Competing risks, interpretation and ignorance

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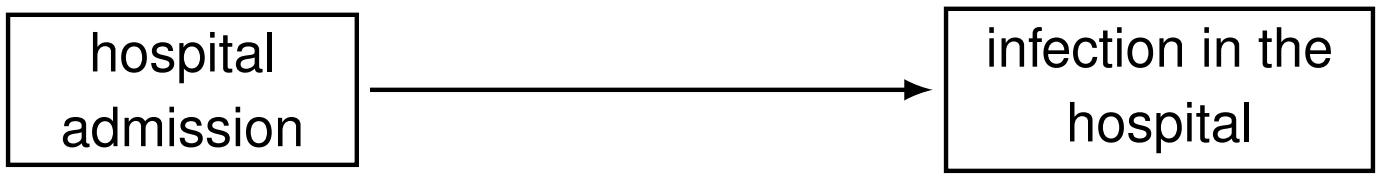
Almost there

http://www.competingrisks.org

Outline

Example I: time to staphylococcus infection in hospital



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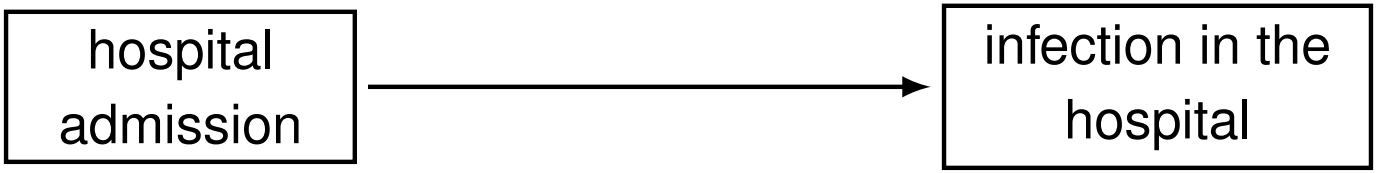

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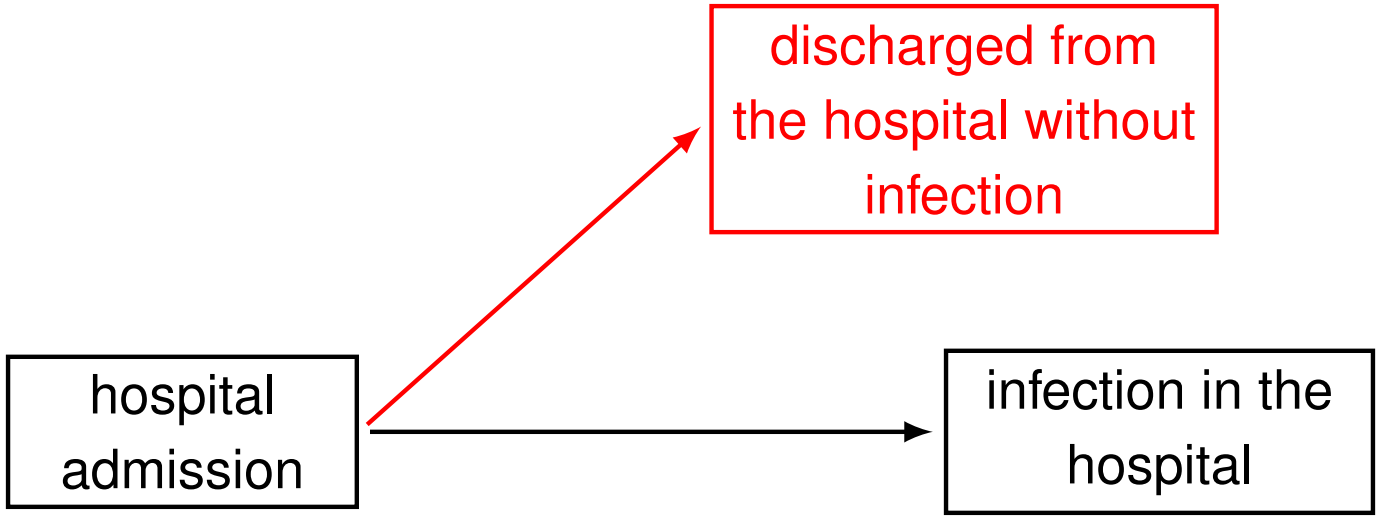

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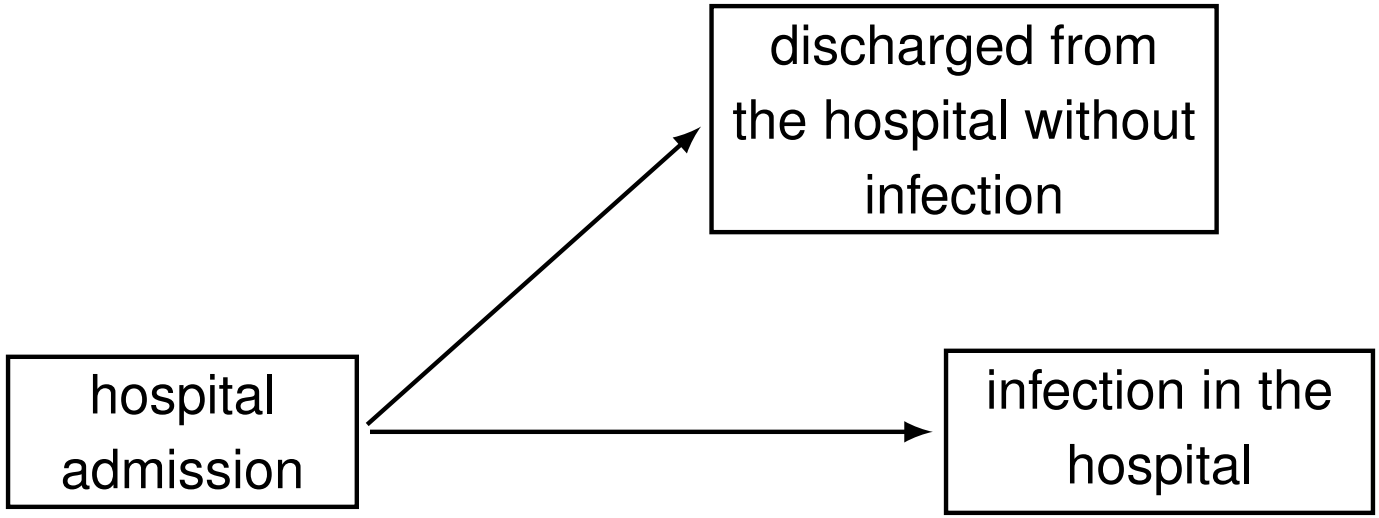

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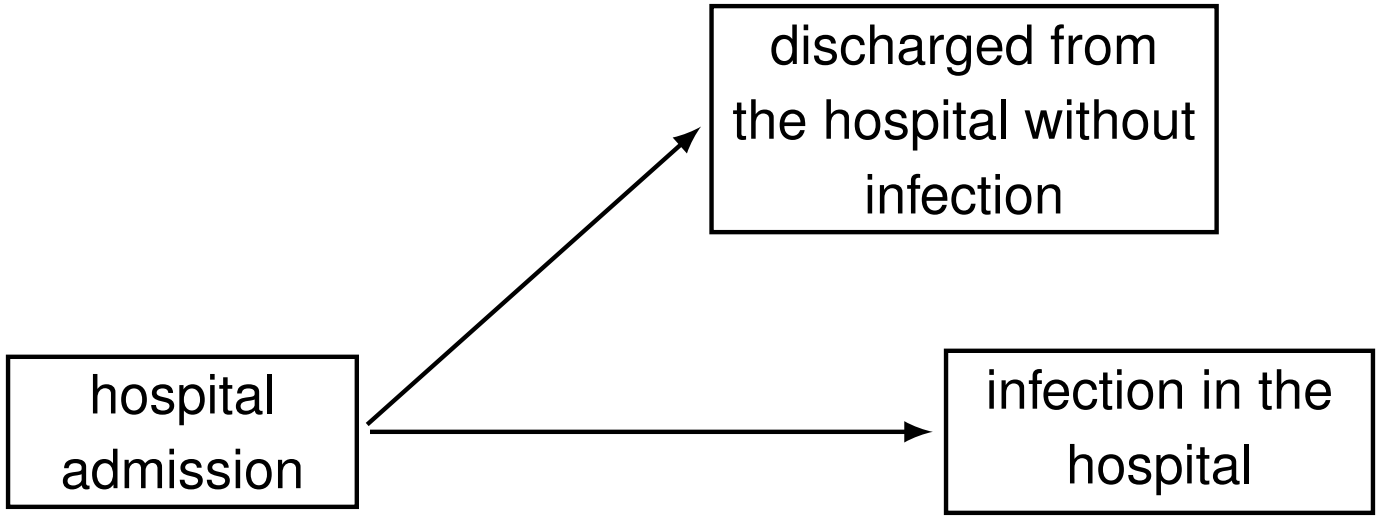

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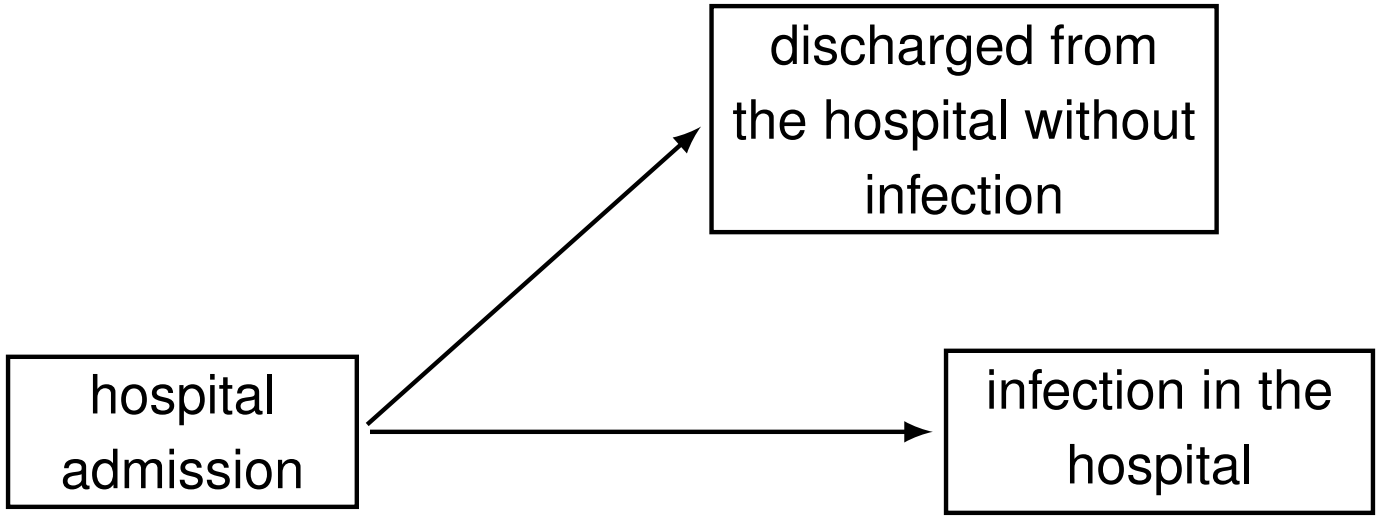

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  - Cause-specific cumulative incidence/crude risk/subdistribution
- Comparison between hospitals may depend on type of analysis

Estimation with complete information (artificial data)

week	0-1	1-2	2-3	3-4	4-5	5-6	6-7	> 7
infection	1	2	6	11	9	11	2	18
cumulative	1	3	9	20	29	40	42	60
discharge	5	9	6	6	9	12	4	35
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$$
\begin{aligned}
P(>6 \text{ weeks no inf}) = P(\text{ year 0-1 no inf }) \times \\
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\times P(\text{ week 5-6 no inf} \mid \text{no inf until week 5}) \\
= (1-\lambda_{0\text{-}1}) \times (1-\lambda_{1\text{-}2}) \times (1-\lambda_{2\text{-}3}) \times \ldots \times (1-\lambda_{5\text{-}6})
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Week 0-1: $\lambda_{0-1} = 1/146 = 0.006849$
Week 1-2: $\lambda_{1-2} = 2/140 = 0.014286$
Week 2-3: $\lambda_{2-3} = 6/129 = 0.046512$ etc.

