Computing the 'Competing Risks'

Modeling Survival Data with Competing Risk Events using SAS Macros

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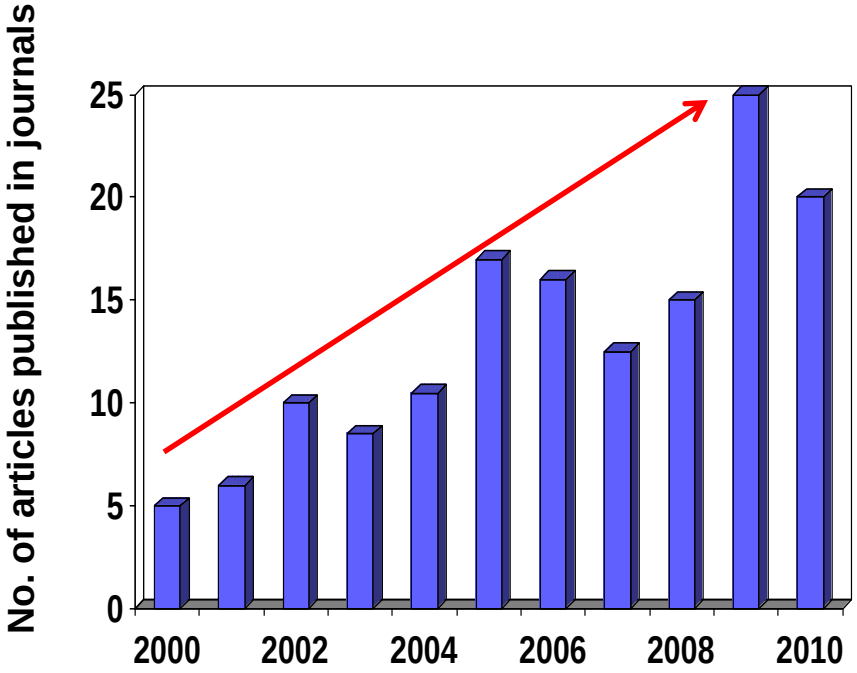
SP06

Why Competing Risk?



Frequency of studies published on the subject of competing risks within the last 10 years steadily increased over time.

Koller, M *et al,* Competing Risks and Clinical Community. *Statist.Med. 2012*

Summary of FDA Public Workshop

The interpretation of overall survival may be confounded by competing risk of mortality, salvage treatments, and crossover..

Outline

- Standard Survival Analysis Techniques
- Concept of Competing Risk (CR) Events
- Analysis techniques in CR setup
  - Estimation of incidence of an event of interest using % CIF (ignoring and accounting for CR)
  - Comparison of incidence among treatment groups using % CIF
  - Assessing effect of covariates on incidence using % PSHREG

Survival Analysis

- Survival Analysis - Time to event analysis
- Event of interest :
  - Cancer relapse
  - Myocardial infarction
  - Discharge from hospital
  - Death due to a specific cause
- Survival Function
- Hazard Function

Censoring

- What is censoring ?

Not all subjects enrolled in the study will have experienced the event of interest

- Assumed to have the same probability of experiencing the event of interest (non-informative censoring)
- Standard survival analysis techniques: Assumption of non-informative censoring

