

## Lecture 24

1. Checking whether hazards are proportional: relations between survivor and hazard functions
2. Testing whether hazards are proportional
3. Subset selection
4. Time-varying explanatory variables

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### Proportional hazards assumption

Proportional hazards regression assumes

- there is a baseline hazard  $h_0(t)$  that affects the whole population
- the hazard function for each subgroup  $k$  is  $r_k h_0(t)$ , for a positive constant  $r_k$

The regression part is

$$\log(r_k) = \beta_1 x_1 + \beta_2 x_2 + \cdots + \beta_p x_p.$$

for predictors  $x_1$  (the subgroup label) and other predictors related to survival.

$$\log\left(\frac{h_k(t)}{h_0(t)}\right) = \beta_1 x_1 + \beta_2 x_2 + \cdots + \beta_p x_p.$$

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## Graphs to check whether hazards are proportional

Proc Lifetest makes 3 graphs that provide visual checks of this assumption:  
plot = (S, LS, LLS)

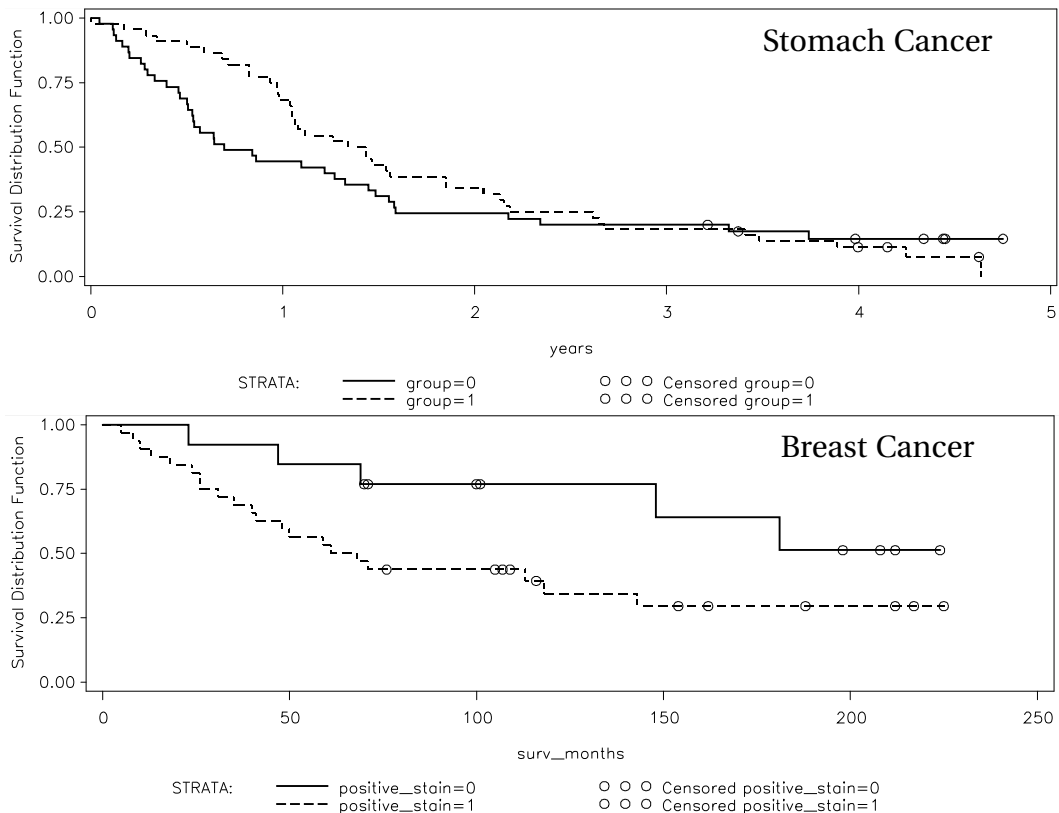
**S** gives the plot of the Kaplan-Meier estimated survivor functions.

If  $h_k(t) = r_k h_0(t)$  then  $S_k(t) = \{S_0(t)\}^{r_k}$  (shown later)

Depending on whether  $r_k > 1$  or  $r_k < 1$ ,  $S_k(t)$  must always be above or below  $S_0(t)$ , respectively.

Either way,  $S_k(t)$  and  $S_0(t)$  *cannot cross*.

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## Relations between $S(t)$ , $h(t)$ , and $r$

The meaning of the other 2 plots depends on relations between the hazard  $h(t)$  and the survivor function  $S(t)$ .

- relative frequency histogram, also known as the **density**  $f$
- cumulative distribution function

$$F(t) = \int_0^t f(u) du \quad \text{or equivalently,} \quad \frac{d}{dt}F(t) = f(t).$$

- survivor function  $S(t) = 1 - F(t)$ .

