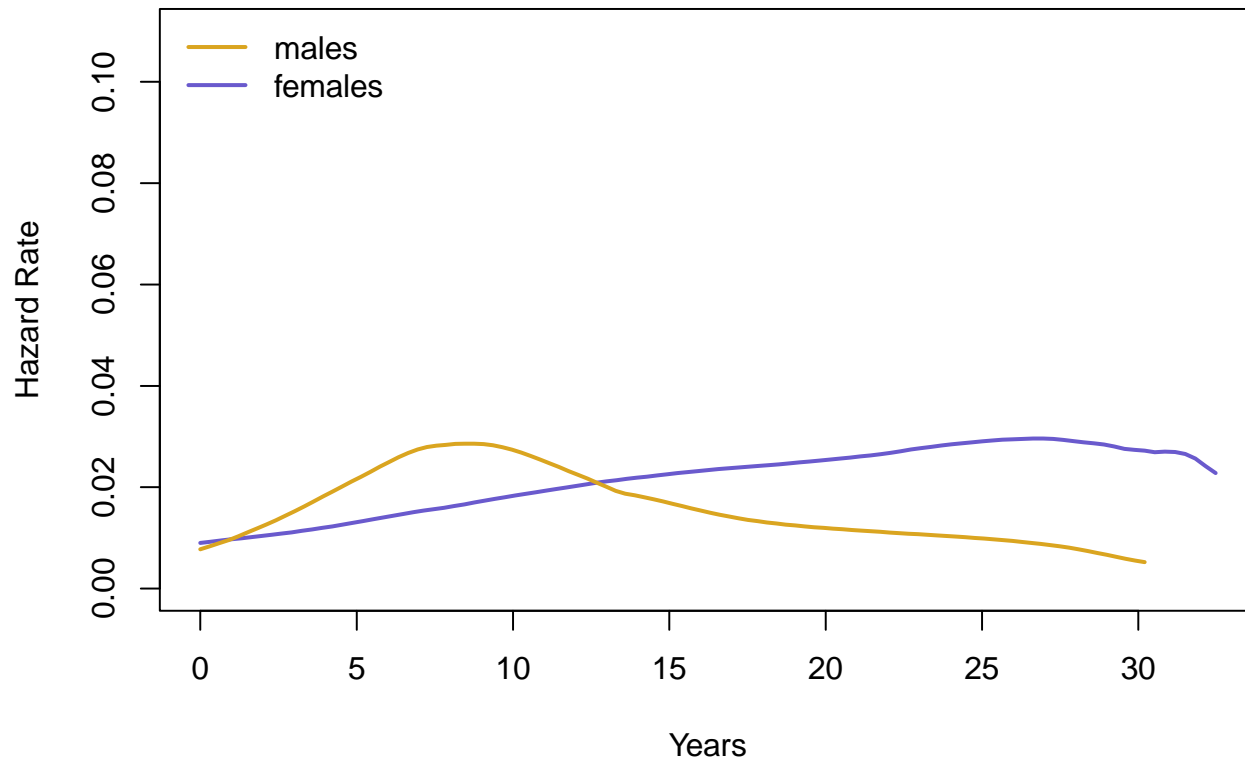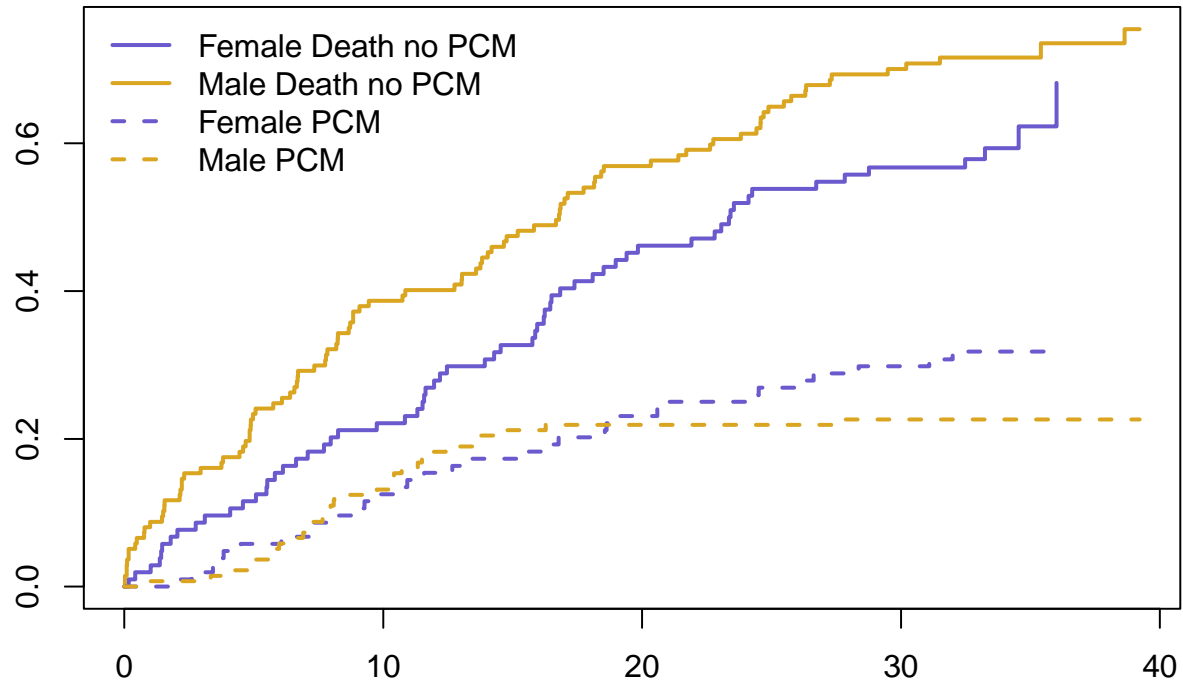