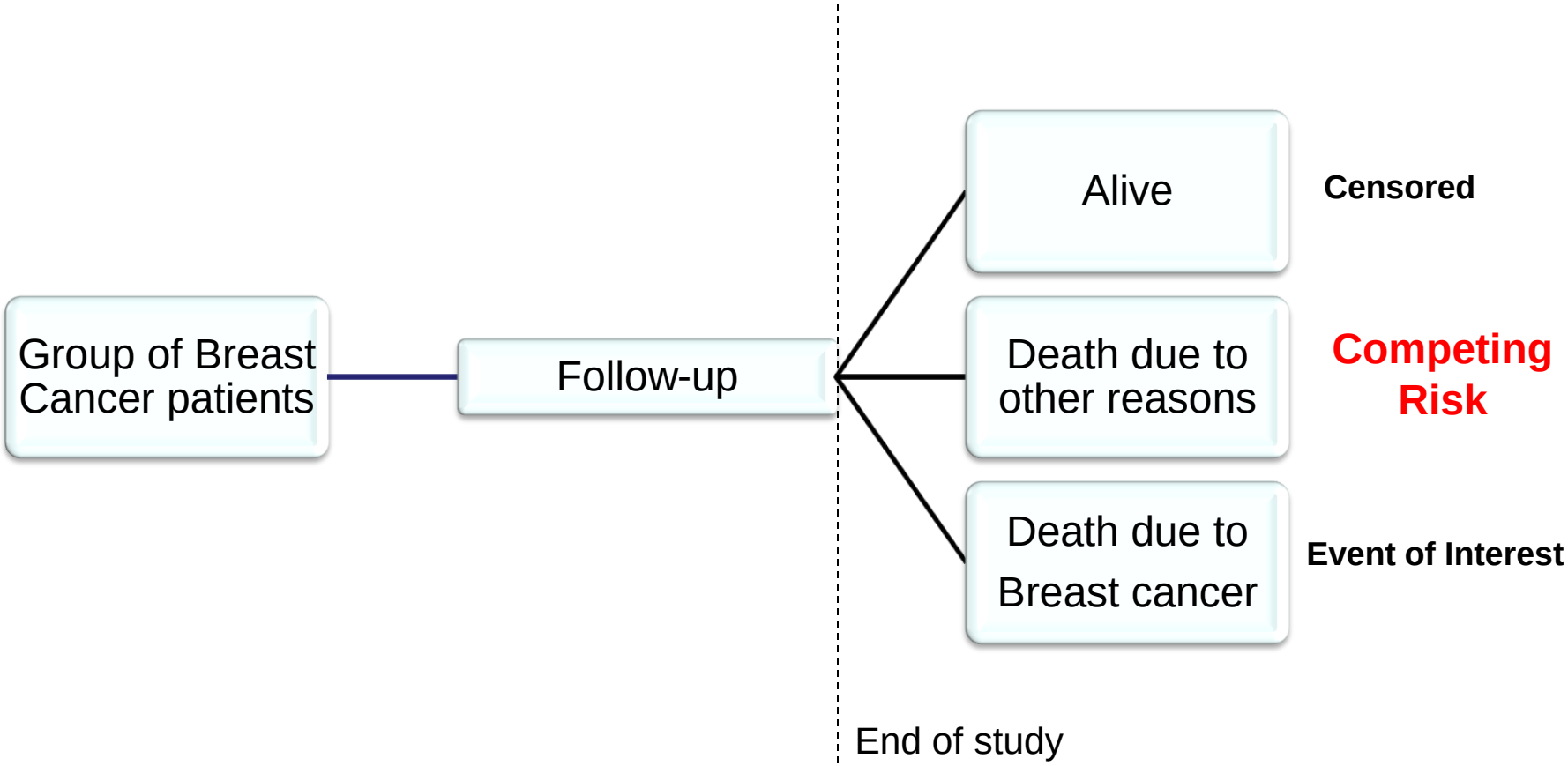
Standard Survival Analysis Techniques

Purpose	Method	SAS Proc
Estimating Survival Function	Kaplan Meier method	Proc lifetest
Comparison of Survival Functions	Log Rank Test	Proc lifetest
Assessing effect of covariates	Cox Regression Model	Proc phreg

Concept of Competing Risk

- A cohort of Breast Cancer (BC) patients
- Event of Interest is ‘death of a patient due to breast cancer’
- Some deaths due to causes unrelated to the disease.
- Researcher: Is it an event of interest ? – No
- Cases to be treated as censored ????

Competing Risk Event



Competing Risk (CR)

- Either precludes the occurrence of another event or
- Alters the probability of occurrence of other event
- Use of classical survival analysis methods lead to a bias

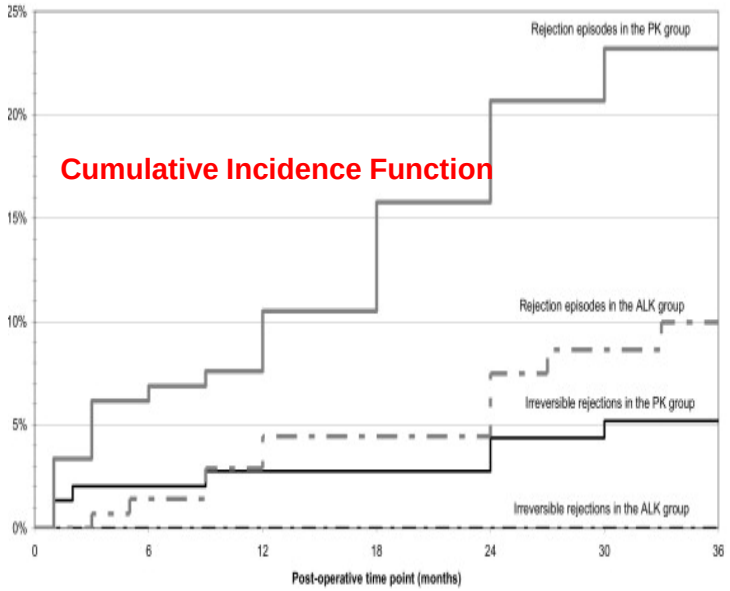
Gooley, TA; Leisenring, W; Crowley, J; Storer, BE, "Estimation of failure probabilities in the presence of competing risks: new representations of old estimators" Statistics in Medicine 1999 pp. 695-706