- hazard function

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

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Derivative of the survivor function:

$$\frac{d}{dt}S(t) = \frac{d}{dt}\{1 - F(t)\} = -f(t)$$

Use this in taking derivatives of  $\log(\text{survivor function})$ :

$$\frac{d}{dt}\log S(t) = \frac{\frac{d}{dt}S(t)}{S(t)} = \frac{-f(t)}{S(t)}$$

or (fixing the sign)

$$\frac{d}{dt}\{-\log S(t)\} = \frac{f(t)}{S(t)} = h(t).$$

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From this relation,

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

integrating both sides with respect to  $t$  gives the **cumulative hazard function**

$$H(t) = \int_0^t h(u)du = -\log S(t)$$

`plot=(LS)` plots the cumulative hazard function(s)  $H(t) = -\log S(t)$

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Now let's see how the proportional hazards assumption  $h_1(t) = r h_0(t)$  fits in.

We assume that the hazard ratio  $r$  *does not depend on time*.

Integrating  $h_1(t) = r h_0(t)$  gives

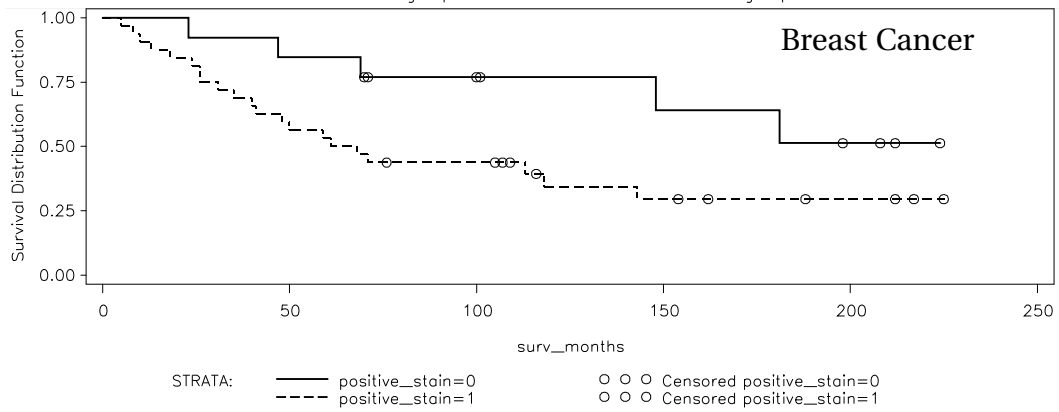
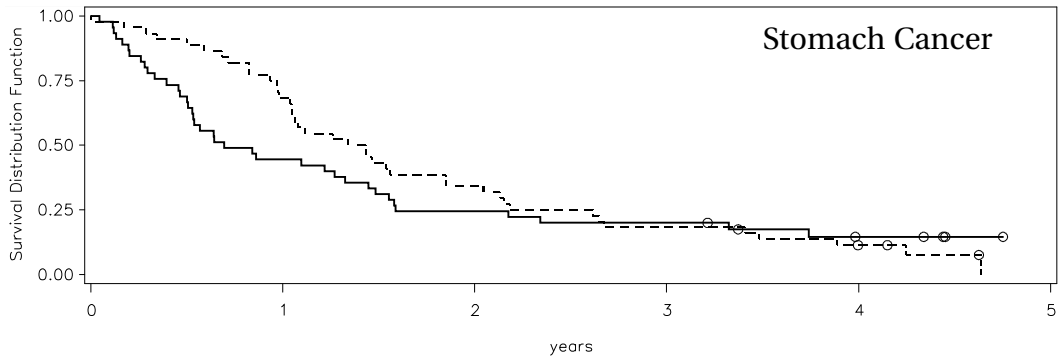
$$H_1(t) = \int_0^t h_1(u)du = \int_0^t r h_0(u)du = r H_0(t)$$

So proportional hazards give proportional cumulative hazards:

$$H_1(t) = r H_0(t)$$

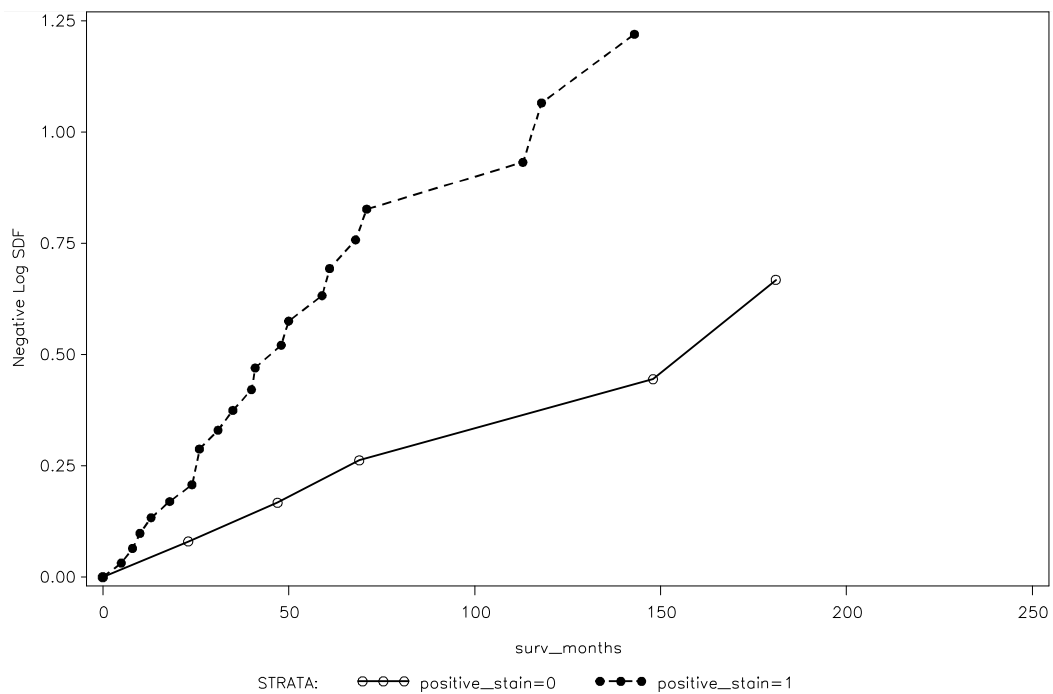
If the hazards are proportional, then the two cumulative hazards should look proportional.

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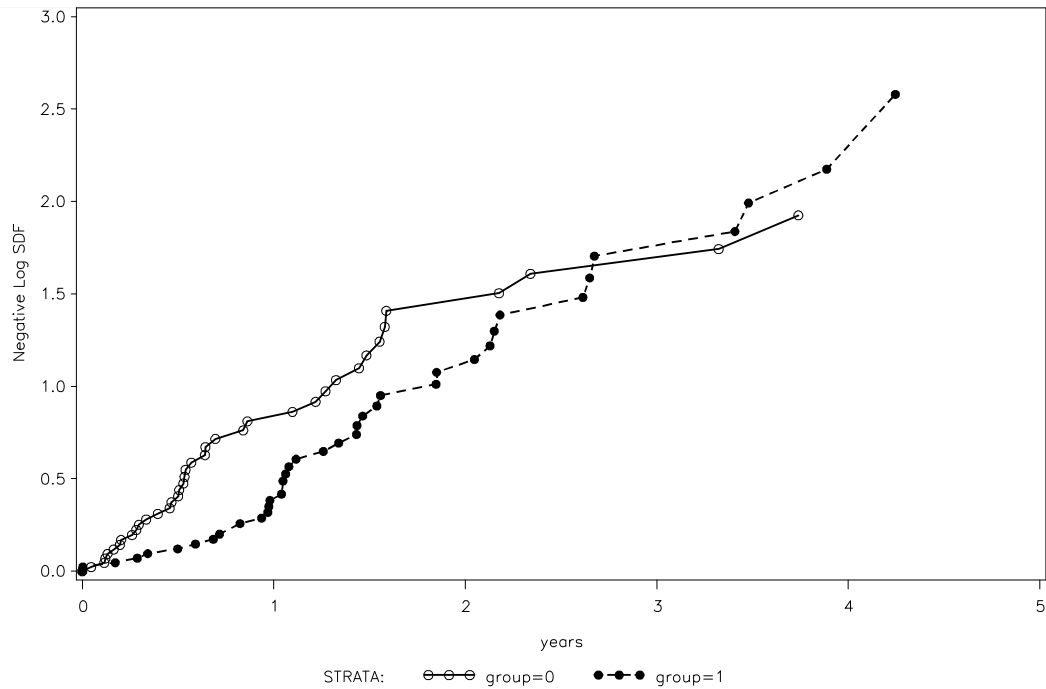
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plot = (LS) for the breast cancer example:



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plot = (LS) for the stomach cancer example:



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$$H_1(t) = r H_0(t)$$

is the same as

$$-\log S_1(t) = r * \{-\log S_0(t)\}$$

Multiply by  $-1$ , and exponentiate both sides:

$$S_1(t) = S_0(t)^r,$$

which was the earlier claim:

*if hazards are proportional, survivor curves do not cross.*

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Take logs of the cumulative hazards:

$$-\log S_1(t) = r * \{-\log S_0(t)\}$$

then

$$\begin{aligned} \log\{-\log S_1(t)\} &= (\log r) + \log\{-\log S_0(t)\} \\ &= c + \log\{-\log S_0(t)\} \end{aligned}$$