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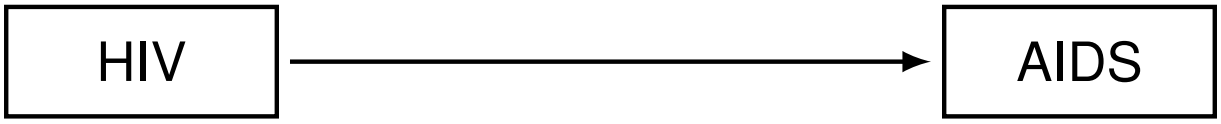
- Marginal: Kaplan-Meier, leave risk set when discharged. Discharged (censored) individuals represented by those that remain in hospital
- Competing risks:
  $\widehat{P}(\text{infection } \leq 6 \text{ weeks}) = 40/146$,
  $\widehat{P}(\text{discharge } \leq 6 \text{ weeks}) = 47/146$.
  Individuals with competing event remain in denominator.
  Competing risks estimation ignores competing risk

Example II: Natural history of HIV infection



- Compare MSM and IDU; 99 IDU and 127 MSM

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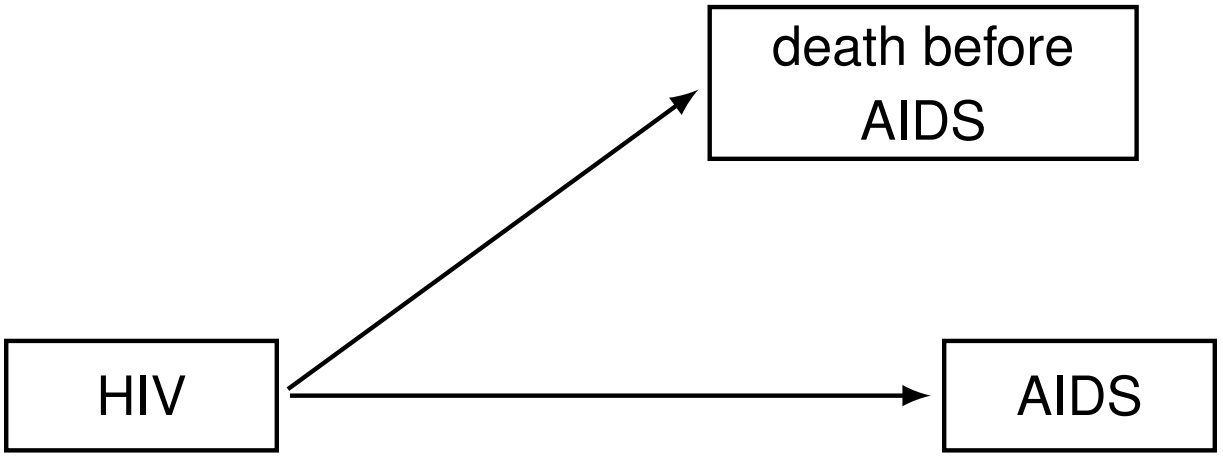

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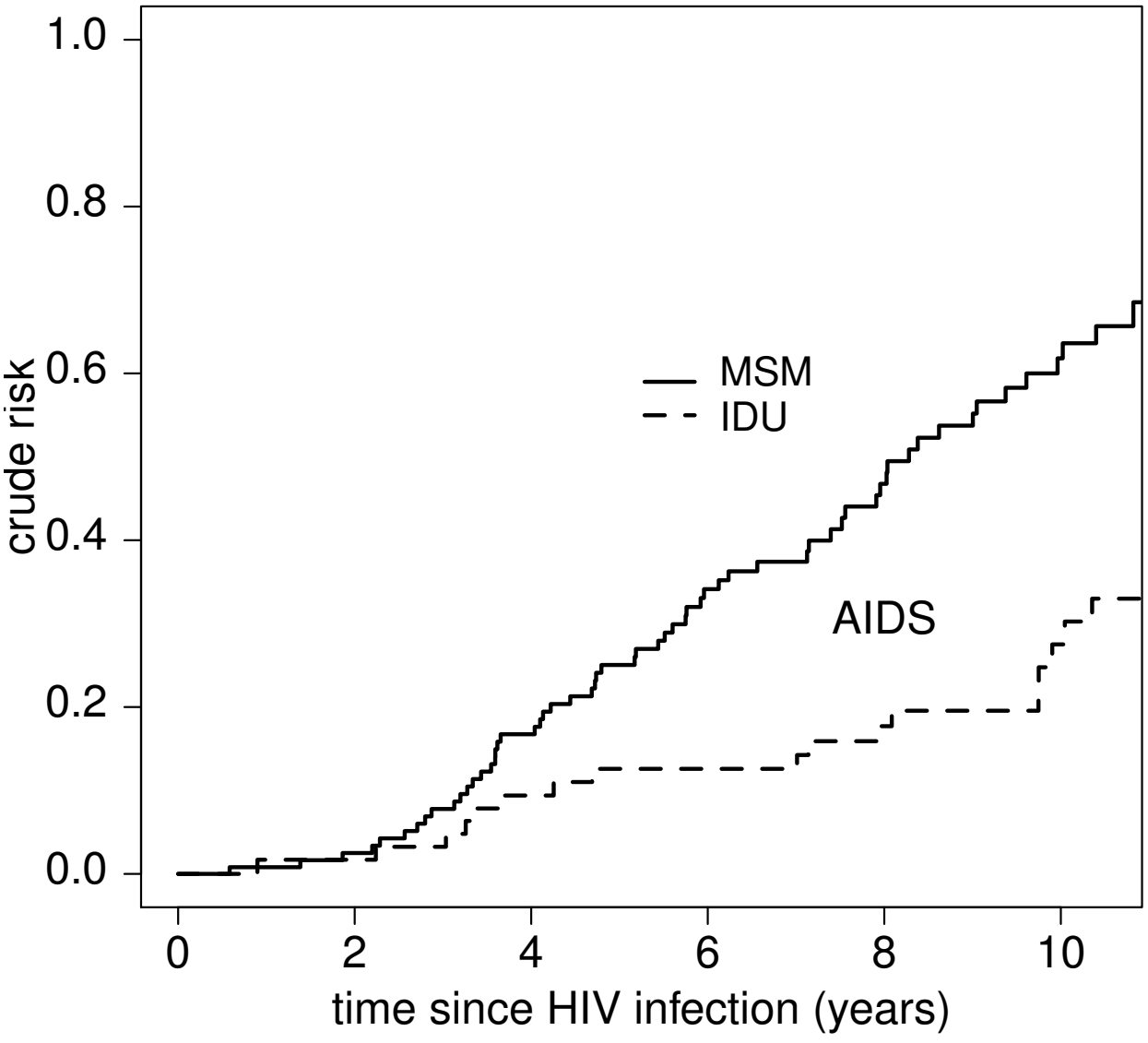
Death before AIDS another end point



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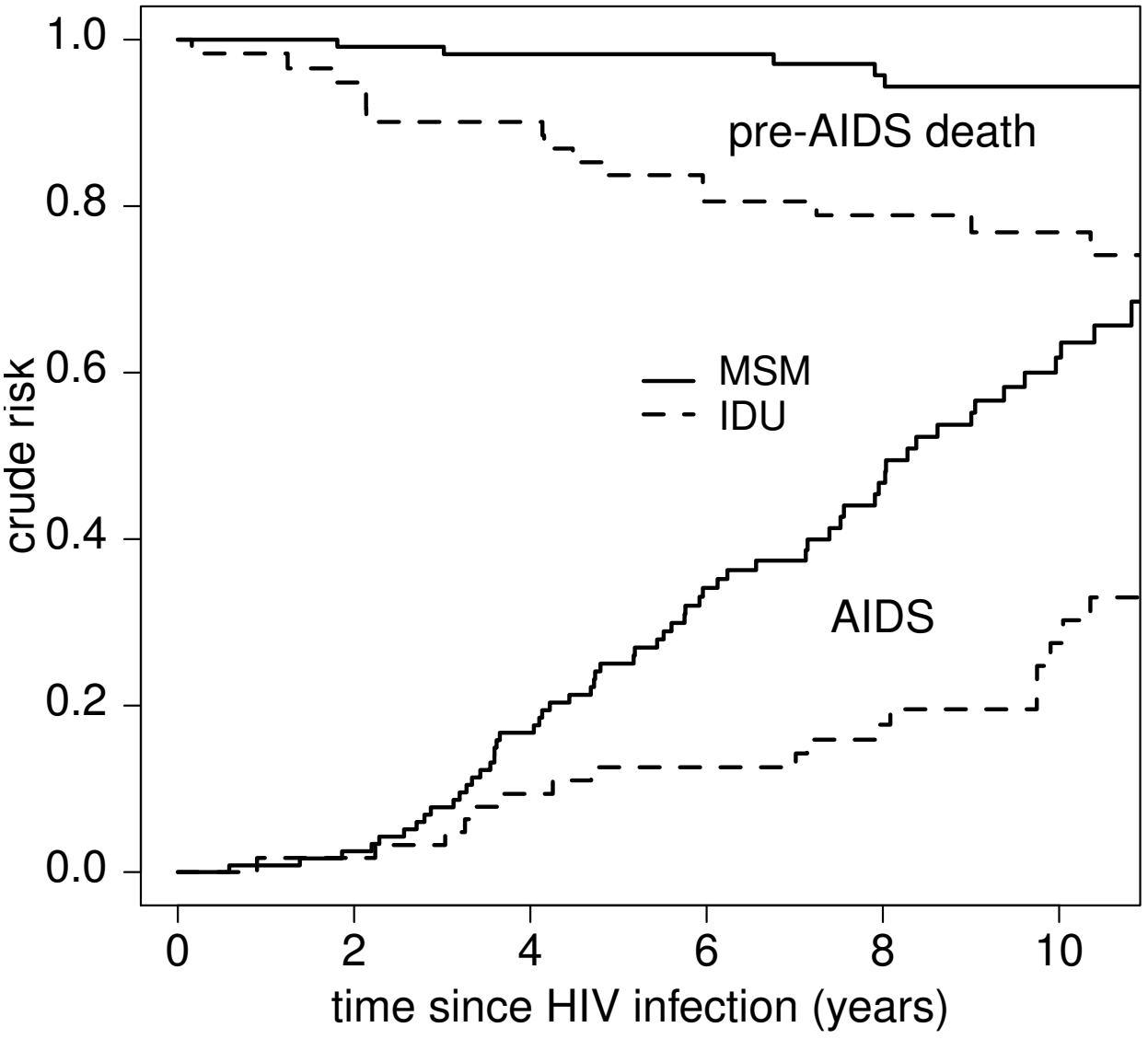

