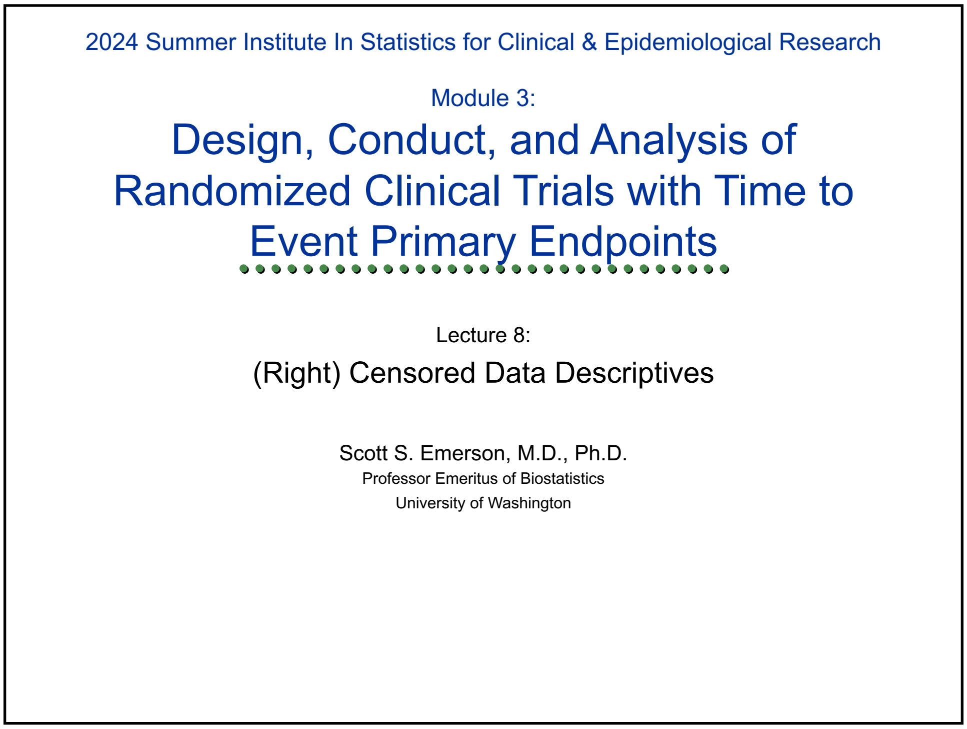

2024 Summer Institute In Statistics for Clinical & Epidemiological Research

Module 3:

Design, Conduct, and Analysis of Randomized Clinical Trials with Time to Event Primary Endpoints

Lecture 8:

(Right) Censored Data Descriptives

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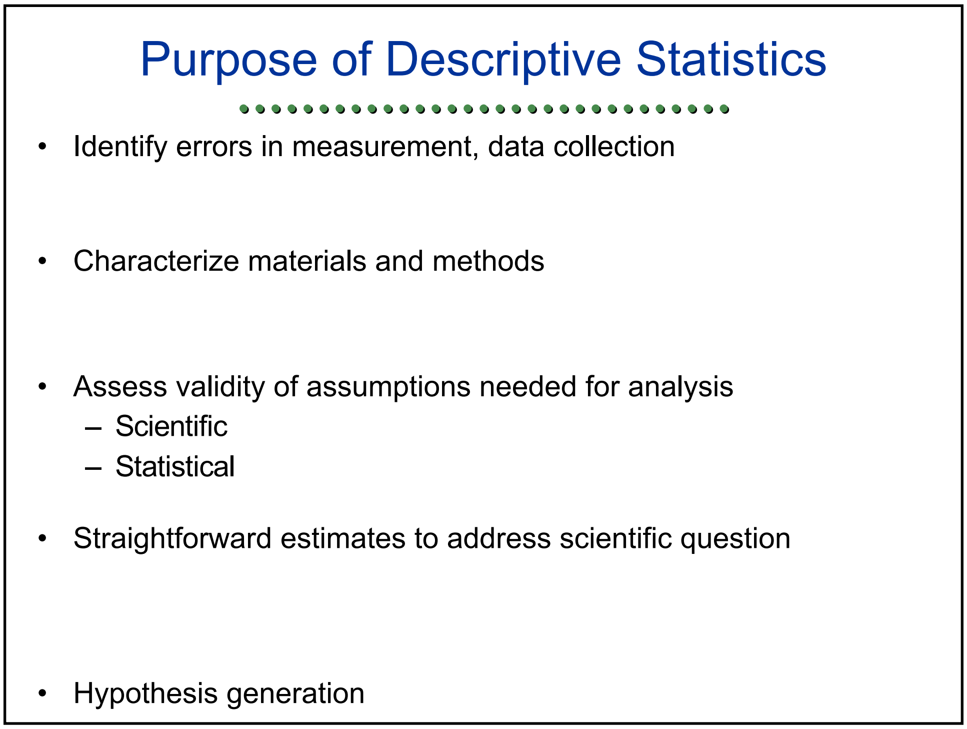