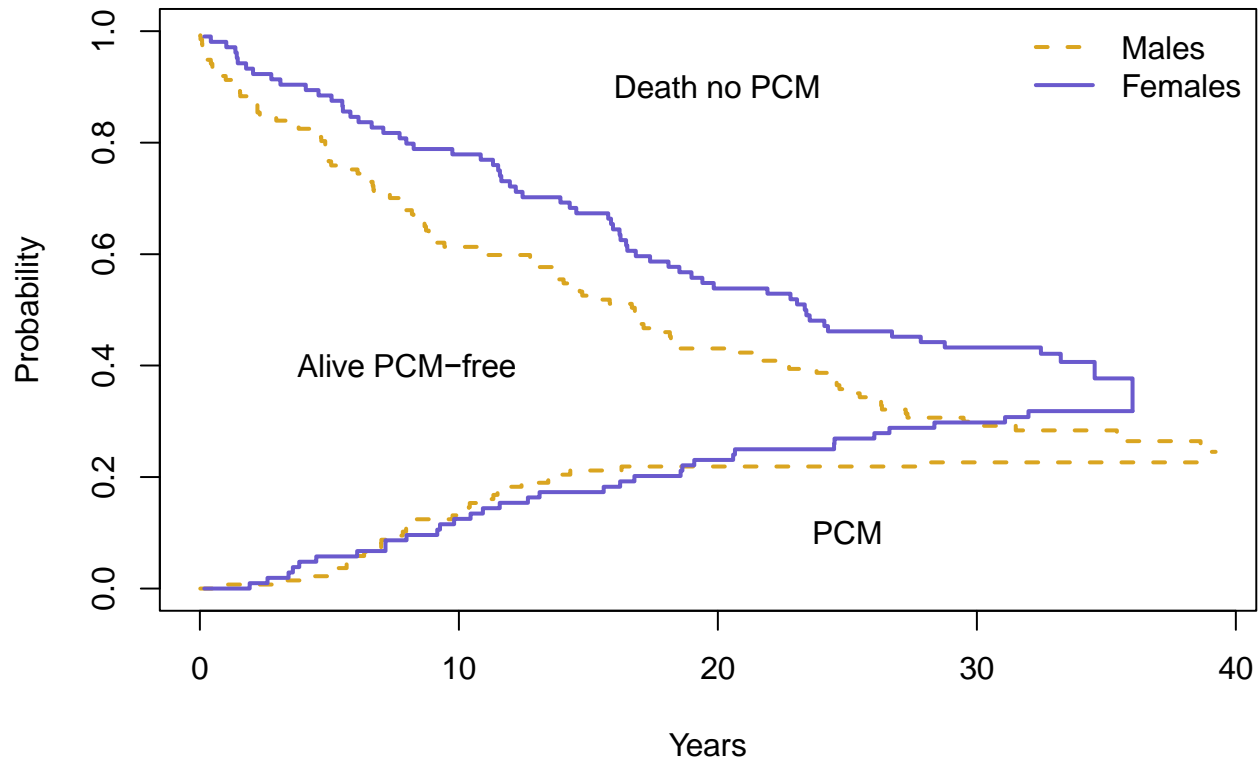
CAUSE-SPECIFIC HAZARD ESTIMATES

