

# Biost 517

## Applied Biostatistics I

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### Lecture 15: Two Sample Inference with Right Censored Data

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## Lecture Outline

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- Comparing Independent Proportions
  - Large Samples (Censored)
    - Using Kaplan-Meier Estimates
- Comparing Hazard Functions
  - Logrank Test
  - Wilcoxon Test for Censored Data
- Comparing Quantiles
  - Parametric Accelerated Failure Time Models

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## Right Censored Data

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## Right Censored Data

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- Recall from Lecture 6: Censored variables
  - A special type of missing data (the exact value is not always known)
    - Right censoring: for some observations it is only known that the true value exceeds some threshold
    - Left censoring: for some observations it is only known that the true value is below some threshold
    - Interval censoring: for some observations it is only known that the true value is between some thresholds

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## Examples

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- PSA data set
  - Subjects were followed with serial PSAs
  - Interested in time to relapse
  - Some still in remission at time of analysis
  - (Ignoring these subjects is ignoring successes)
- University salary data set
  - Interest is in sex discrimination
  - Interested in time to promotion from associate
  - Some subjects have not yet been promoted
  - (Ignoring these subjects may be ignoring discrimination)

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## Descriptive Statistics

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- Sample mean, sample median (and other quantiles), sample standard deviation and variance are not appropriate
- Instead, descriptive statistics must be computed from Kaplan-Meier estimates
  - Only exception: You could use binomial proportions to estimate survival to the first censoring time
    - E.g., PSA data: All subjects followed at least 24 months

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## Noninformative Censoring

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- Recall: Our estimation methods only appropriate if censoring is not informative about subjects who were either more or less likely to have an event in the immediate future
  - Censored subjects must look like a random sample of those at risk at time of censoring
  - (Later we shall say that they are a random sample from all subjects at risk having similar modeled covariates)

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## Comparing Independent Proportions

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Large Samples with Right Censored Data

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## Kaplan-Meier Estimates

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- Estimate  $S(t) = Pr ( T^0 > c )$  for arbitrary  $c$ 
  - Nonparametric
    - Works for all distributions
    - (Also works for uncensored data)
  - Consistent for true value in infinite samples
  - Can derive estimates of quantiles
  - Can only estimate mean if estimated survival curve goes to 0
    - But can define “restricted mean” up to some time

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## Approximate Distribution

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- If interested in  $\theta = S(c) = Pr ( T^0 \geq c )$  in presence of right censoring

Kaplan - Meier estimates for  $i$ th group

$$\theta_i = \hat{S}_i(c) = \prod_{j:t_j \leq c} \left( 1 - \frac{d_{ij}}{n_{ij}} \right) \sim N \left( S_i(c), \left[ se(\hat{S}_i(c)) \right]^2 \right)$$

(with  $se(\hat{S}_i(c))$  from Greenwood's formula)

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## Stata: Kaplan-Meier Commands

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- Syntax for “setting survival data”
  - `“stset endtime eventind, t0(entrytime)”`
    - *endtime*: name of the variable measuring the time at the end of the interval
    - *eventind*: name of an indicator (0 or 1) variable indicating event status at the end of the interval
    - *entrytime*: name of the variable specifying the time at the start of the interval
      - (does not need to be supplied)
  - `“stset, clear”` resets the data set

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## Stata: Kaplan-Meier Commands

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- Syntax for getting estimates, plots
  - Plotting survival curves
    - `“sts graph”`
    - `“sts graph, atrisk”`
    - `“sts graph, cens(s)”`
  - Listing survival estimates
    - `“sts list”`
  - Saving survival estimates
    - `“sts gen newvar = s”`

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## Two Group Comparisons

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- To compare survival probabilities, we would compute SE for each group individually, then use methods for combining estimates