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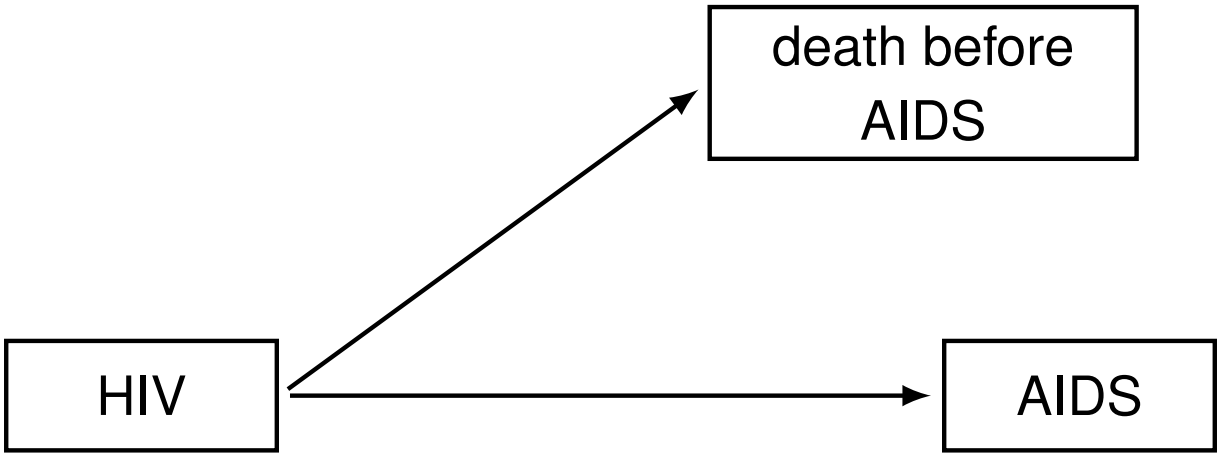
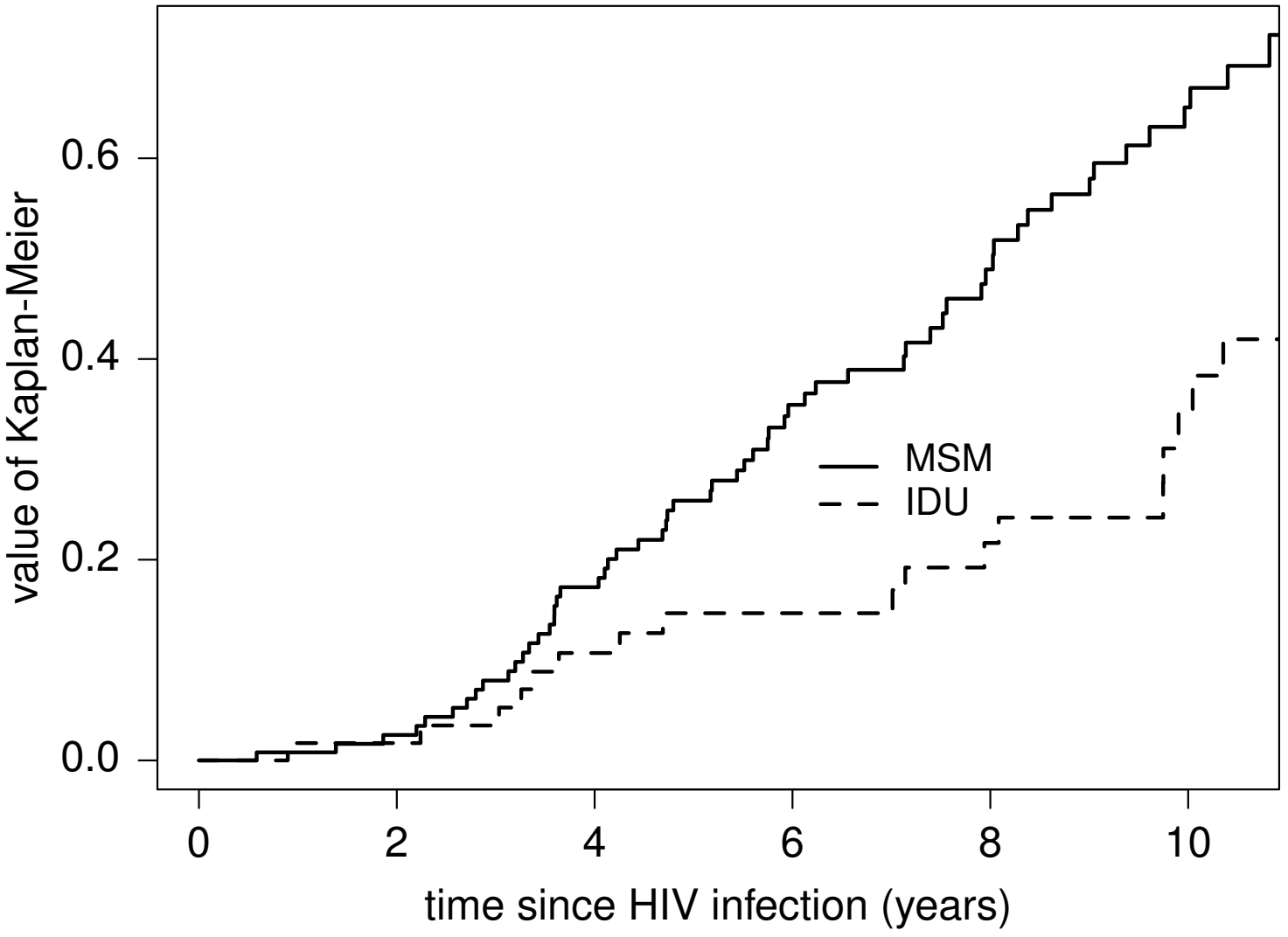


- Compare MSM and IDU; 99 IDU and 127 MSM
- Competing risks analysis
- Interest in time to AIDS if there were no pre-AIDS death
  Interest in etiology and marginal distribution
  Kaplan-Meier: censor at death before AIDS

Results: IDU much slower progression ($p = 0.001$)



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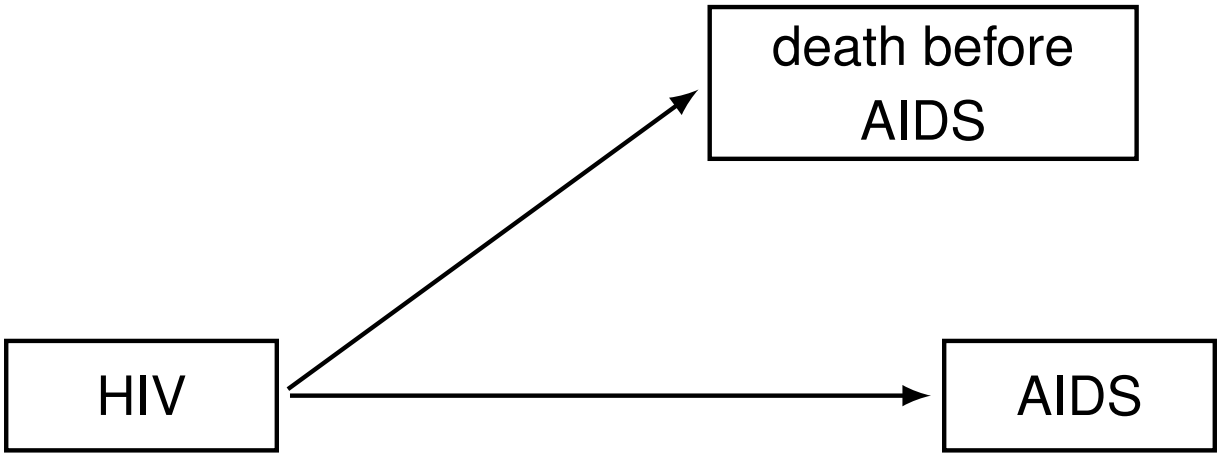

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- Competing risks analysis
- Interest in time to AIDS if there were no pre-AIDS death
  Interest in etiology and marginal distribution
  Kaplan-Meier: censor at death before AIDS
  - Assumption: can be represented by the ones that do not die

Outline

Explanation: informative censoring

- Extra information on cause of death before AIDS

	IDU	MSM
Reason of death	Number	
HIV related infections	3	0
overdose/suicide	6	0
violence/accident	2	0
liver cirrhosis	2	0
cancer	0	1
heart attack	0	1
unknown	4	3

- Some pre-AIDS death causes in IDU related to AIDS progression. Censoring close to AIDS, hence marginal hazard estimate for IDU biased downwards

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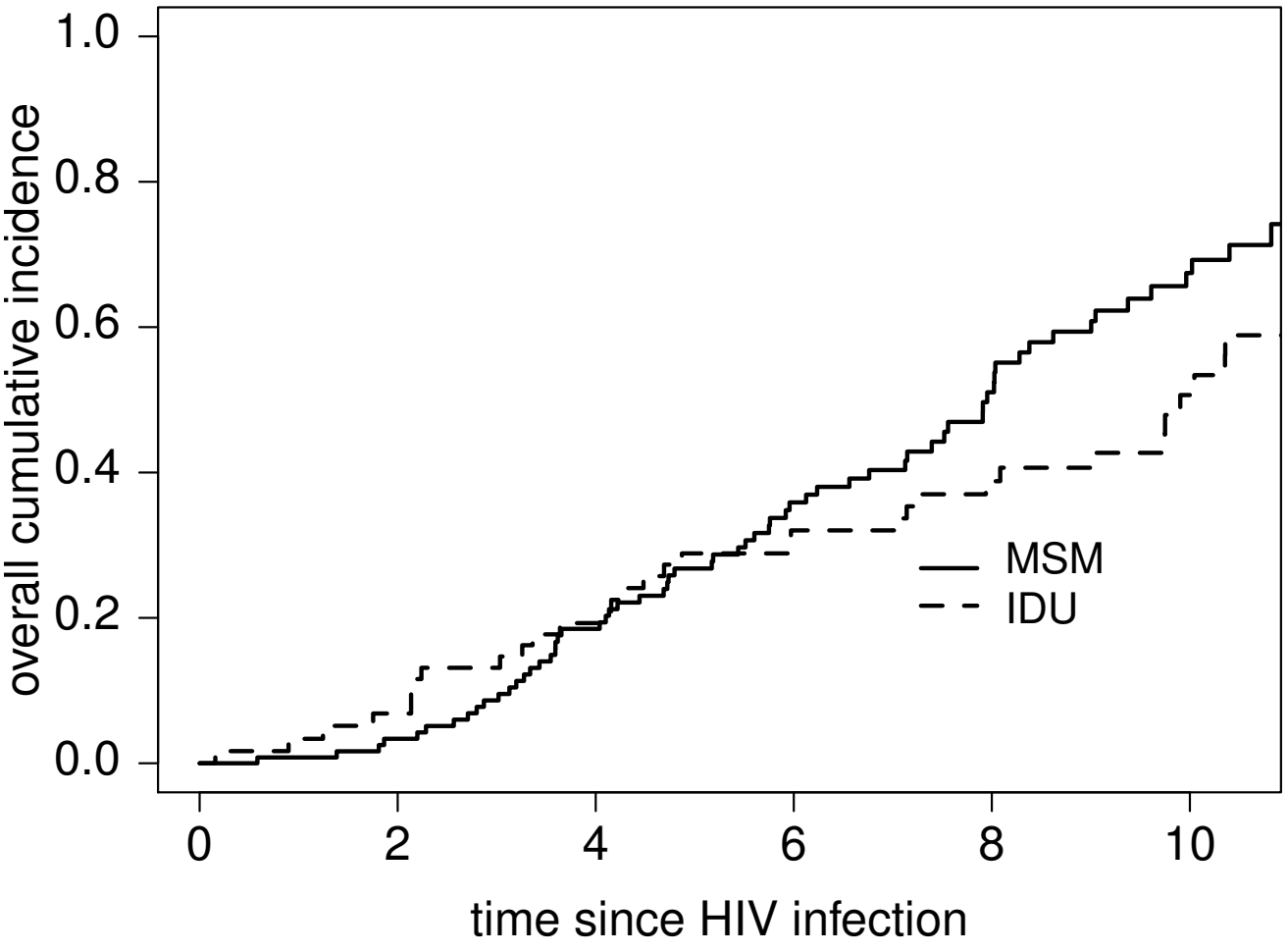
Combine AIDS and pre-AIDS death ($p = 0.14$)



Can we conclude that IDU and MSM have similar time to AIDS?

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- What if: would have developed AIDS right after death
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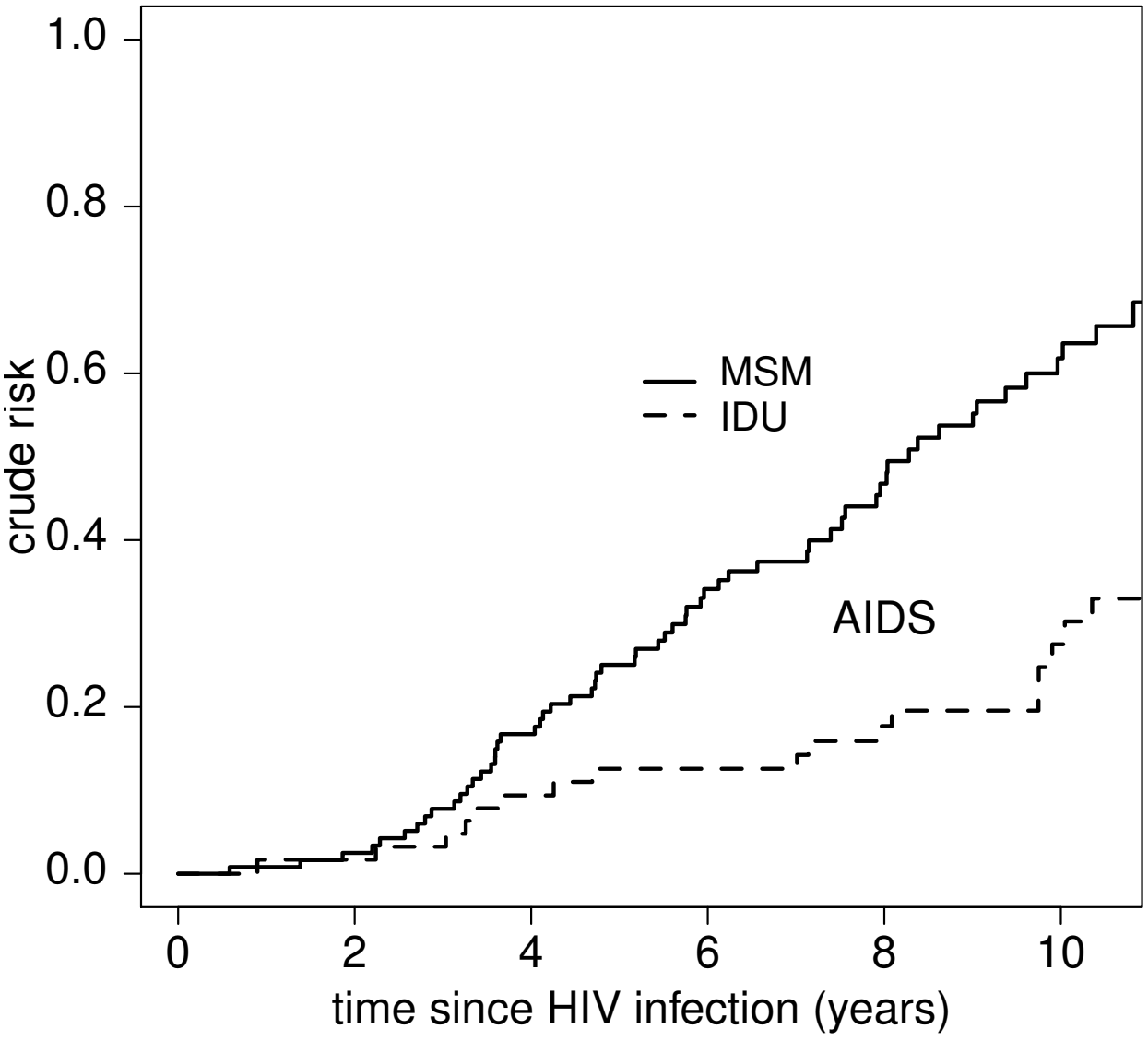
Subdistribution



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- Same data can represent independent as well as dependent censoring
  - We cannot test for independence based on observed event/censoring data
  - No correction possible based on observed event/censoring data
- Extra information may allow to show dependence, but independence can never be tested for

Informative censoring?