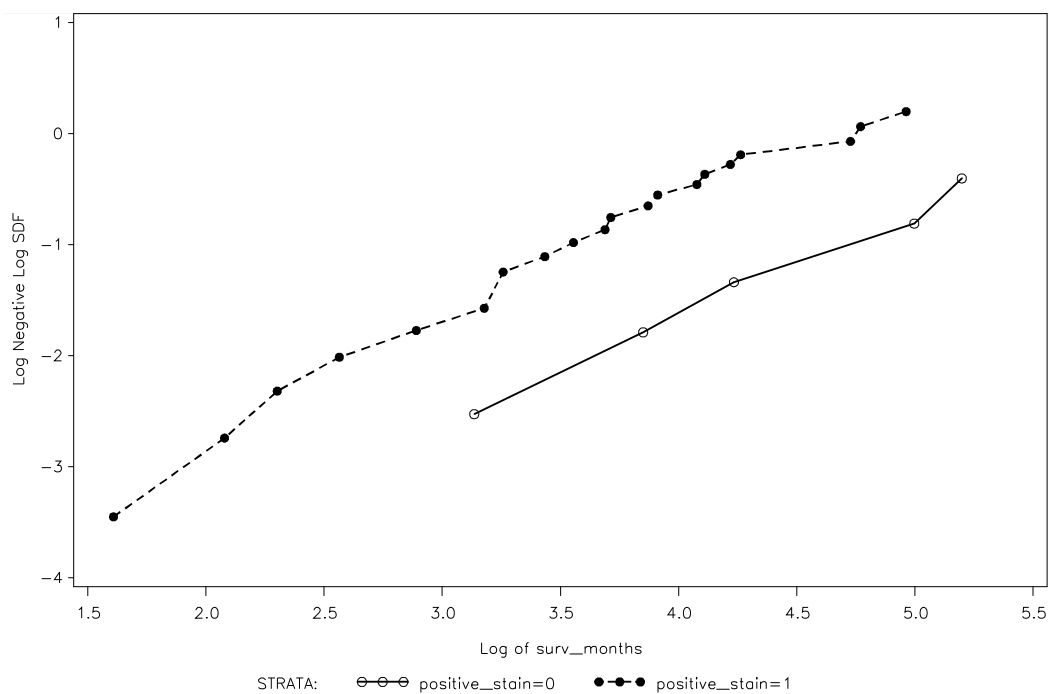
LLS gives a plot of  $\log\{-\log S(t)\} = \log H(t)$

If hazards are proportional, then the LLS plot should show *parallel* curves that differ by the constant  $\log r$ .

It looks like we're taking log of a negative quantity above. Are we?

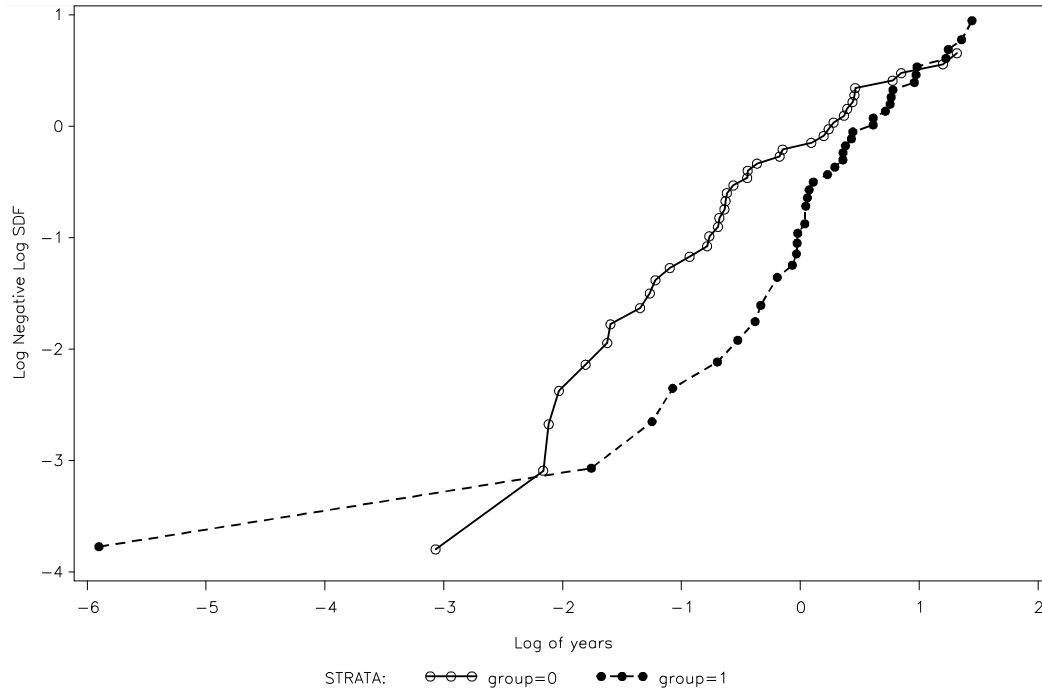
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plot = (LLS) for the breast cancer example:



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plot = (LLS) for the stomach cancer example:



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plot = (LS) plots cumulative hazard functions.