For independent  $\hat{\theta}_1 \sim N(\theta_1, se_1^2)$ ,  $\hat{\theta}_2 \sim N(\theta_2, se_2^2)$

$$\hat{\theta}_1 + \hat{\theta}_2 \sim N(\theta_1 + \theta_2, se_1^2 + se_2^2)$$

$$\hat{\theta}_1 - \hat{\theta}_2 \sim N(\theta_1 - \theta_2, se_1^2 + se_2^2)$$

$$\hat{\theta}_1 / \hat{\theta}_2 \sim N\left(\frac{\theta_1}{\theta_2}, \frac{1}{\theta_2^2} \left( se_1^2 + \frac{\theta_1^2}{\theta_2^2} se_2^2 \right)\right)$$

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## Two Group Inference

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- As with any (approximately) normally distributed estimator, CI and P values are computed using

100(1- $\alpha$ )% confidence interval

$$(est) \pm z_{1-\alpha/2} \times (std\ err)$$

Normalized Z statistic for  $H_0 : \theta = \theta_0$

$$Z = \frac{(est) - (null\ hyp)}{(std\ err)}$$

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## Example: PSA Data

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- Men with prostate cancer
  - Hormonal treatment
  - Followed for signs of progression
- Interested in estimating probability of remaining in remission for three years
  - Testing hypothesis that three year survival differs between bone scan score less than 3 or bone scan score equals 3

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## Example: Preparing Data

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- Reading in data (note string variable)

```
. infile ... obstime str8 inrem using psa.txt
```
- Creating indicator of relapse

```
. g relapse = 0
. replace relapse = 1 if inrem=="no"
```
- "Setting" survival variables

```
. stset obstime relapse
```

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## Dichotomizing Bone Scan Score

- Method 1 (must consider missing data)

```
. g bss3= 0
. replace bss3=1 if bss==3
. replace bss3=. if bss==.
```
- Method 2 (recode handles missing data)

```
. g bss3= bss
. recode bss3 1/2=0 3=1
```

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## Stata: KM Listing

```
. sts list, by(bss3) at(12 24 36 48)
Beg.          Surv   Std.
Time Total Fail   Fctn Error [95% Conf Int]
bss3=0
  12   18   1   0.9444 0.0540   0.6664 0.9920
  24   14   3   0.7778 0.0980   0.5110 0.9102
  36   12   1   0.7130 0.1092   0.4398 0.8699
  48    6   3   0.4801 0.1356   0.2101 0.7082
bss3=1
  12   22  10   0.6667 0.0861   0.4692 0.8047
  24   15   6   0.4667 0.0911   0.2839 0.6304
  36    9   5   0.2963 0.0841   0.1464 0.4630
  48    2   4   0.1058 0.0659   0.0209 0.2713
```

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## Stata: Difference and SE

- Three year survival probabilities
  - Bone scan score < 3: 0.7130 (SE 0.1092)
  - Bone scan score = 3: 0.2963 (SE 0.0841)
- Estimated diff in 3 year survival probability

```
. display 0.7130 - 0.2963
.4167
```
- Standard error of estimated difference

```
. display sqrt( 0.1092^2 + 0.0841^2 )
.13783124
```

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## Stata: 95% CI and P value

- 95% confidence interval: 0.147 to 0.687

```
. display invnorm(.975)
1.959964
. display .4167 - invnorm(.975) * 0.13783124
.14655573
. display .4167 + invnorm(.975) * 0.13783124
.68684427
```
- Two-sided P value : P = 0.0025  
– (note use of negative)

```
. display 2 * norm( - .4167/.13783124 )
.00250065
```

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## Interpretation

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- The Kaplan-Meier estimate of difference in survival is that men with a bone scan score less than 3 have an absolute improved 3 year survival of 41.7% relative to  $bss=3$
- With 95% confidence, such an observation is not consistent with a true absolute improvement less than 14.7% or greater than 68.7%
- Based on the P value of 0.0025, we reject the null hypothesis of no association between bone scan score and 3 year survival prob

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## Comparing Hazard Functions

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Logrank Test

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## Scientific Questions

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- With time to event data, we are generally interested in probability that an event will occur in a specified time
  - Right censored data presented problems, because the measurement of events was over varying amounts of time
    - Effect modification by time?
    - Confounding by time?
    - Increased precision by accounting for time?