Here we are…

- Standard Survival Analysis Techniques
- Concept of Competing Risk (CR) Events
- **Analysis Techniques in CR setup**
  - **Estimation of incidence of an event of interest using % CIF (ignoring and accounting for CR)**
  - **Comparison of incidence among treatment groups using % CIF**
  - **Assessing effect of covariates using % PSHREG**

Cumulative Incidence Function (CIF)

- Kalbfleisch and Prentice (1980) introduced 'Cumulative Incidence Function' approach to analyze survival data when CRs exist.
- Cumulative probability of an event of interest over time.
- Also referred as 'subdistribution function'



Gray's Test

- Two or more groups : To test the difference in the cumulative incidence rates among treatment groups.

- Gray (1988) proposed a modified Chi-square test approach

Gray, R. (1988), *A Class of K-Sample Tests for Comparing the Cumulative Incidence of a Competing Risk*. *The Annals of Statistics*, 16, 1141–1154.

%CIF Macro

- SAS inbuilt macro '%CIF'
- Estimates crude cumulative incidence function .
- Also compares cumulative incidence functions across treatment groups.
- Statement:
  %CIF (Data=, Out=, Time=, Status=, Event=, Censored=, Group=, options=)

Test the Effect of Covariates

- Probability of cumulative incidence for subjects with a given set of covariate
- Fine and Gray (1999) and Klein and Andersen (2005) proposed approaches to directly model the effect covariates on CIF.
- Fine and Gray (F&G) method will be discussed.
- Based on proportional hazards model.

% PSHREG

- Developed by researchers from Medical University of Vienna.
- Available in Public Domain
- Implements model proposed by F&G (1999).
- Facilitates to use various options offered by proc phreg.
- Statement:
  %pshreg (Data=, Time=, Cens=, Failcode=, Cencode=, Varlist=, Cengroup=, Options=);

Website: http://cemsiis.meduniwien.ac.at/en/kb/science-research/software/statistical-software/pshreg/

Example

BYAR Study

- Randomized Clinical Trial (Byar study by Byar and Green, 1980)
- Primary interest - To assess the effect of treatment (Rx) on prostate cancer related deaths.
- 502 prostate cancer patients with clinical stage III or IV.
- Randomized to either low or high doses of diethylstilbestrol (DES).

BYAR Study Data

Pat_ID	Stage	Rx	Dtime	status	age	wt	Performance	Lesion	Gleason
1	3	0.2 mg estrogen	72	alive	75	76	normal activity	2	8
2	3	0.2 mg estrogen	1	dead - other ca	54	116	normal activity	42	
3	3	5.0 mg estrogen	40	dead - cerebrovascular	69	102	normal activity	3	9
4	3	0.2 mg estrogen	20	dead - cerebrovascular	75	94	in bed < 50% daytime	4	8
5	3	placebo	65	alive	67	99	normal activity	34	8
6	3	0.2 mg estrogen	24	dead - prostate ca	71	98	normal activity	10	11
7	4	placebo	46	dead - heart or vascular	75	100	normal activity	13	9
8	4	placebo	62	alive	73	114	normal activity	3	9
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501	4	placebo	49	dead - prostate cancer	55	112	normal activity	4	9
502	3	5.0 mg estrogen	20	dead - cerebrovascular	73	88	normal activity	15	10

CR Analysis Dataset

ID	Follow-up (months)	Status	Scenario (I)		Scenario (II)	
001	72	Alive	C	0	C	0
002	1	Dead other cause	C	0	E-CR	2
003	20		C	0	C	0
004	40		C	0	C	0
005	65	Dead Prostate Cancer	E	1	E	1
006	24	Dead Prostate Cancer	E	1	E	1
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501	34	Dead cerebrovascular	C	0	E-CR	2
502	25	Dead heart disease	C	0	E-CR	2

Non cancer deaths censored

Non cancer deaths grouped as 'Competing Risk'

Event of Interest (E): death due to cancer ,
Event of competing risk (E-CR): death due to heart disease, cerebrovascular, other causes etc.
Scenario I : Event and censored without accounting for CR, Scenario II: Event and censored accounting for CR
C : Censored