Purpose of Descriptive Statistics

- Identify errors in measurement, data collection
- Characterize materials and methods
- Assess validity of assumptions needed for analysis
  - Scientific
  - Statistical
- Straightforward estimates to address scientific question
- Hypothesis generation

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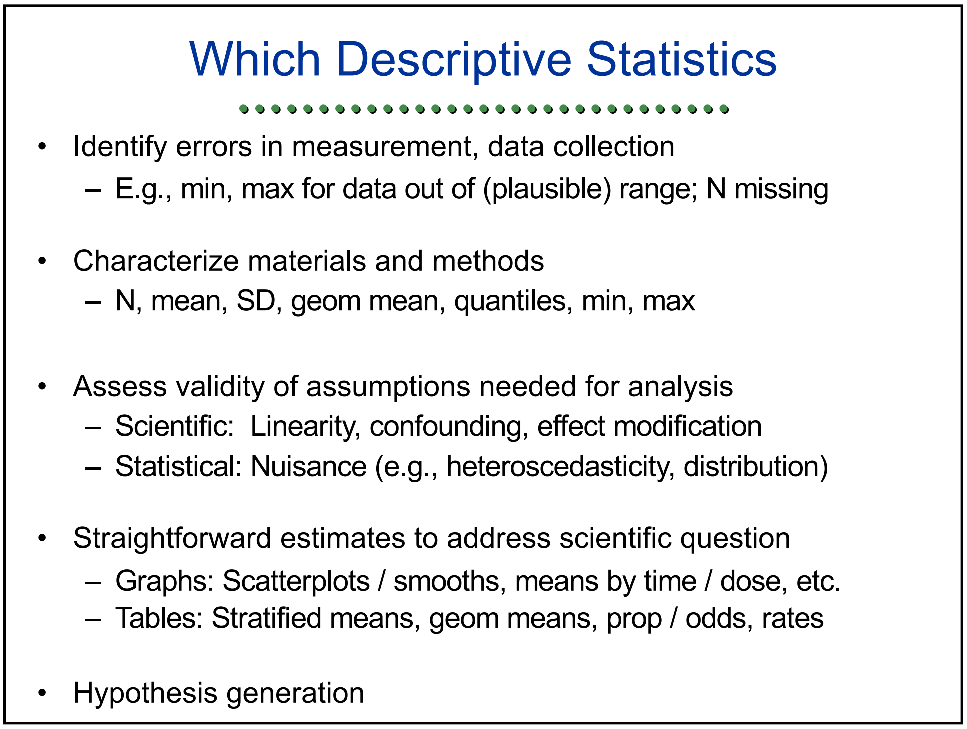

Which Descriptive Statistics

- Identify errors in measurement, data collection
  - E.g., min, max for data out of (plausible) range; N missing
- Characterize materials and methods
  - N, mean, SD, geom mean, quantiles, min, max
- Assess validity of assumptions needed for analysis
  - Scientific: Linearity, confounding, effect modification
  - Statistical: Nuisance (e.g., heteroscedasticity, distribution)
- Straightforward estimates to address scientific question
  - Graphs: Scatterplots / smooths, means by time / dose, etc.
  - Tables: Stratified means, geom means, prop / odds, rates
- Hypothesis generation

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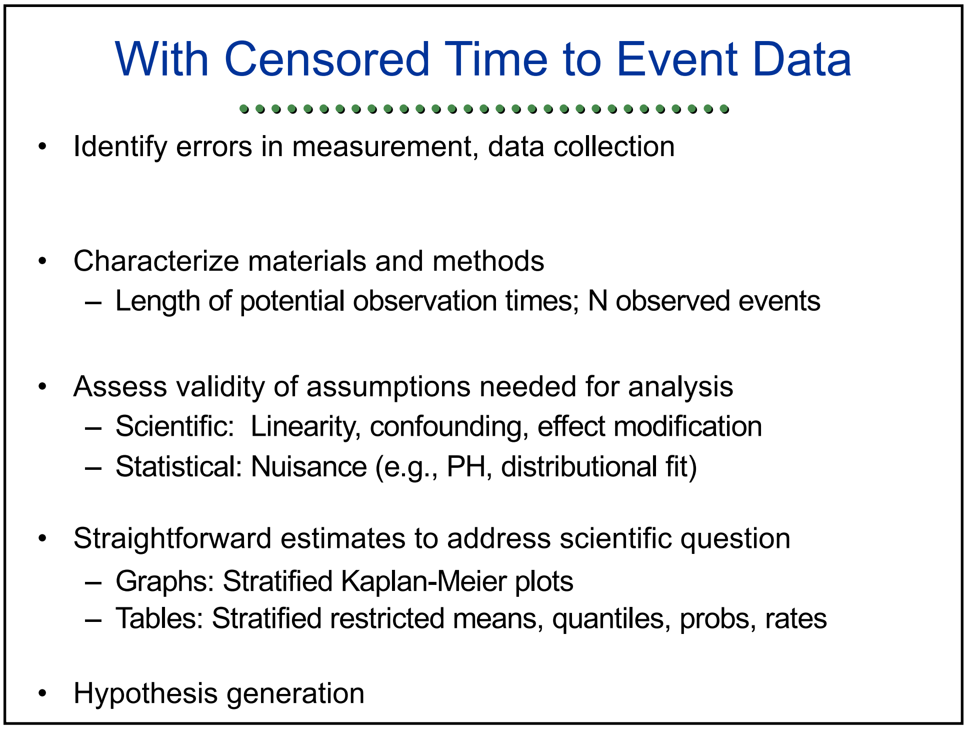