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## General Strategy

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- We want to use methods that adjust for the time of observation
  - Kaplan-Meier estimates at a fixed time
  - Logrank and modified Wilcoxon statistics by averaging effects over time

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## Hazard Function

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- With censored data, we often compare probability distns using hazard functions
  - Hazard = Instantaneous risk of an event
    - Among subjects at risk of an event, what is the probability of having an event in the next instant
  - Advantage of using hazard with censored data
    - Only need to consider subjects currently at risk
    - Only need to consider whether they have an event right then

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## Hazard Function

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- Estimates of the hazard at each time look somewhat like a binomial proportion
  - We do not often estimate the hazard function over time
  - However, we do compare hazard functions
    - Usually we estimate a hazard ratio: relative risk of an event
    - We want to average the estimates of the hazard ratio over all times

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## Stratified Analyses

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- Recall that we are often interested in comparing groups within strata
  - Confounding:
    - Comparisons within strata are all similar, but failure to stratify results in a comparison that is misleading due to bias
      - There are nuances here as we go from analyses of means to analyses of nonlinear summary measures (e.g., odds- more later)
  - Interactions:
    - Comparisons within strata result in different estimates

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## Adjusting for Covariates

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- We can remove confounding by “adjusting” for the confounder using a stratified test statistic
  - “Adjustment” for a covariate means making comparisons between subjects who have similar levels of that covariate
    - E.g., in FEV data, compare smoking children to nonsmokers of same age, height
    - Average the differences seen in age, height strata

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## Role of Effect Modification

- Adjustment for a covariate does not remove interactions
  - Interactions means that the question has different answers in different strata
- Adjustment for a covariate will merely average the effect across strata
  - Usually weighted by the sample size in each stratum

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## Stratified Estimates

- Obtained by combining estimates from each (independent) stratum
  - Generally, best to average the estimates (sometimes weighted) rather than Z scores
  - SEs for the stratified estimates are obtained using properties of independent random variables
    - Standard errors are the sum of squared standard errors from the independent strata

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## Example

- Effect of hepatomegaly on survival after adjustment for sex?
  - Summarize response by 5 year survival
  - Hepatomegaly effect by sex: For each sex, compute difference in survival across hepatomegaly groups
  - Adjusted measure of effect: Compute the average difference between hepatomegaly effects
    - Usually a weighted average

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## SE for Stratified Estimates

	Males	Females
Hepatomegaly	$\hat{\theta}_{M1} \sim N(\theta_{M1}, se(\hat{\theta}_{M1}))$	$\hat{\theta}_{F1} \sim N(\theta_{F1}, se(\hat{\theta}_{F1}))$
No Hepatomegaly	$\hat{\theta}_{M0} \sim N(\theta_{M0}, se(\hat{\theta}_{M0}))$	$\hat{\theta}_{F0} \sim N(\theta_{F0}, se(\hat{\theta}_{F0}))$
	↓	
Weighted average	$p(\hat{\theta}_{M1} - \hat{\theta}_{M0}) - (1-p)(\hat{\theta}_{F1} - \hat{\theta}_{F0})$	
Approx Distn	$\sim N(\text{mean} = p(\theta_{M1} - \theta_{M0}) - (1-p)(\theta_{F1} - \theta_{F0}),$	
	$se = \sqrt{p^2(se^2(\hat{\theta}_{M1}) + se^2(\hat{\theta}_{M0})) + (1-p)^2(se^2(\hat{\theta}_{F1}) + se^2(\hat{\theta}_{F0}))}$	

## Mantel-Haenszel Statistic

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- Generally regarded as the best choice of methods for comparing binary data across strata
  - Based on the odds rather than the proportion
    - It is rare that we might expect the difference in proportions to be constant across strata
  - Other methods can be based on the asymptotic distribution of the log odds
    - (More on these methods next quarter)

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## Logrank Test

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- The Mantel-Haenszel test is also the basis for a very popular method of comparing censored survival data across populations: The logrank statistic
  - The data are stratified by time of event
    - Often only a single event is observed in each stratum
    - Stratified estimates of the odds ratio are obtained