We want to estimate the incidence of cardiac events (CE) in childhood cancer survivors. A person that dies of another cause is considered censored at his date of death. This type of censoring is informative since this patient is censored due to the occurrence of an intervening event (DOC).

This example was inspired by Satagopan *et al.* A note on competing risks in survival data analysis. Br. J. Cancer, 91(7):1229-1235, 2004

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Censoring is not necessarily informative just because it is caused by an intervening event.

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Competing risks (includes artificial censoring)

Often informative. In competing risks analysis, independence is not required

Informative censoring?

Some individuals died without CE, but they had already left the study before they died. Therefore, for CE as end point, no competing risk of DOC is present in our data and the Kaplan-Meier curve is a valid estimate of the marginal distribution of time to CE.

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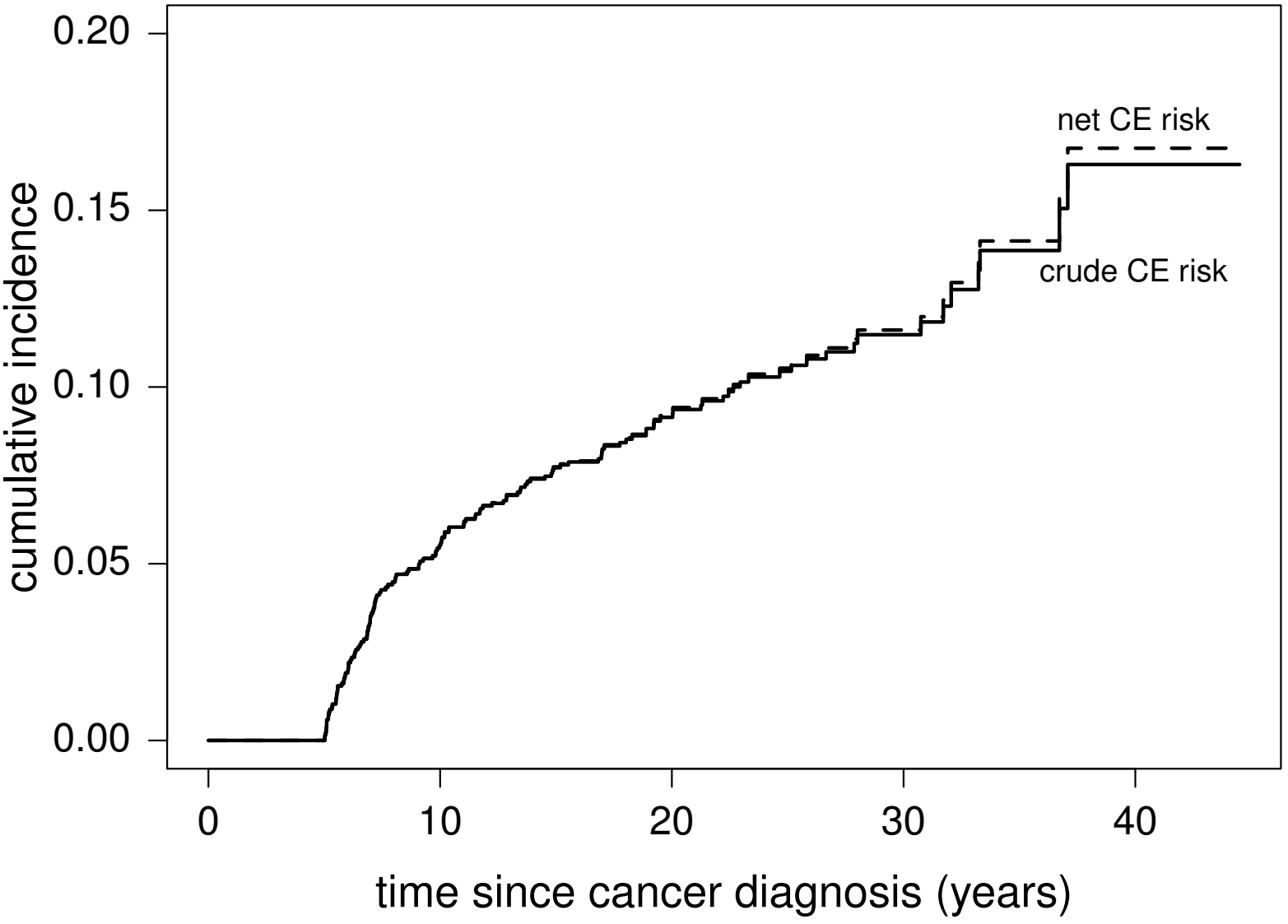
The Kaplan-Meier estimates the marginal distribution if all censoring is non-informative. Removing individuals from the risk set before they experience the competing event removes the competing risk, but does not solve the problem of informative censoring.

Childhood cancer survivors; CE, DOC competing



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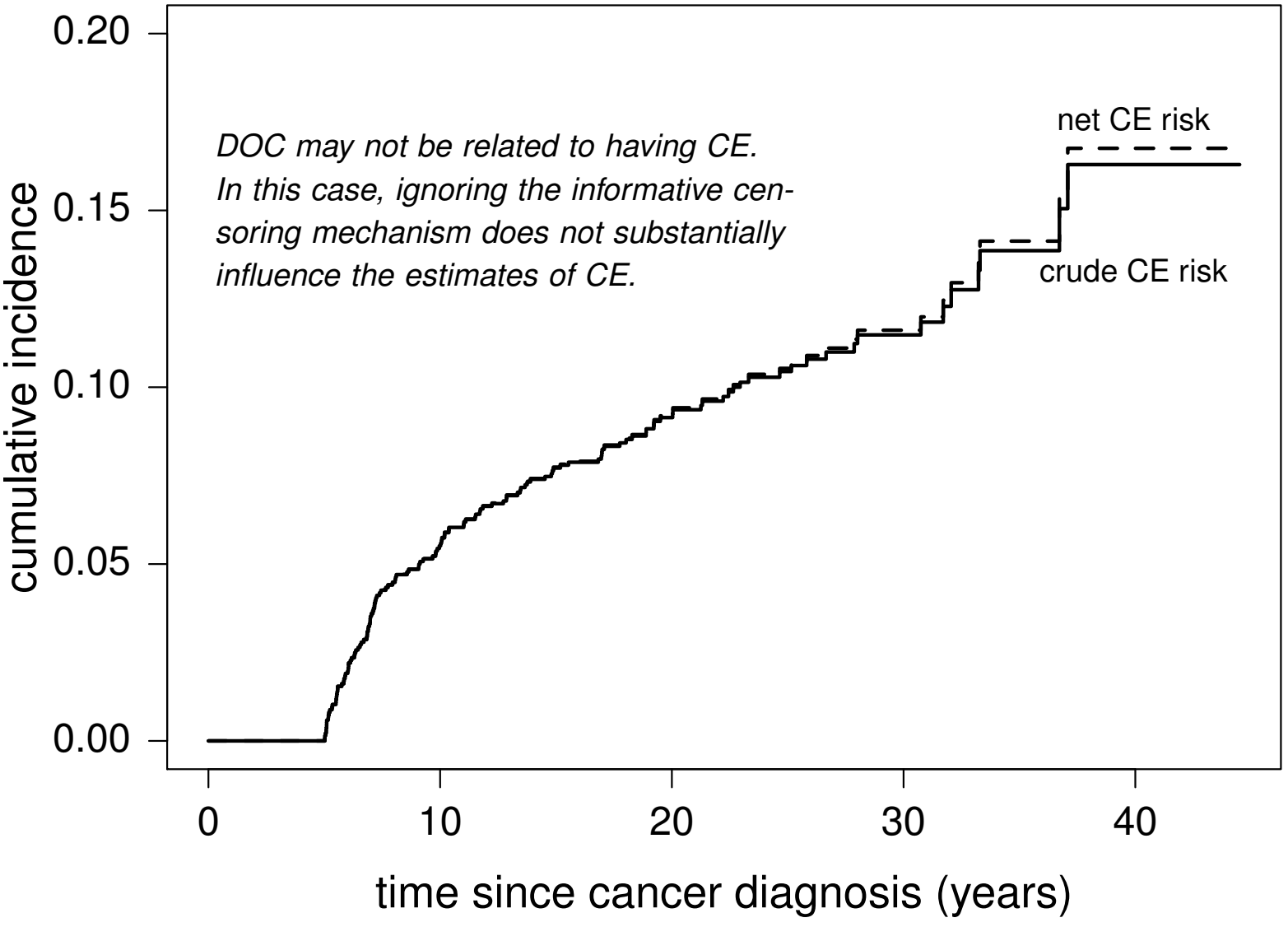