If hazards are proportional, should have form:  $H_i = r H_j$

plot = (LLS) plots log cumulative hazard functions.

If hazards are proportional, should have form:  $\log H_i = c + \log H_j$

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## Testing the proportional hazards assumption

The proportional hazards assumption is that the ratio of hazards is a constant that does not depend on time:

$$\frac{h_A(t)}{h_B(t)} = r.$$

When this assumption fails, it is because the hazard ratio changes over time.

To test this, we will add a term for interaction with time and then test whether its regression coefficient is zero.

Evidence that this regression coefficient is not zero is evidence against proportional hazards.

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In the breast cancer example, the proportional hazards regression model has only one predictor, the indicator variable  $X_1 = \text{positive\_stain}$ .

Define a new predictor,  $X_2 = X_1 t$  and include this in the model:

$$\log\left(\frac{h_P(t)}{h_N(t)}\right) = \beta_1 x_{1k} + \beta_2 x_{2k}$$

Then the two hazards are

$$h_N(t) = h_0(t), \text{ the baseline hazard}$$

$$h_P(t) = \exp(\beta_1 + \beta_2 t) h_0(t)$$

because for a patient in the positive-stain group,  $X_1 = 1$  and  $X_2 = X_1 t = t$ .

The test of  $H_0 : \beta_2 = 0$  is a test for proportional hazards.

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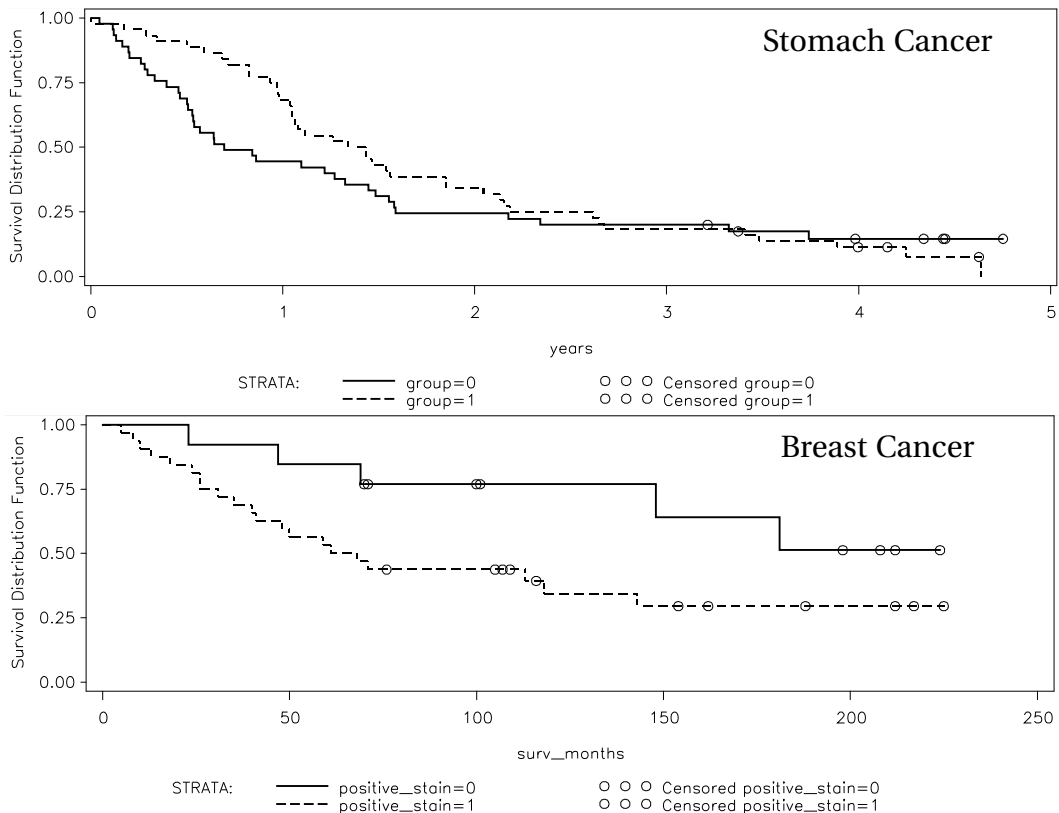
How do we actually define this interaction,  $PS\_time = positive\_stain * t$ ?

Predictors that change with time are defined *inside* the PHreg or TPHreg procedures.

In the breast cancer example, time is given in the variable `surv_months`

```
Proc TPHreg data=pubh.breast_cancer;
  class positive_stain;
  model surv_months * died(0) = positive_stain PS_time
    / risklimits ties=efron;
  PS_time = positive_stain*surv_months;
```

Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq
positive_stain 0	1	-1.88112	0.98093	3.6775	0.0551
PS_time	1	-0.01371	0.01070	1.6412	0.2002



In the stomach cancer example, time is years

```
proc PHreg data=pubh.stomach_cancer ;  
  model years*censor(1) = group group_time / risklimits ties=efron;  
  group_time = group* years;
```

Variable	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq
group	1	-1.11806	0.39591	7.9752	0.0047
group_time	1	0.78008	0.27731	7.9129	0.0049

In this case the group-time interaction is highly significant, as we expected, strong evidence for non-proportional hazards.