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## Noninformative Censoring

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- Most often the same subjects are used in several different strata
  - Noninformative censoring argues that the estimates are independent across strata asymptotically

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## Tests Equality of Hazards

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- Equal hazard functions implies equal distributions
  - The P value for this test is interpretable as a test that the survival distributions are similar for the two groups
  - This test is more powerful when the true alternative is “proportional hazards”
    - Proportional hazards = constant risk ratio over time
    - Proportional hazards regression will provide estimates of the risk ratio

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## Logrank Test: Stata Commands

- The logrank test can be obtained from Stata using the “sts test” command (after defining survival variables using “stset”
  - “sts test *groupvar*, logrank”
    - *groupvar* indicates the groups to be compared
    - logrank test is default
    - P value based on a chi square statistic
      - Hence a two-sided P value
      - (Obtaining a one-sided P value is deferred until we discuss proportional hazards regression next quarter)

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## Example: PSA Survival by bss

```
. sts test bss3
Log-rank test for equality of survivor functions
```

	Events	Events
bss3	observed	expected
0	9	17.18
1	25	16.82
Total	34	34.00

```
chi2(1) =      8.30
Pr>chi2 =     0.0040
```

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## Example: Interpretation

- Based on the two-sided P value of 0.004, we reject the null hypothesis of equal relapse free survival probabilities between the bone scan score groups
  - (Because the expected events are less than observed in the bss=3 group, we can presume that the higher bss is associated with worse relapse free survival)

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## Hazard Ratio Estimates

- Logrank test does not give estimates
  - However, it is closely related to “proportional hazards regression” (“Cox regression”)
    - Provides estimates of the (average) hazard ratio over time
- Hazard ratio
  - Groups with higher hazards have higher event rates
    - Hazard ratio greater than 1 = Worse “survival”

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## Proportional Hazard Regression

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- HR estimates approximately normal in large samples
- Stata commands
  - “`stcox groupvar, robust`”
    - “robust” eliminates need for proportional hazards
    - Gives hazard ratio, 95% CI
      - CI is computed on log hazard ratio scale
    - P values
      - “Wald test” (based on approximately normal estimate)
      - “Likelihood ratio test”
      - (“Score test” would be the logrank test)

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## Example: PSA Survival by bss

.....

```
. stcox bss3
No. of subjects = 48      Number of obs =      48
No. of failures = 34      Time at risk  =    1408
                               LR chi2(1)    =      8.35
Log likelihood = -106.9   Prob > chi2    = 0.0038
```

Robust						
t	HazRat	StdErr	z	P> z	[95% CI]	
bss3	2.96	1.11	2.89	0.004	1.42	6.16

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## Example: Interpretation

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- We estimate that at any given time the risk of relapse in men with bss=3 tends to be 2.96 times that of men with lower bss
- 95% CI suggests these results typical if true risk of relapse with bss=3 is 1.42 to 6.16 times that in men with lower bss
- Based on P value of 0.004 we would reject null hypothesis of no association between relapse and bss

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## Comparing Hazard Functions

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Wilcoxon Form of Logrank Test

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## Modification of Wilcoxon Test

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- Recall that the Wilcoxon test compares distributions based on  $\Pr(Y > X)$ 
  - We need to define what we mean by  $Y > X$  in presence of censoring
    - $Y > X$  if
      - uncensored  $Y >$  uncensored  $X$
      - censored  $Y >$  uncensored  $X$
    - Regard as unknown (and omit from analysis)
      - censored  $Y <$  uncensored  $X$
      - $Y$  and  $X$  both censored

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## Wilcoxon Test Distribution

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- The modified Wilcoxon statistic can be shown to be asymptotically normally distributed
  - The standard errors for the modified Wilcoxon test under the null hypothesis can be computed from permutation distributions
    - Hence, a test of equality of the entire distribution

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## Other Interpretations

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- The modified Wilcoxon statistic can also be viewed as a weighted logrank statistic
- A weighted average of difference in hazards
- Places greater weight on differences in the survival curve that appear “early”
- Other ways to weight logrank statistics also exist
  - Logrank test is best if hazard ratio is constant over time

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## Stata Commands

.....