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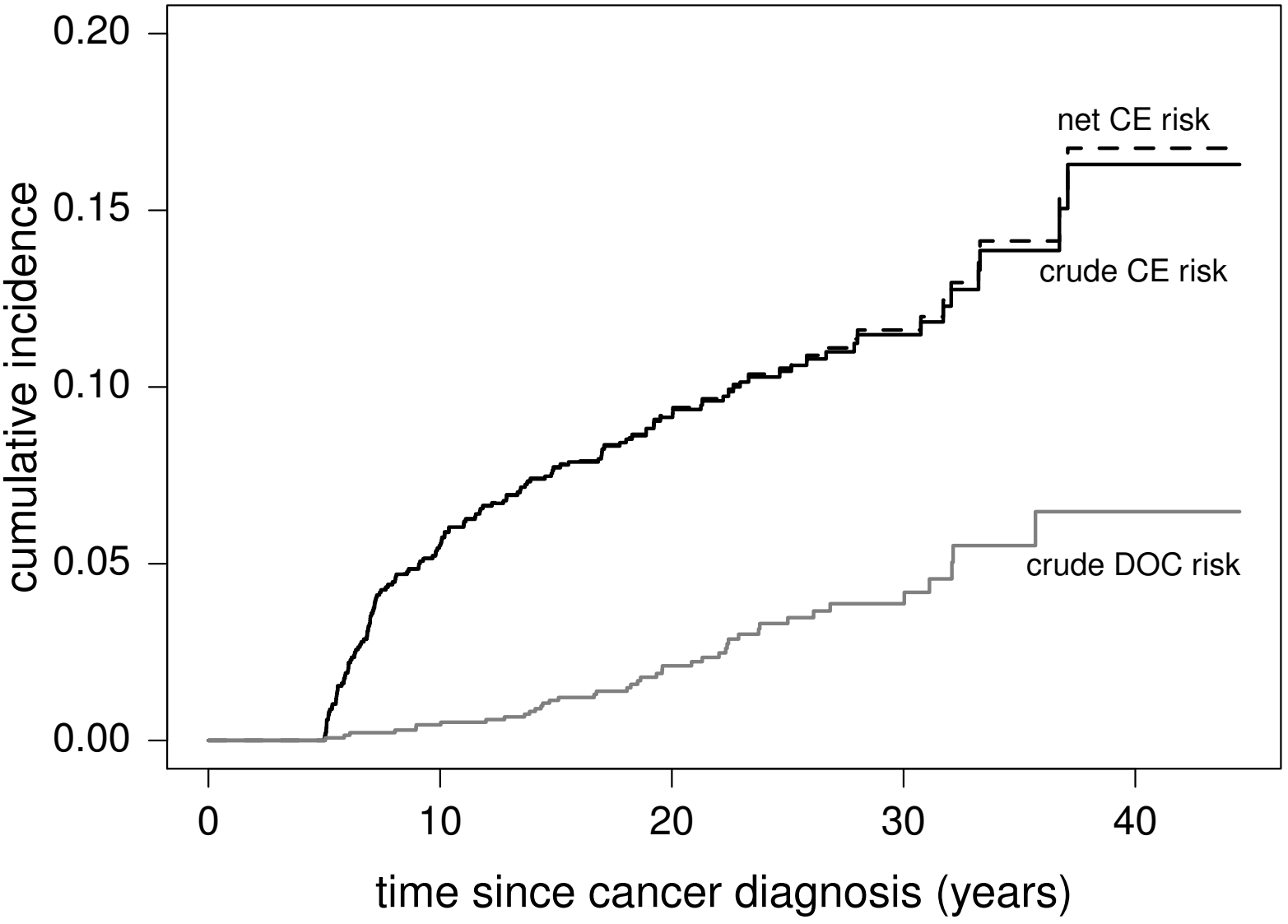
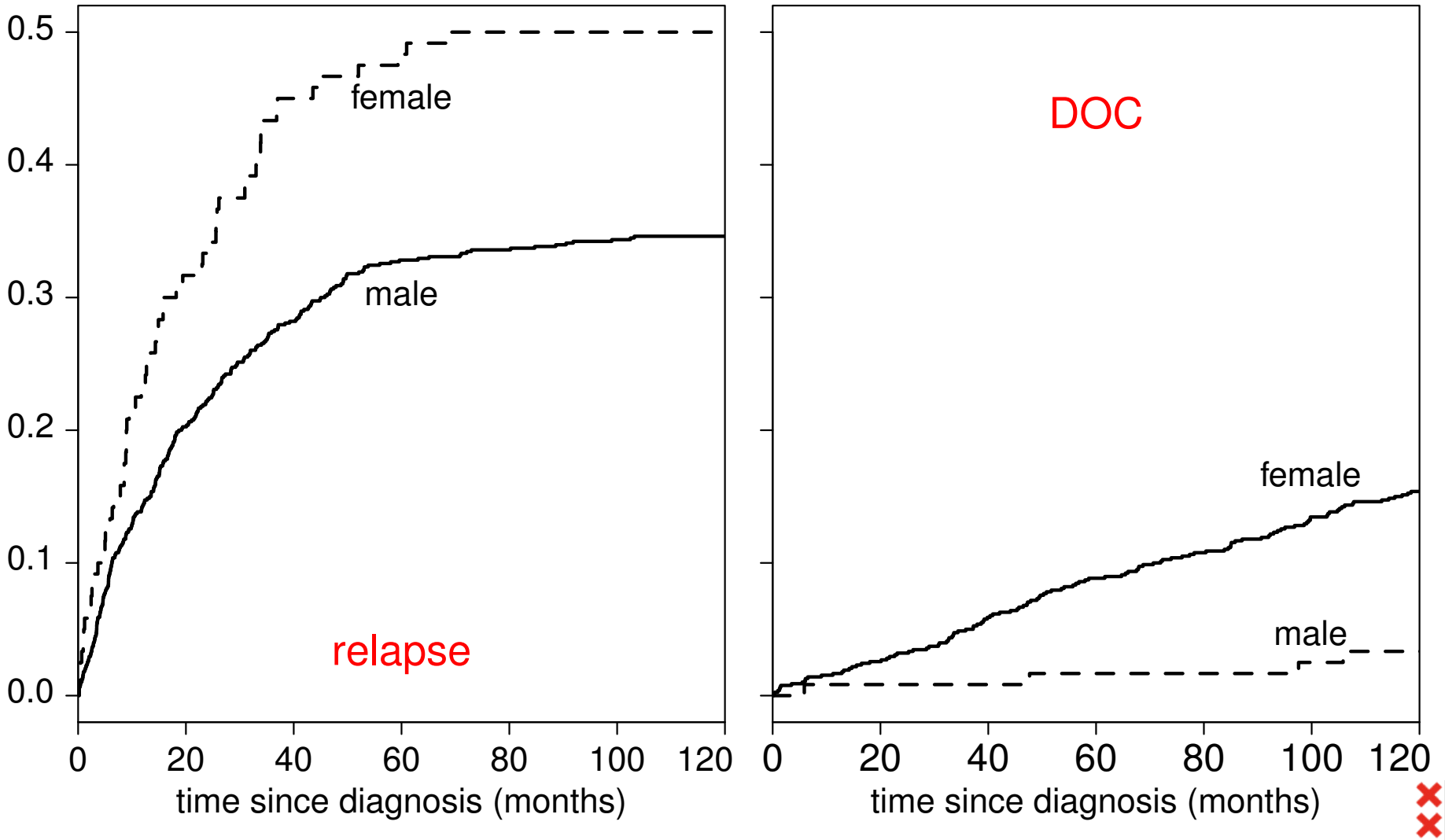


Answer

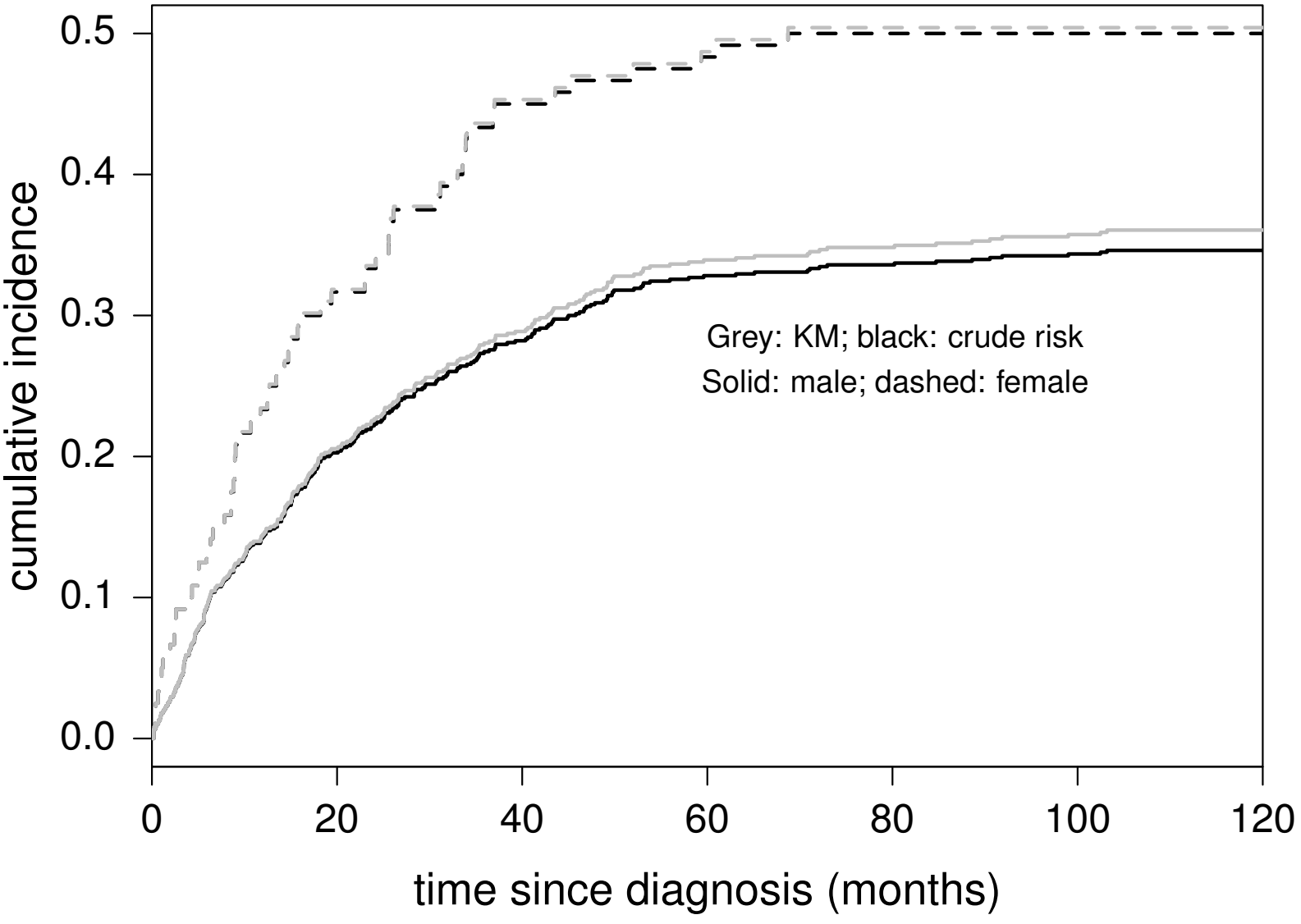
- The Kaplan-Meier and the estimator of the CE-specific cumulative incidence try to estimate different quantities
- Both curves are similar because there is little mortality due to other causes, at least during the first 20 years, when most of the CE's occur.
- Note that on one hand it is said that death due to other causes may not be related to CE events, whereas on the other hand it is called "informative censoring".

This example was taken from Satagopan *et al.* A note on competing risks in survival data analysis. Br. J. Cancer, 91(7):1229-1235, 2004