Incidence of Cancer Deaths

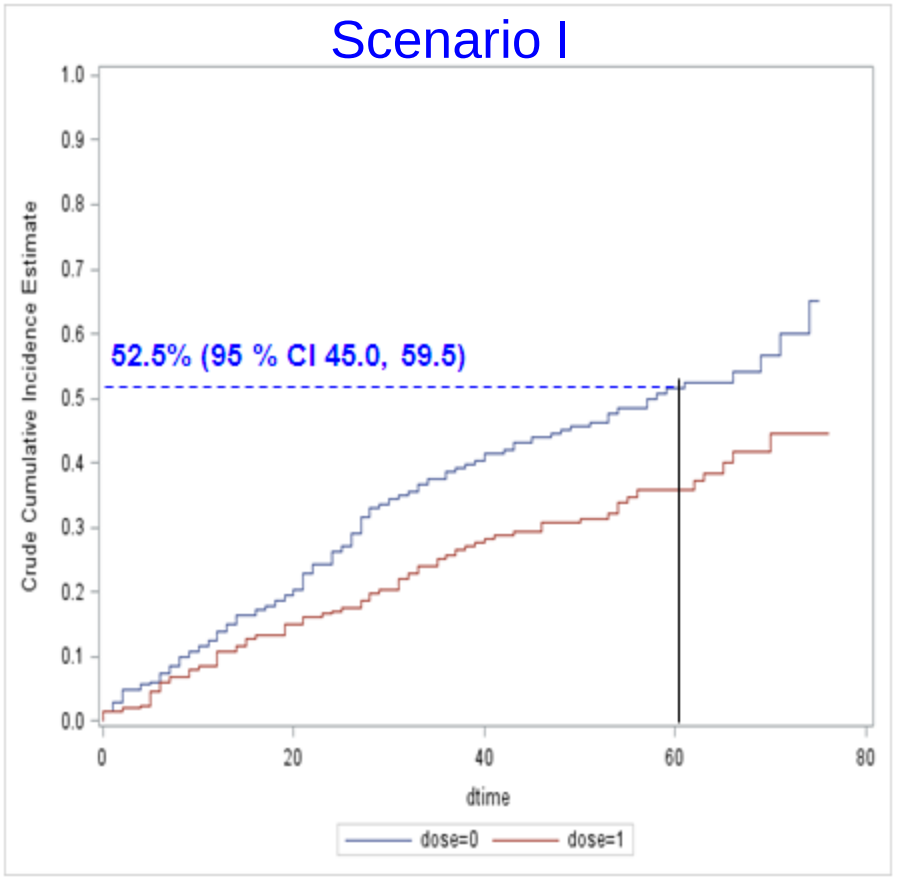
Scenario I	Scenario II
• Ignores CR	• Accounting for CR
• Subjects alive / Loss to FUP / died due to other causes 'censored'	• Subjects alive / Loss to FUP / withdrew 'censored'
	• Death due to other causes grouped as 'CR'.
• KM method	• % CIF macro