With Censored Time to Event Data

- Identify errors in measurement, data collection
- Characterize materials and methods
  - Length of potential observation times; N observed events
- Assess validity of assumptions needed for analysis
  - Scientific: Linearity, confounding, effect modification
  - Statistical: Nuisance (e.g., PH, distributional fit)
- Straightforward estimates to address scientific question
  - Graphs: Stratified Kaplan-Meier plots
  - Tables: Stratified restricted means, quantiles, probs, rates
- Hypothesis generation

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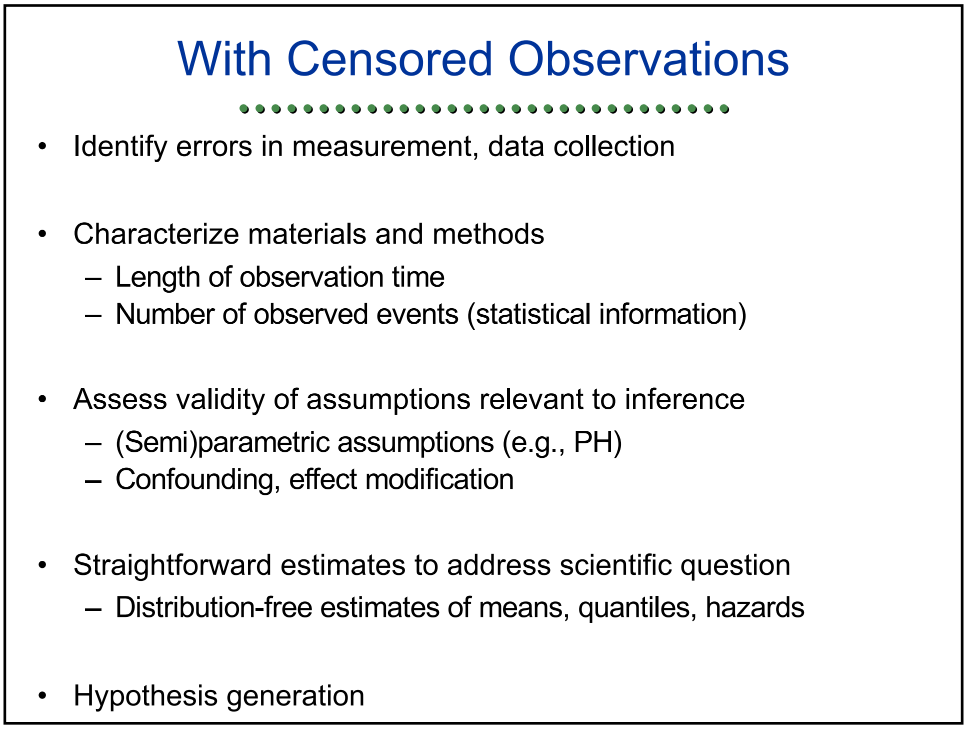
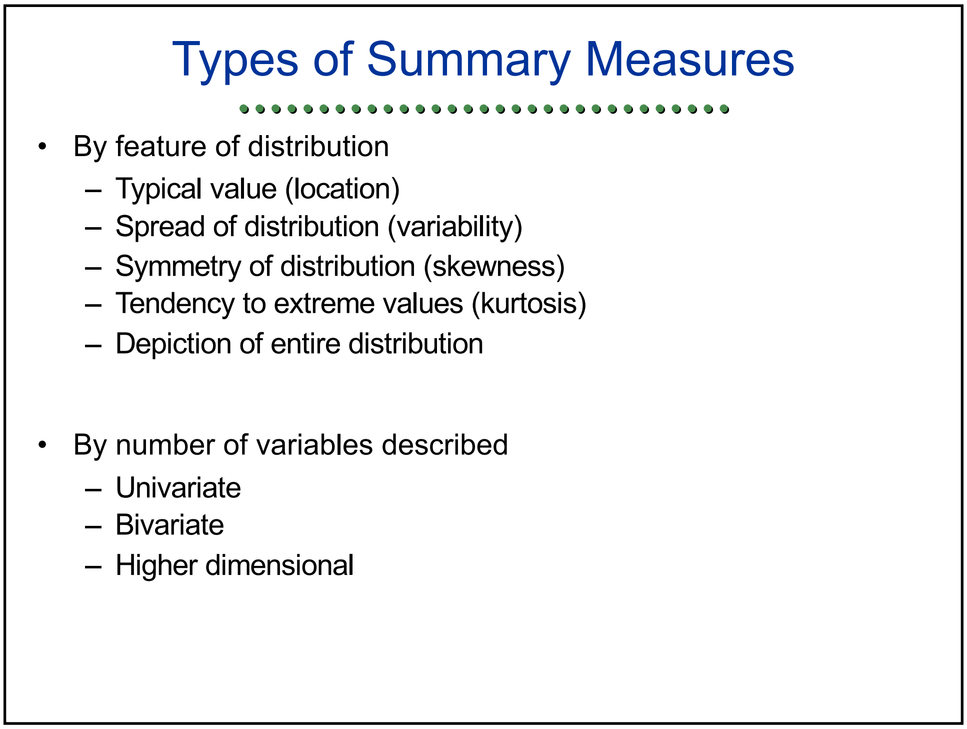