Bladder cancer; relapse, DOC competing



Bladder cancer; net and crude risk



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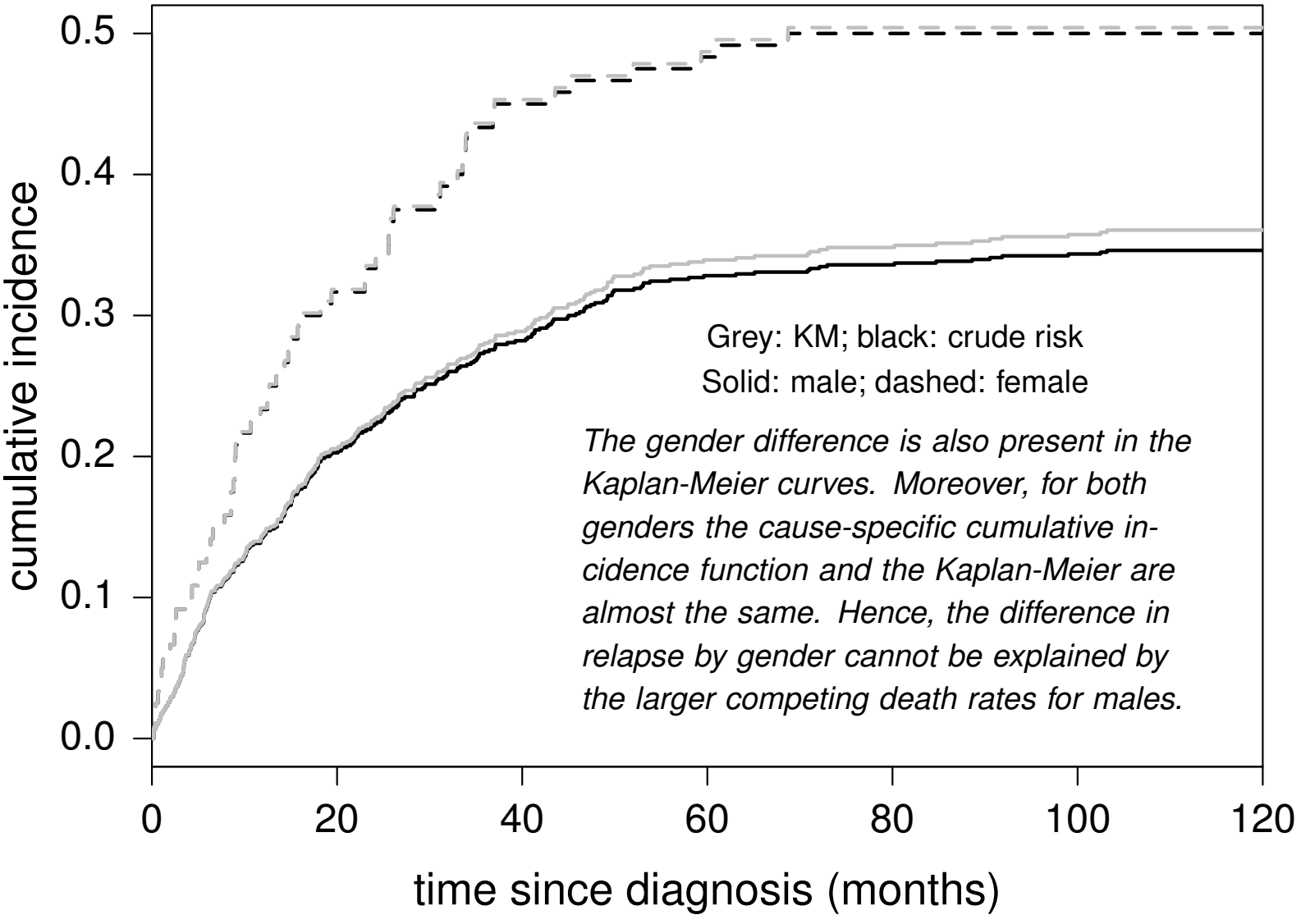
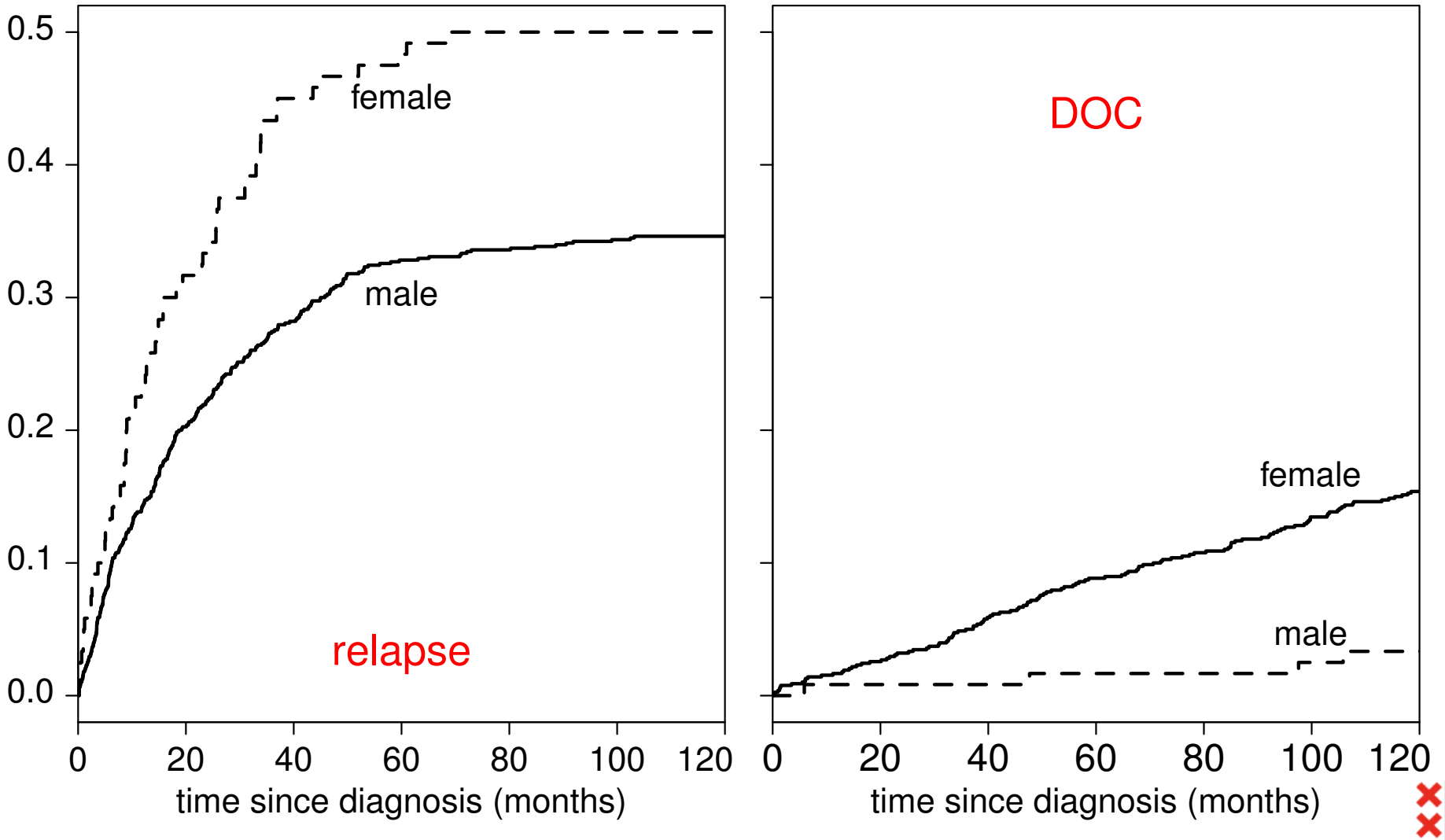


Answer

- The Kaplan-Meier tries to compare the marginal distribution of time to relapse for males and females. Only valid if DOC is noninformative for progression.
- Estimates almost equal because there is little mortality due to other causes, at least during the first 40 months.
- If we combine both event times, the curves for males and females will become similar. Would estimate marginal hazard if every person that died would have progressed on the next day.

Bladder cancer; relapse, DOC competing



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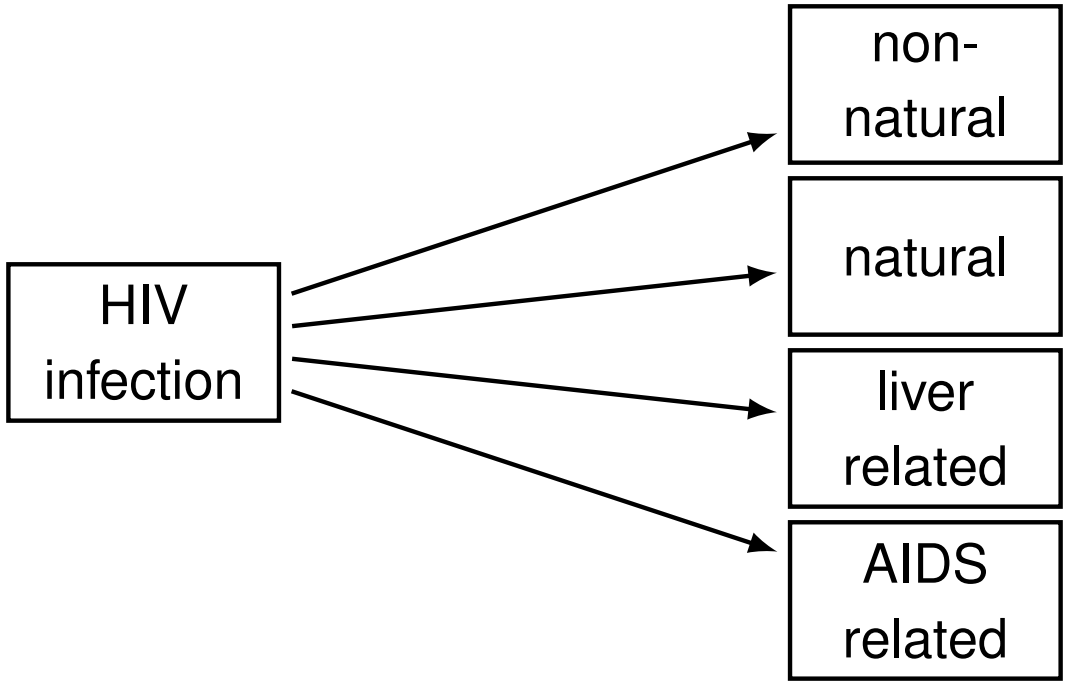
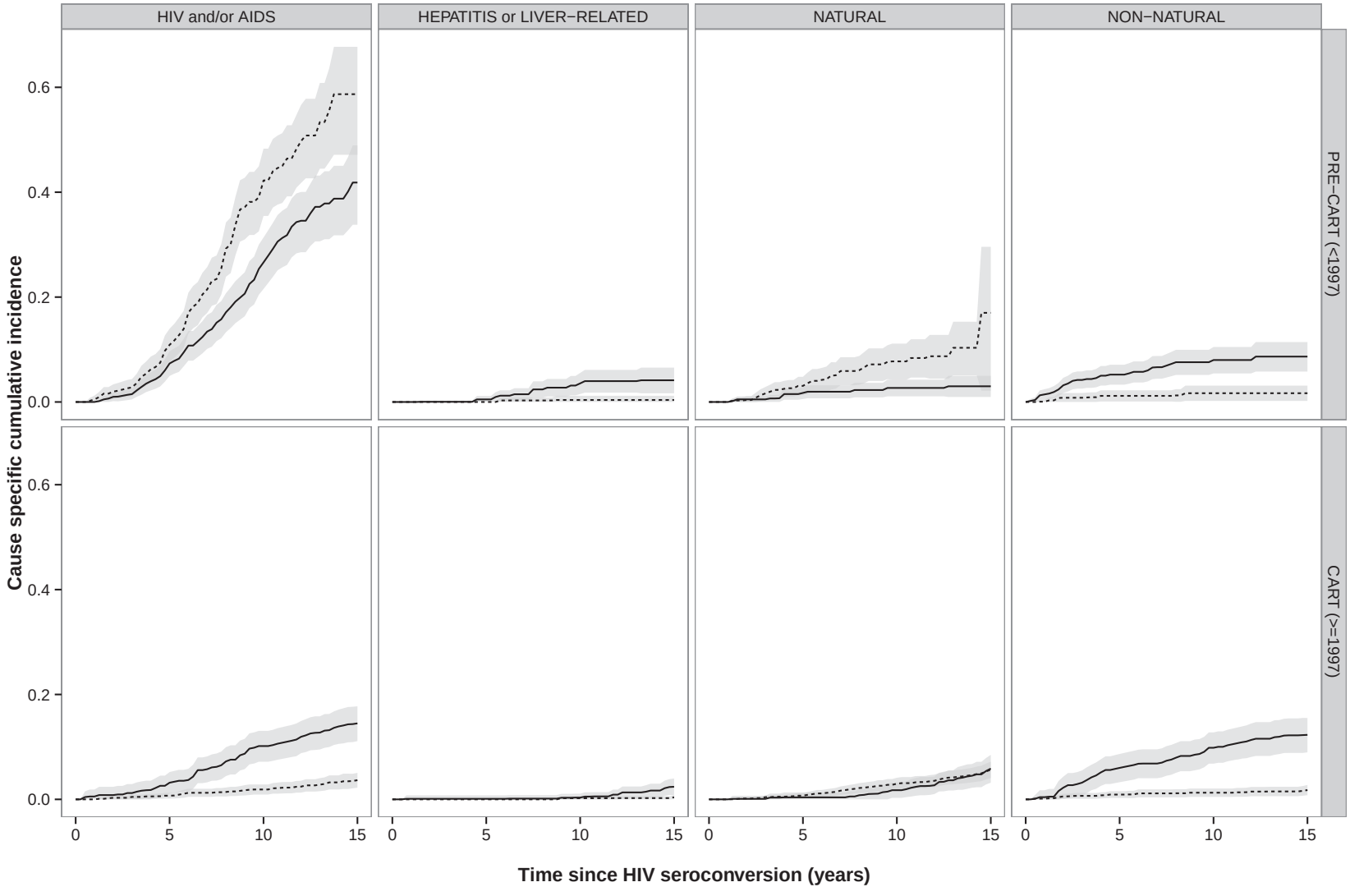
Example III: Causes of death after HIV infection



- Has the spectrum of causes of death changed after the introduction of cART (combination Anti-Retroviral Therapy)
- Competing risks analysis most interesting
  No interest in change in AIDS-related death in world in which other COD's do not exist

Crude risk by calendar period and HCV status



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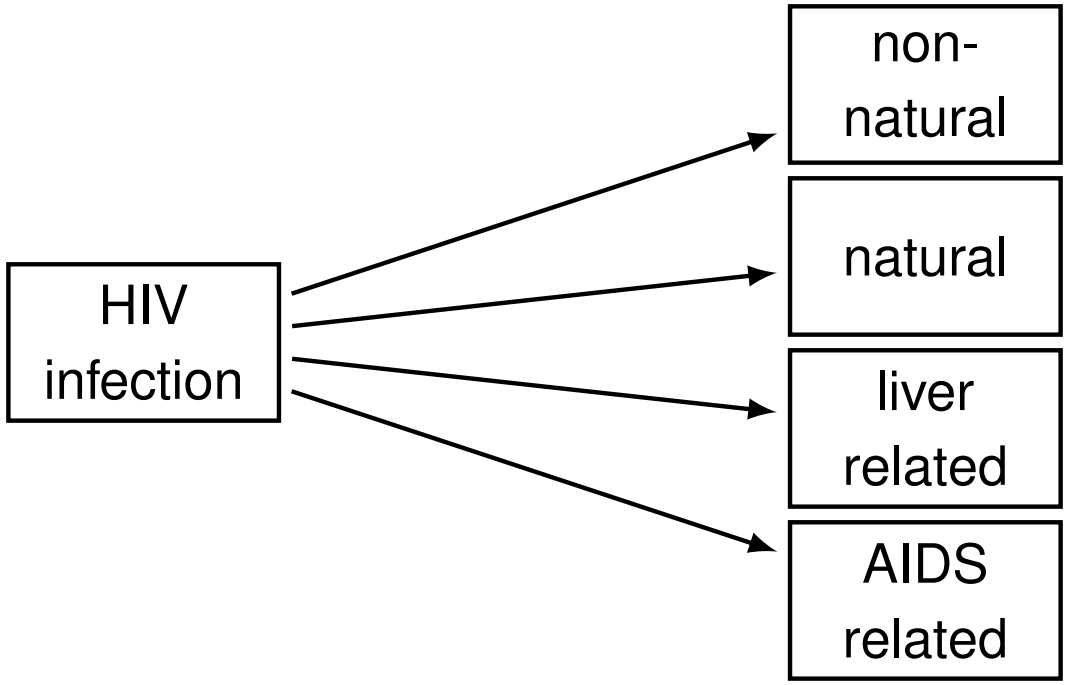