% CIF Macro

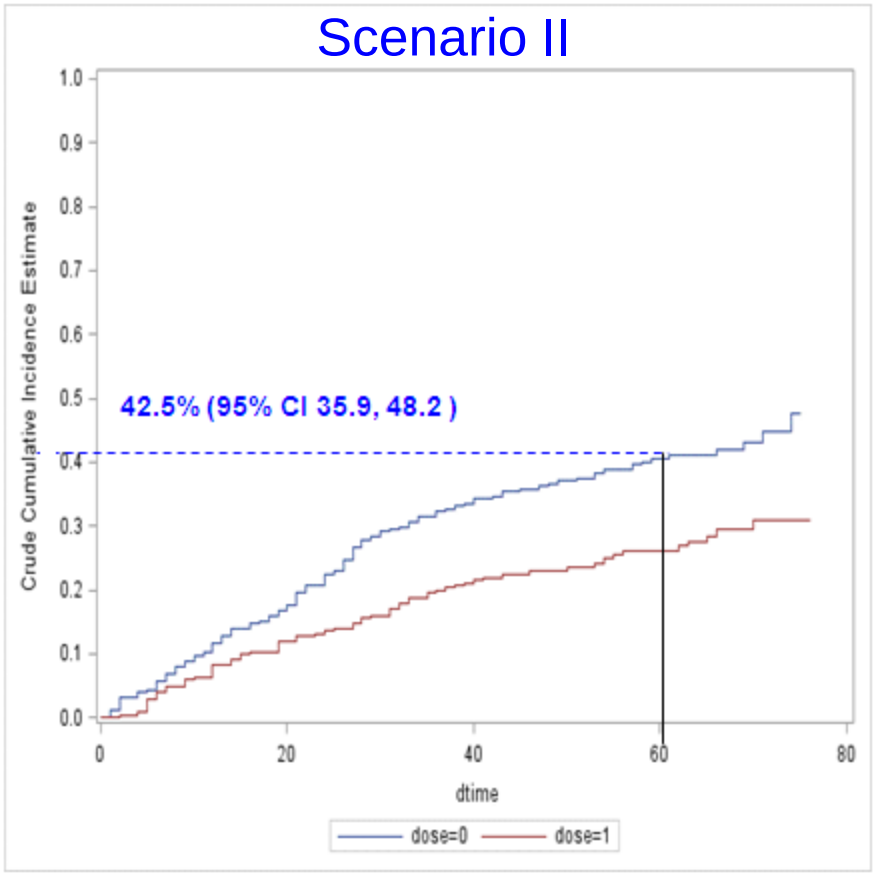
```
%CIF (DATA=BYAR,          /*** DATA=Byar data set to analyze **************/
      TIME= dtime,        /*** dtime: follow-up time in months **************/
      STATUS=stat,        /*** Stat: Response at the time of follow-up******/
      EVENT=1,            /*** EVENT =1: Code for event of interest********/
      CENSORED=0,         /***CENSORED=0: code to indicate censoring**/
      GROUP=dose,         /***dose' (Rx) requests a CI curve for DES arms**/
     TITLE= Cumulative Incidence Function in lower vs. higher  DES arms);
```

Incidence of Disease

Scenario I



Scenario II



Cumulative incidence of event of interest gets overestimated if CR events are present and ignored during estimation.

Testing the Equality of Cumulative Incidence

- Gray's approach to assess the equality between treatment groups in competing risk setting.

Gray's Test for Equality of Cumulative Incidence Functions		
Chi-Square	DF	Probability
10.885	1	0.0010

- Incidence of cancer deaths is significantly different (p=0.0010) between two treatment groups.
- By default using %CIF

To Estimate the difference in CIF between Groups with Covariates

- A set of covariates as age, weight, performance, Gleason score and lesion.
- % pshreg macro directly models the difference in CIF in presence of covariates.

% PSHREG Macro

```
% pshreg (DATA=BYAR,     /*** DATA=Byar data set to analyze ***/
  TIME= dtime,           /*** dtime: follow-up time in months ***/
  CENS=stat,             /*** Stat: Response at the time of follow-up*/
  FAILCODE=1,            /*** 1: code for event of interest***/
  CENCODE=0,             /*** 0 : code to indicate censoring***/
  VARLIST = dose age wt performance gleason lesion /*covariates*/
  CUMINC=1 ,             /** 1:Plots the cumulative incidence curves **/
 OPTIONS =rl);           /*** rl: limits for hazards ratio***/
```

Output of % pshreg macro

The PSHREG macro: Fine-Gray model

The PHREG Procedure

Analysis of Maximum Likelihood Estimates

Parameter	DF	Parameter Estimate	Standard Error	StdErr Ratio	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits		Label
DOSE	1	-0.60268	0.15523	0.994	15.0742	**0.0001**	**0.547**	0.404	0.742	
age	1	-0.02084	0.00992	0.952	4.4138	0.0356	0.979	0.961	0.999	age
wt	1	-0.00848	0.00569	0.989	2.2147	0.1367	0.992	0.981	1.003	wt
hx	1	-0.20670	0.16291	1.009	1.6098	0.2045	0.813	0.591	1.119	hx
performance	1	0.28631	0.24062	1.052	1.4159	0.2341	1.332	0.831	2.134	
gleason	1	0.89924	0.16689	1.001	29.0348	**<.0001**	**2.458**	1.772	3.409	
lesion	1	0.97633	0.18373	0.984	28.2364	**<.0001**	**2.655**	1.852	3.805	

Quick Recap

Purpose	Method	SAS Tool
Incidence estimation	CIF	% CIF
Comparison Incidence	Gray Test	% CIF
Assessing effect of covariates	Fine and Gray method	% PSHREG

Conclusion

Estimating disease incidence accurately is a key factor for successful drug development programme.

Presence of competing risks may hamper the estimation of true disease incidence.

Disease incidence gets overestimated if presence of competing risks is ignored during analysis.

References

- Gray, R. (1988), A Class of K-Sample Tests for Comparing the Cumulative Incidence of a Competing Risk. *The Annals of Statistics*, 16, 1141–1154.
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Thank-You

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