### Selecting a subset of explanatory variables

A great appeal of proportional hazards is that we can use what we've learned about linear regression. One issue is selecting a subset of useful explanatory variables from a larger group of predictors.

**Prostate Cancer example.** In this 1967 study, men were randomly assigned to an active drug or placebo treatment for prostate cancer. Time (months) to death was the endpoint and a number of characteristics were measured at baseline:

- treatment (active/placebo)
- age (years)
- serum hemoglobin (g/100 ml)
- tumor size (cm<sup>2</sup>)
- Gleason index (higher values indicate more advanced tumor)

Source: Example 1.4 in Collett (2003) *Modelling Survival Data in Medical Research, 2nd ed.*

We can test the proportional hazards assumption with respect to treatment:

```
Proc TPHreg data=pubh.prostate;
  class treatment;
  model surv_months* died(0) =
    treatment age hemoglobin tumor_size gleason_index trt_time /
    risklimits ties=efron ;
  if treatment = "Placebo" then trt=0; need a numeric version of treatment
  else trt=1;
  trt_time = surv_months*trt;
```

Parameter		DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq
treatment	Active	1	-2.96497	4.01771	0.5446	0.4605
age		1	0.03994	0.07123	0.3144	0.5750
hemoglobin		1	0.00699	0.45714	0.0002	0.9878
tumor_size		1	0.09464	0.05158	3.3670	0.0665
gleason_index		1	0.70107	0.34741	4.0724	0.0436
trt_time		1	0.03987	0.08086	0.2432	0.6219

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```
Proc TPHreg data=pubh.prostate;
  class treatment;
  model surv_months * died(0) =
    treatment age hemoglobin tumor_size gleason_index /
    risklimits ties=efron ;
```

#### Analysis of Maximum Likelihood Estimates

Parameter		DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq
treatment	Active	1	-1.18206	1.21030	0.9539	0.3287
age		1	0.04397	0.07201	0.3729	0.5414
hemoglobin		1	-0.02214	0.45273	0.0024	0.9610
tumor_size		1	0.09397	0.05209	3.2541	0.0712
gleason_index		1	0.72343	0.34996	4.2732	0.0387

What should we drop?

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```

Proc TPHreg data=pubh.prostate;
class treatment;
model surv_months * died(0) =
    treatment age tumor_size gleason_index /
    risklimits ties=efron ;

```

Parameter		DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq
treatment	Active	1	-1.17194	1.19420	0.9631	0.3264
age		1	0.04421	0.07184	0.3786	0.5383
tumor_size		1	0.09317	0.04947	3.5474	0.0596
gleason_index		1	0.72564	0.34791	4.3503	0.0370

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```

Proc TPHreg data=pubh.prostate;
class treatment;
model surv_months * died(0) =
    treatment tumor_size gleason_index /
    risklimits ties=efron ;

```

Parameter		DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq
treatment	Active	1	-1.11276	1.20312	0.8554	0.3550
tumor_size		1	0.08257	0.04746	3.0273	0.0819
gleason_index		1	0.71022	0.33790	4.4178	0.0356

Parameter		Hazard Ratio	95% Hazard Ratio Confidence Limits		Variable Label
treatment	Active	0.329	0.031	3.474	treatment Active
tumor_size		1.086	0.990	1.192	
gleason_index		2.034	1.049	3.945	

What is the effect of the active treatment?

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## Automatic selection

Both PHReg and TPHReg have options to perform automatic subset selection, using forward, backward, or stepwise selection. They will also use the score statistic, related to the log-rank, to select models.