- Has the spectrum of causes of death changed after the introduction of cART (combination Anti-Retroviral Therapy)
- Competing risks analysis most interesting
  No interest in change in AIDS-related death in world in which other COD's do not exist
- Still, different types of analysis can be chosen

Outline

Some notation

- Time to event (all types combined): $\mathrm{P}(T \leq t)$
- Relates 1-1 with hazard h: $\mathrm{P}(T > t) = \exp\{-\int_0^t h(s)ds\}$

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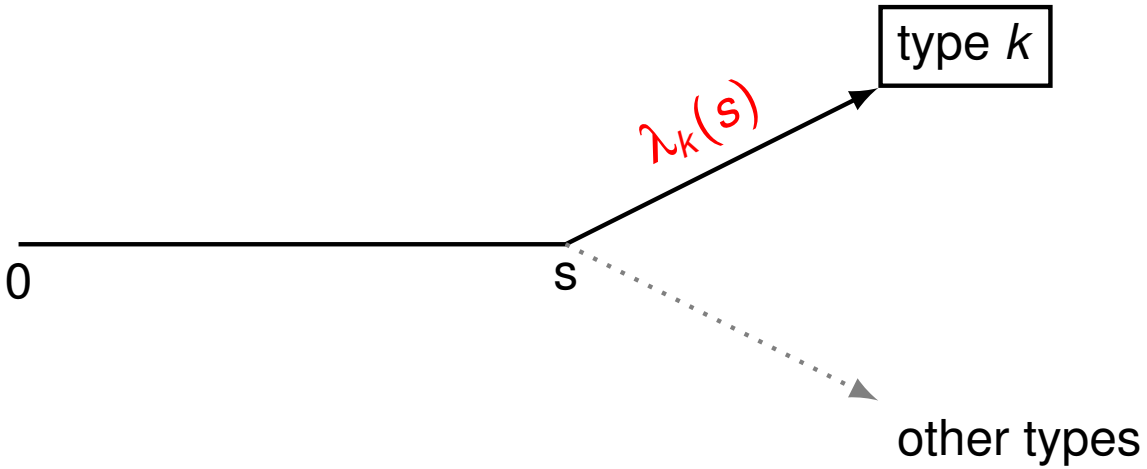
- Relates 1-1 with hazard h: $\mathrm{P}(T > t) = \exp\{-\int_0^t h(s)ds\}$
- K competing risks, $E \in K$; crude risk $\mathrm{P}(T \leq t, E = k)$

Approach I: via cause-specific hazard



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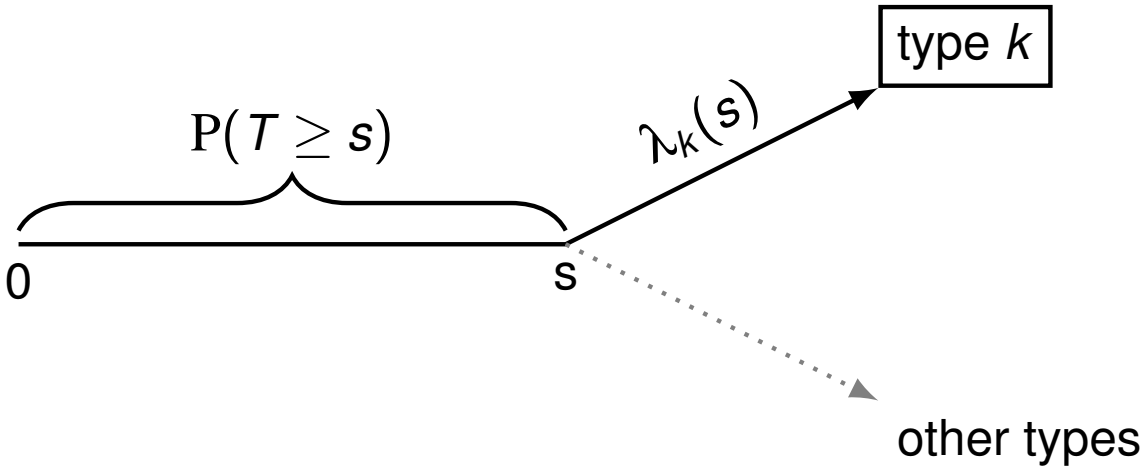

- Relation with crude risk

$$P(T \geq s)\lambda_k(s)$$

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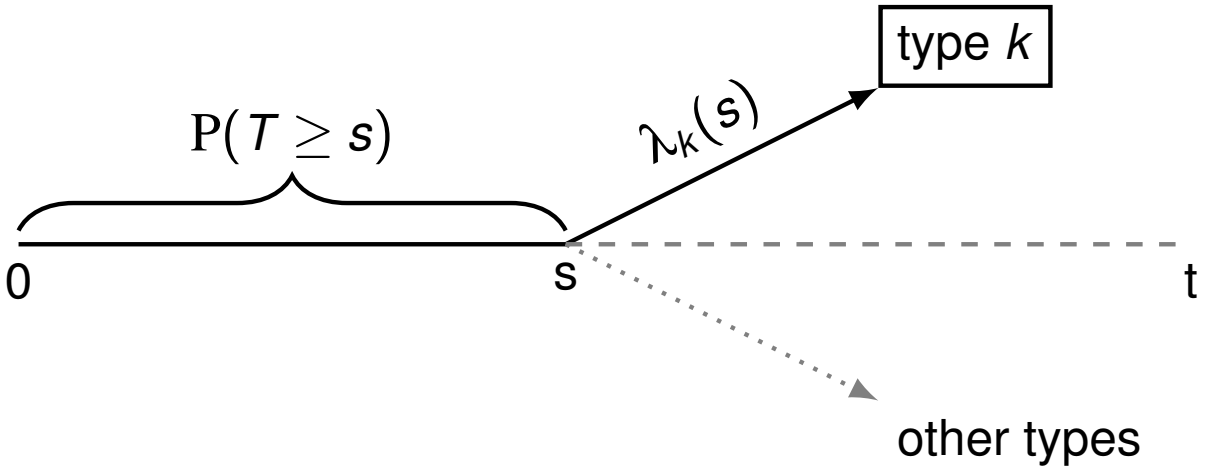

- Relation with crude risk

$$P(T \leq t, E = k) = \int_0^t P(T \geq s)\lambda_k(s)ds$$

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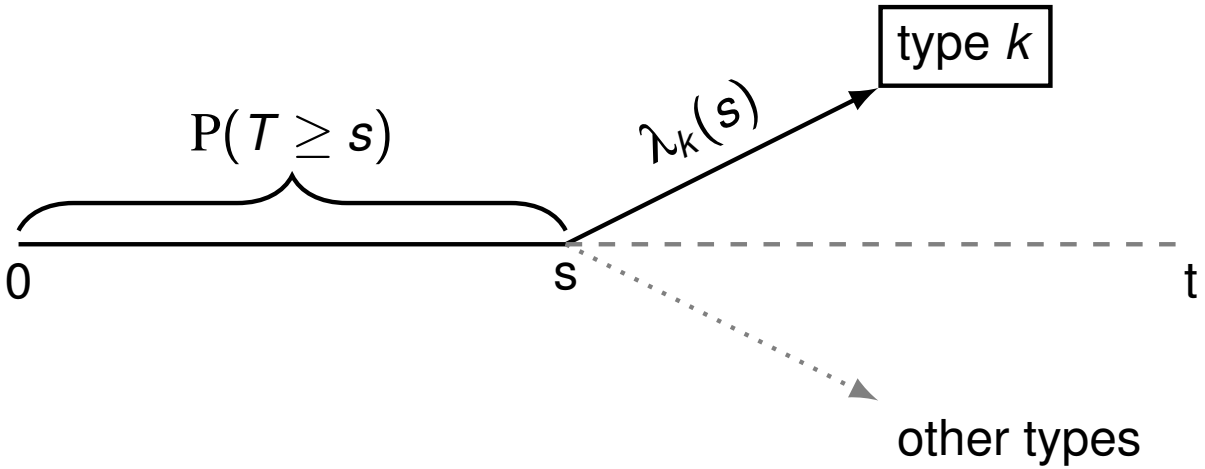

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- Sum of cause-specific hazards is overall hazard: $\sum_{e=1}^{K} \lambda_e(s) = h(s)$

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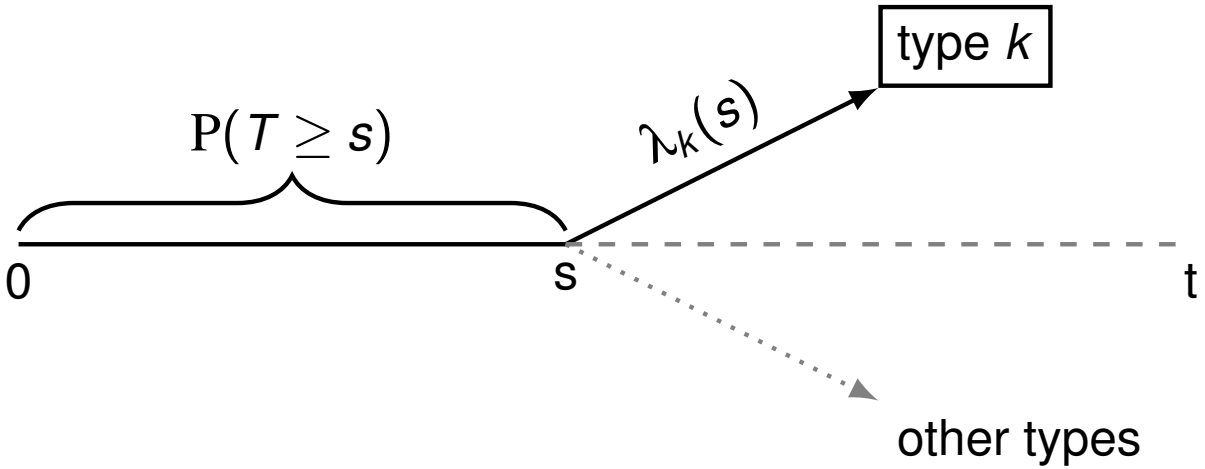

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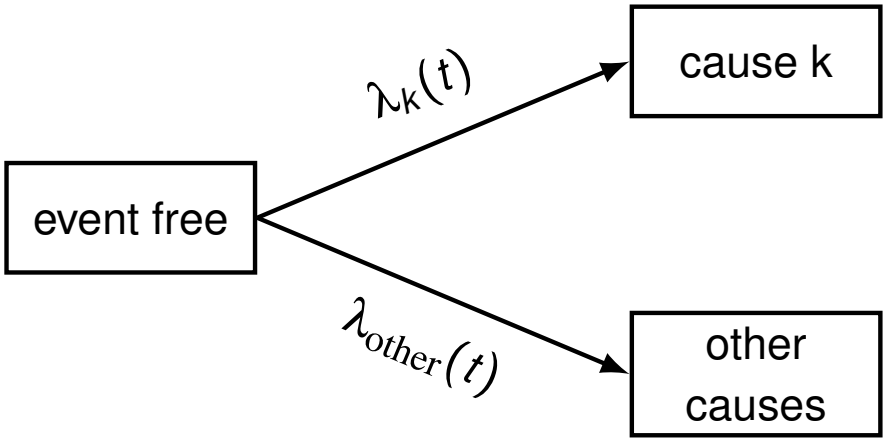
- Sum of cause-specific hazards is overall hazard: $\sum_{e=1}^{K} \lambda_e(s) = h(s)$
- Sum of crude risks is overall risk: $P(T \leq t) = \sum_{e=1}^{K} P(T \leq t, E = e)$