- The Wilcoxon test for censored data can be obtained from Stata using the “sts test” command (after defining survival variables using “stset”
  - `sts test groupvar, wilcoxon`
    - groupvar indicates the groups to be compared
    - P value based on chi square statistic
      - Hence a two-sided P value

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## Comparing Quantiles

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### Parametric Models for Censored Data

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## Parametric Models for .....Censored Data.....

- There are times that inference for censored data is based on parametric models
  - Accelerated failure time models
    - Assume a constant ratio between groups for all quantiles of survivor distribution
    - E.g., dogs live 7 years for each year of human life

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## Parametric Models for .....Censored Data.....

- Commonly used parametric models
  - Exponential:
    - Constant hazard independent of past
  - Weibull:
    - Theoretical derivation: First failure in a series of components (weakest link in a chain)
    - Log hazard is linear
    - Exponential is special case
    - Only accelerated failure time model that is also proportional hazards

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## Parametric Models for .....Censored Data.....

- Commonly used parametric models (cont.)
  - Gamma:
    - Theoretical derivation: Final failure in parallel components
    - Exponential is special case
  - Lognormal
  - Many other generalizations

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## Caveats

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Choice of Summary Measures

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## Parametric Models

- .....
- All of the parametric models will be sensitive to violation of the distributional assumptions
    - Because these models assume constant ratio of all quantiles, we do not have robustness to other distributions in any particular model (including lognormal)
    - (We will discuss these models with regression next quarter)

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## Semiparametric Models

- .....
- We do know how to use the proportional hazards model, even when the hazard ratio is not constant
    - However, you need to be careful– it may not estimate anything you care about

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## Hypothetical Example: Setting

- .....
- Consider survival with a particular treatment used in renal dialysis patients
    - Extract data from registry of dialysis patients
      - To ensure quality, only use data after 1995
        - Incident cases in 1995: Follow-up 1995 – 2002 (8 years)
        - Prevalent cases in 1995: Data from 1995 - 2002
          - » Incident in 1994: Information about 2<sup>nd</sup> – 9<sup>th</sup> year
          - » Incident in 1993: Information about 3<sup>rd</sup> – 10<sup>th</sup> year
          - » ...
          - » Incident in 1988: Information about 8<sup>th</sup> – 15<sup>th</sup> year

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## Hypothetical Example: Analysis

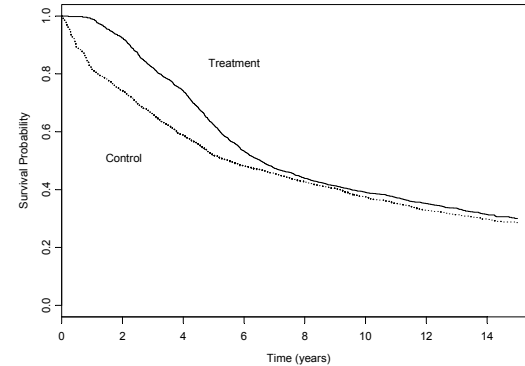
- Choice of summary measure
  - Survival at fixed point in time
  - Median, other quantiles
  - Mean (or restricted mean)
  - Hazard ratio (or weighted average of hazard ratio over time)
- Choice of methods
  - Parametric, semiparametric, nonparametric

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## Hypothetical Example: KM

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Kaplan-Meier Curves for Simulated Data (n=5623)



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## Who Wants To Be A Millionaire?.....

Proportional hazards analysis estimates a

**Treatment : Control** hazard ratio of

- A: 2.07 (logrank P = .0018)
- B: 1.13 (logrank P = .0018)
- C: 0.87 (logrank P = .0018)
- D: 0.48 (logrank P = .0018)

- Lifelines:
  - 50-50? Ask the audience? Call a friend?

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## Who Wants To Be A Millionaire?.....

Proportional hazards analysis estimates a

**Treatment : Control** hazard ratio of

- B: 1.13 (logrank P = .0018)
- C: 0.87 (logrank P = .0018)

- Lifelines:
  - 50-50? Ask the audience? Call a friend?

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