```
Proc TPHreg data=pubh.prostate;
  class treatment;
  model surv_months* died(0) =
    treatment age hemoglobin tumor_size gleason_index /
    risklimits ties=efron
    selection = score
    best=2 list the two best models of each size
    include=1 ; include the first predictor in all models
```

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### Regression Models Selected by Score Criterion

Number of Variables	Score Chi-Square	Variables Included in Model
1	4.4210	treatmentActive
2	10.8910	treatmentActive gleason_index
2	10.7516	treatmentActive tumor_size
3	14.9015	treatmentActive tumor_size gleason_index
3	11.1972	treatmentActive age gleason_index
4	14.9910	treatmentActive hemoglobin tumor_size gleason_index
4	14.9015	treatmentActive age tumor_size gleason_index
5	14.9923	treatmentActive age hemoglobin tumor_size gleason_index

Look for the last model that produces a large increase in the score.

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## Example: Alport mice

Males have an X and a Y chromosome, while females have two X chromosomes, and so one is turned off more or less randomly.

Alport syndrome is an X-linked genetic defect that leads to kidney disease. To study the X-inactivation effect, 90 female mice were bred with one Alport X chromosome.

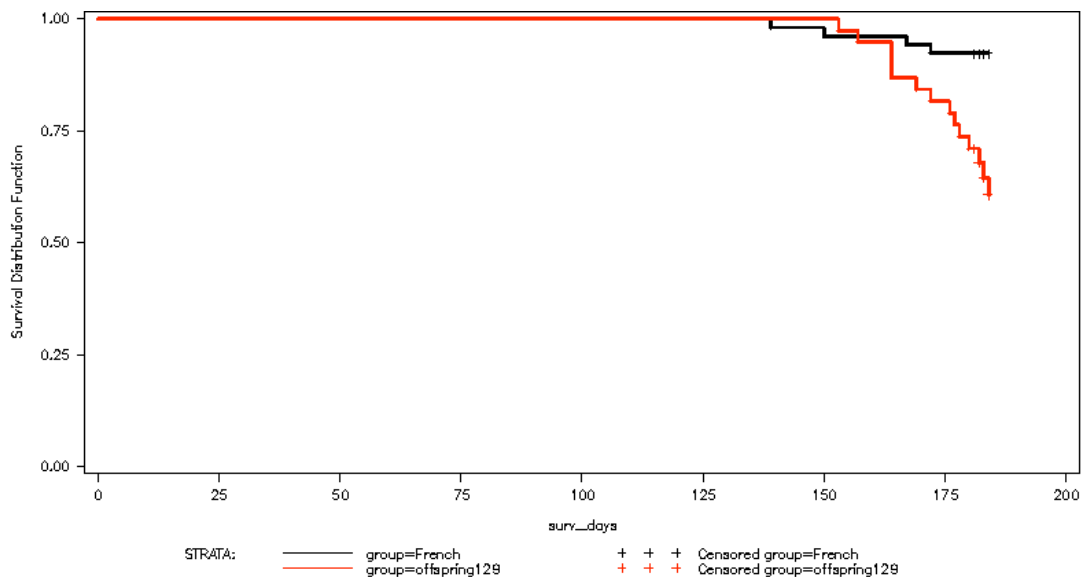
The mice were in two groups (French, Offspring 129) that differed in the gene region that controlled X-inactivation.

Experimental design: urine would be collected at 2, 4, and 6 months after birth and the mice were to be sacrificed at 6 months.

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Kaplan-Meier estimates of survival curves

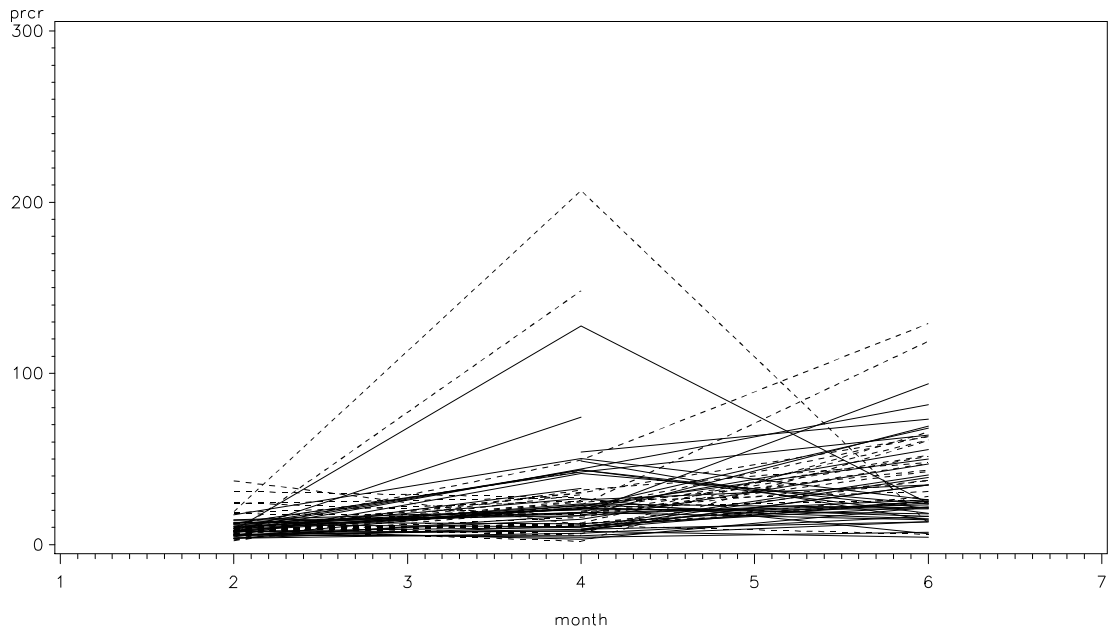
(log rank test  $p = .0014$ , Wilcoxon test  $p = .0031$ ).



Surprising result: all mice expected to live 6 months.

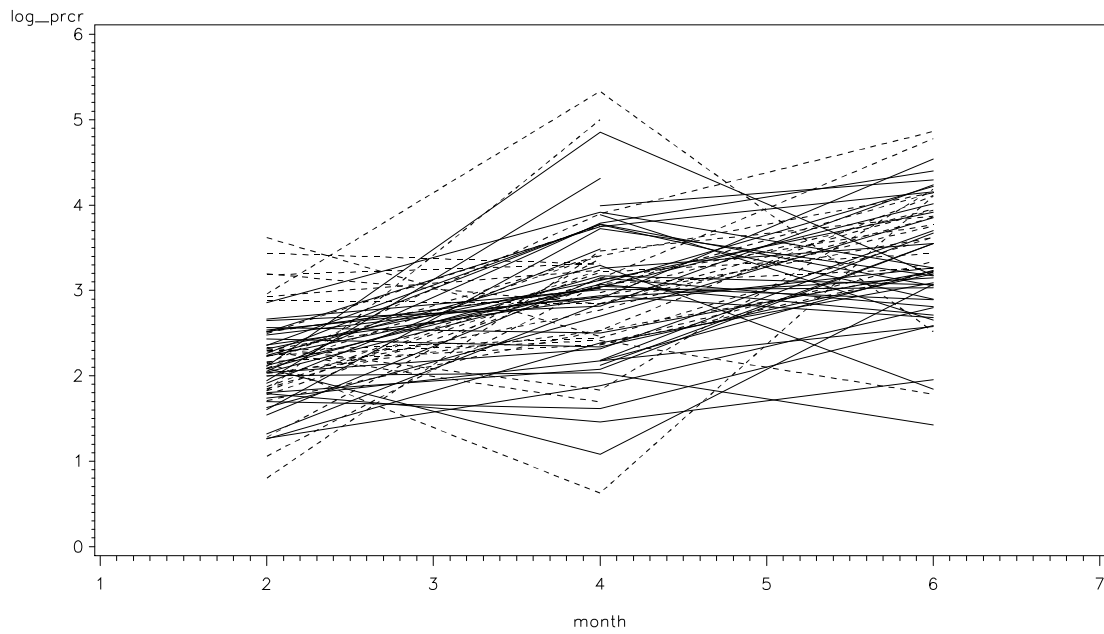
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Is there a connection between the Alport defect and survival? Here is the measurement of kidney function from the urine collections:



Transformation?

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This predictor of outcome measured at 2, 4, 6 months *changes over time*.

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## Time-varying predictor

We used a *time-varying predictor* in the test for non-proportional hazard. The capability of modeling predictors that change over time is one of the great advantages of proportional hazard regression.

For the Alport mice, we need a predictor that changes at 2, 4, and 6 months.

Urine was not collected at baseline (birth) and mice were sacrificed at 6 months.

What time intervals should the measurements apply to?

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In this data, survival is measured in days.