Estimation



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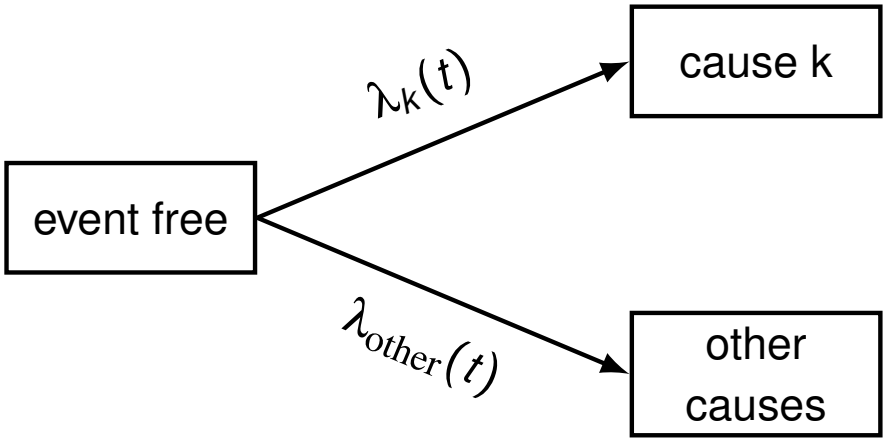

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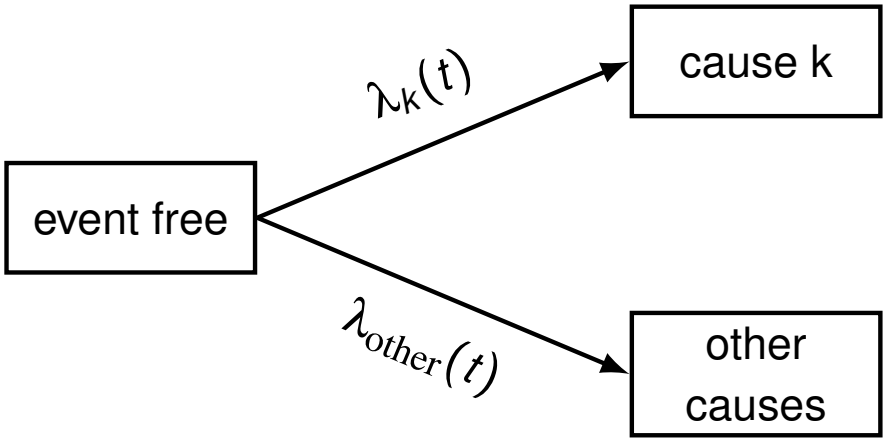

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- Crude risk: Aalen-Johansen estimator $(\int_0^t \mathrm{P}\{T \geq s\}\lambda_k(s)ds)$

$$\widehat{\mathrm{P}}(T \leq t, E = k) = \sum_{i:t_{(i)} \leq t} \mathrm{KM}(t_{(i)}-) \times \widehat{\lambda_k}(t_{(i)})$$

Approach II: via subdistribution hazard

Some notation

- K competing risks, $E \in K$; crude risk $\mathrm{P}(T \leq t, E = k)$
- Subdistribution random variable T_k:
  $T_k = T \times I\{E = k\} + \infty \times I\{E \neq k\}$

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- Interpretation controversial
  - Not a rate in epidemiological sense

Rates and risks in competing risks setting

	hazard		cumulative
competing risks	marginal	*	net risk marginal survival function marginal cumulative incidence
	cause-specific	λ_k	no corresponding quantity
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  - Etiology; cause-specific event rate among event-free individuals
- Proportional subdistribution hazards model (Fine and Gray)
  - Ignores occurrenc of competing risks in estimation
  - Combines etiology and prediction

Choice of hazard

Study on the effect of the use of β-blockers on prostate cancer (PCa). Individuals that used β-blockers had lower subdistribution hazard for PCa-specific death but higher for DOC.

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They want to study etiology, which is better described by cause-specific hazards.

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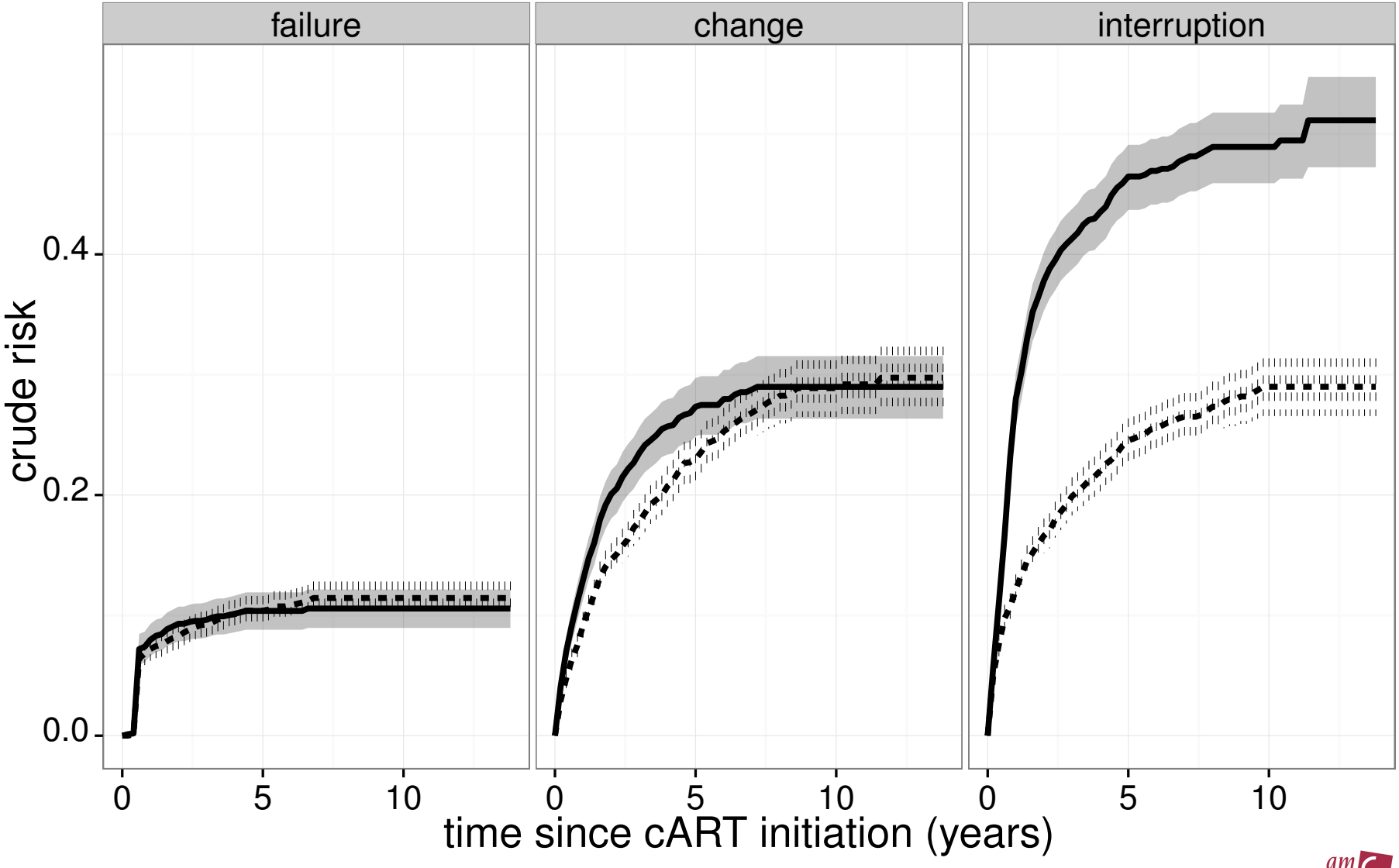
Reaction by K. Bhaskaran *et al.* 64(4):e86–87, 2013

Interpretation of hazard; cART, early versus late starters



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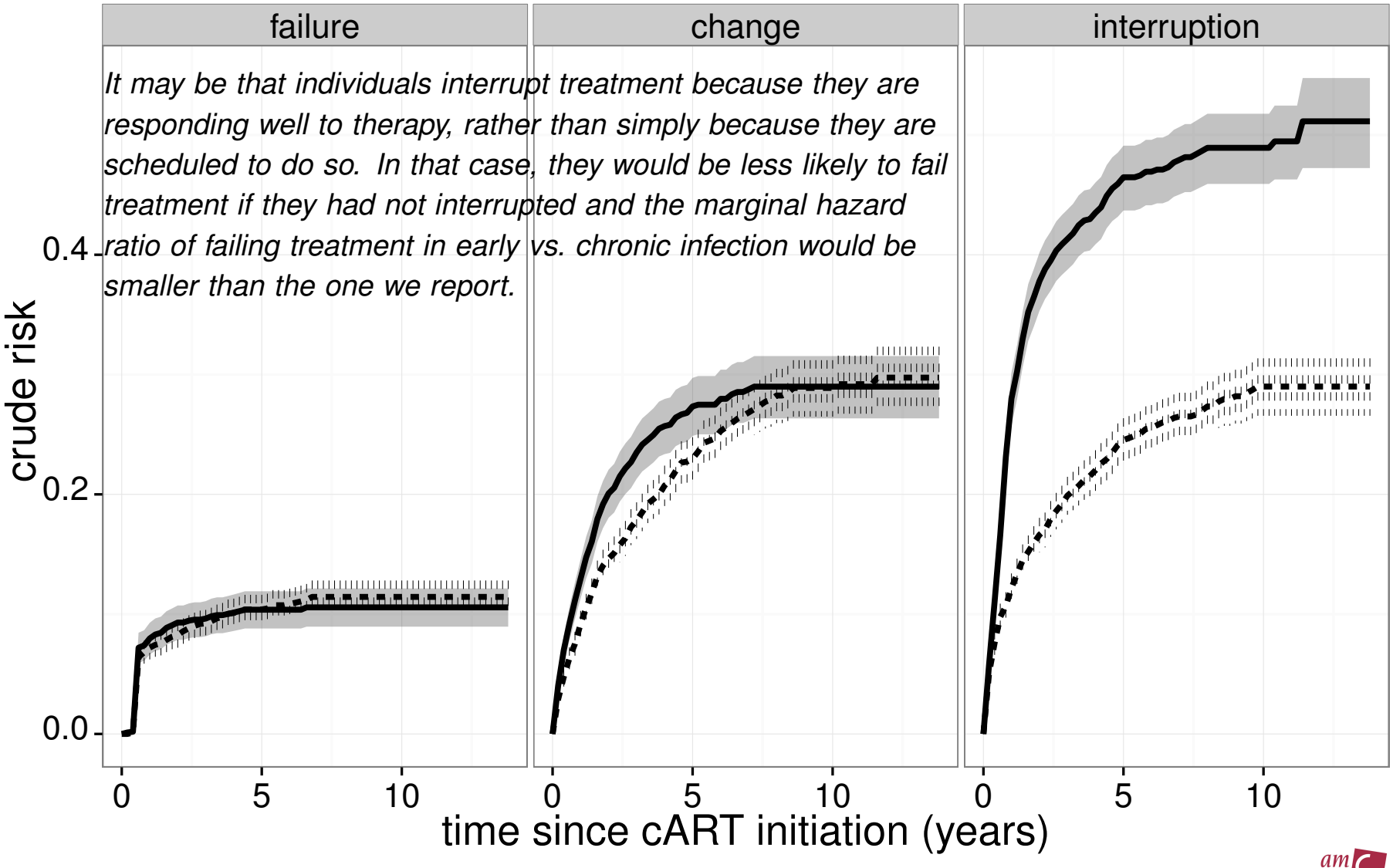

Answer

- Assume that treatment failure and treatment interruption are the only two competing events
- Most extreme scenario: those who interrupt treatment will never fail. Marginal hazard same as the subdistribution hazard, i.e. the reported one.
- It may be true if the effect was observed for the cause-specific hazard.

Choices. . .

- Marginal analysis or competing risks analysis?
- Competing risks: cause-specific hazard or subdistribution hazard?

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- Extra information may allow to show informative/dependent censoring (IDU and pre-AIDS death), but independence can never be tested for

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- If censoring due to competing event is non-informative, marginal and cause-specific hazard are equal. Cumulative quantities are different (Kaplan-Meier versus Aalen-Johansen)

We want to compare the cancer event rates in the virtual situation when the competing risks did not exist. The analysis of the cause-specific hazard models the event of interest in the absence of competing risk events and thus is the appropriate method.

Melania Pintilie. Analysing and interpreting competing risk data. Statistics in Medicine, 26(6):1360–1367, 2007.

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Reply Latouche *et al.* (Statistics in Medicine, 26(19):3676–9)

Pintilie's work has the potential to further obscure the issues . . . Our main critique concerns the inaccurate assertion: "When modelling the cause specific hazard, one performs the analysis under the assumption that the competing risks do not exist".

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- Example III: causes of death. Competing risks.
  Etiology (cause-specific hazard) and/or prediction (cause-specific cumulative incidence); marginal analysis completely hypothetical

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- When can we interpret results as effects on marginal hazards?
  Independence: cause-specific hazard
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- Both Cox and Fine and Gray model make sense in presence of competing risks

THANKS!