Deaths from Other Causes

COX MODELS

Outcome Type	M/F Hazard Ratio	95% CI	P-value
Plasma Cell Malignancy	0.95	(0.58, 1.56)	0.8441
Death from Other Causes	1.55	(1.13, 2.14)	0.0064

CUMULATIVE INCIDENCE

CUMULATIVE INCIDENCE

FINE-GRAY MODELS

Outcome Type	M/F Hazard Ratio	95% CI	P-value
Plasma Cell Malignancy	0.71	(0.44, 1.16)	0.17
Death from Other Causes	1.45	(1.06, 1.97)	0.02

PCM hazard ratio farther from one here because men are more likely to die from other causes and not survive to develop PCM.

EXAMPLE

- Ashburner et al (2017) studied a cohort of 13,559 subjects diagnosed with atrial fibrillation (AF) at Kaiser Northern California
  - 1092 thromboembolism events (1017 ischemic strokes)
  - 4414 experienced death without thromboembolism event
  - Thromboembolism-free Death rate was 5.5/100 PY among warfarin takers and 8.1/100 PY among non-takers
  - Non-takers were older had higher stroke-risk scores
- They compared Cox and F-G regression with time-dependent current warfarin use as the exposure

EXAMPLE

Event	Model	Adjusted Hazard Ratio	95% CI
Thromboembolism	Cox	0.57	(0.50, 0.65)
	Fine-Gray	0.87	(0.77, 0.99)

- They concluded that the Fine-Gray model that "accounted for" competing risks gave a better "real-world" assessment of the benefit of warfarin.

- What are your thoughts?

Ashburner JM, Go AS, Chang Y, Fang MC, Fredman L, Applebaum KM, Singer DE. J Am Geriatr Soc. 2017 Jan 1;65(1):35–41.

SOME COMPETING RISKS REFERENCES

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- Fine JP, Gray RJ. A Proportional Hazards Model for the Subdistribution of a Competing Risk. Journal of the American Statistical Association. 1999 Jun 1;94(446):496–509.

- Lau B, Cole SR, Gange SJ. Competing risk regression models for epidemiologic data. American journal of Epidemiology. 2009;170(2):244–256.

- Noordzij M, Leffondré K, Stralen V, J K, Zoccali C, Dekker FW, Jager KJ. When do we need competing risks methods for survival analysis in nephrology? Nephrol Dial Transplant. 2013 Nov 1;28(11):2670–2677.

- Prentice RL, Kalbfleisch JD, Peterson Jr AV, Flournoy N, Farewell VT, Breslow NE. The analysis of failure times in the presence of competing risks. Biometrics. 1978;541–554.

- Tsiatis A. A nonidentifiability aspect of the problem of competing risks. Proceedings of the National Academy of Sciences. 1975;72(1):20–22.

TO WATCH OUT FOR

- Interpretation in the presence of competing risks can be tricky and requires extra care.

  - Cannot interpret cumulative incidence or cause-specific hazard as applying in a population without competing risks present.

  - 1 – KM estimator can give upward biased estimate of cumulative incidence.

  - Fine-Gray model is not THE way to account for competing risks. It tells us only what variables are associated with cumulative incidence, and this may not be what you are interested in.