```
Proc Tphreg data=s;
  class group ;
  model surv_days*early_death(0) = pr_cr group pr_cr*group
    / risklimits ties=efron;

  if (surv_days < 60) then pr_cr=log_pr2;
  else if (surv_days < 120) then pr_cr=log_pr4;
  else pr_cr=log_pr6;
```

The time-varying predictor is defined by code within the procedure.

Use the time variable to set conditions for the predictor to change values.

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The TPHREG Procedure

Model Information

Data Set	WORK.S	
Dependent Variable	surv_days	surv_days
Censoring Variable	early_death	early death
Censoring Value(s)	0	
Ties Handling	EFRON	

Number of Observations Read	90
Number of Observations Used	90

Class Level Information

Class	Value	Design Variables
group	French	1
	offspring129	0

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Summary of the Number of Event and Censored Values

Total	Event	Censored	Percent Censored
90	17	73	81.11

How many predictors can we reasonably fit?

Effect	Type 3 Tests		
	DF	Wald Chi-Square	Pr > ChiSq
pr_cr	1	1.8919	0.1690
group	1	2.7776	0.0956
pr_cr*group	1	1.3761	0.2408

Do we need the interaction term?

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Main effects model:

Type 3 Tests

Effect	DF	Wald	
		Chi-Square	Pr > ChiSq
pr_cr	1	0.9442	0.3312
group	1	9.5653	0.0020

Analysis of Maximum Likelihood Estimates

Parameter	DF	Parameter	Standard	Chi-Square	Pr > ChiSq
		Estimate	Error		
pr_cr	1	-0.30267	0.31149	0.9442	0.3312
group	1	-1.98379	0.64142	9.5653	0.0020

Analysis of Maximum Likelihood Estimates

Parameter	Hazard Ratio	95% Hazard Ratio		Variable Label
		Confidence	Limits	
pr_cr	0.739	0.401	1.360	
group	0.138	0.039	0.484	group French

Effect of the kidney measure?