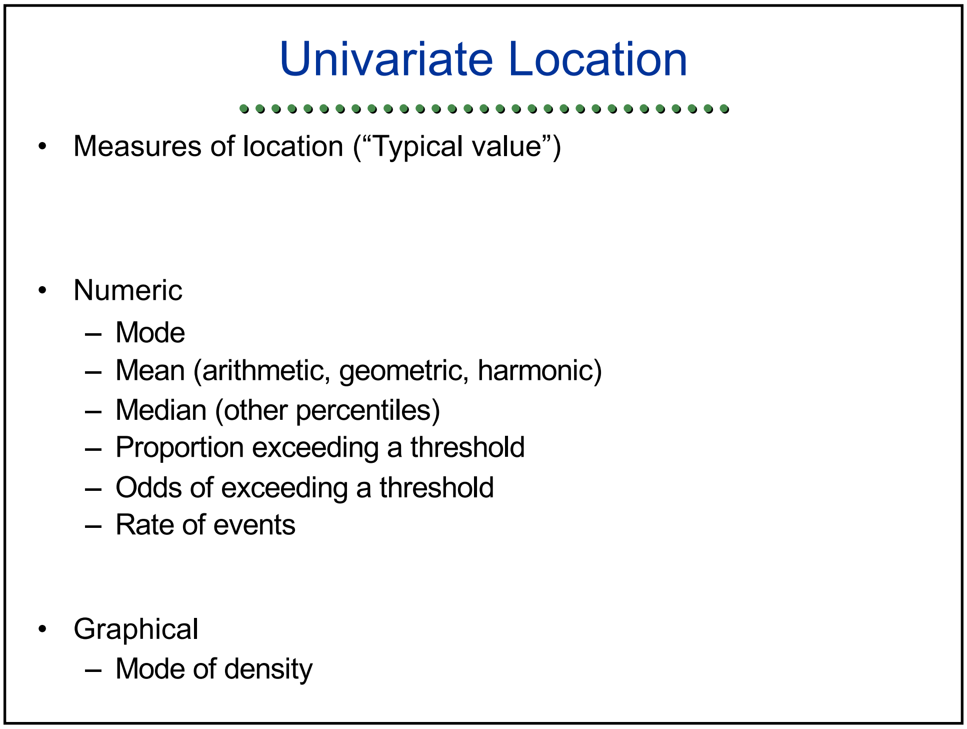
With Censored Observations

- Identify errors in measurement, data collection
- Characterize materials and methods
  - Length of observation time
  - Number of observed events (statistical information)
- Assess validity of assumptions relevant to inference
  - (Semi)parametric assumptions (e.g., PH)
  - Confounding, effect modification
- Straightforward estimates to address scientific question
  - Distribution-free estimates of means, quantiles, hazards
- Hypothesis generation



Types of Summary Measures

- By feature of distribution
  - Typical value (location)
  - Spread of distribution (variability)
  - Symmetry of distribution (skewness)
  - Tendency to extreme values (kurtosis)
  - Depiction of entire distribution
- By number of variables described
  - Univariate
  - Bivariate
  - Higher dimensional



Univariate Location

- Measures of location (“Typical value”)
- Numeric
  - Mode
  - Mean (arithmetic, geometric, harmonic)
  - Median (other percentiles)
  - Proportion exceeding a threshold
  - Odds of exceeding a threshold
  - Rate of events
- Graphical
  - Mode of density

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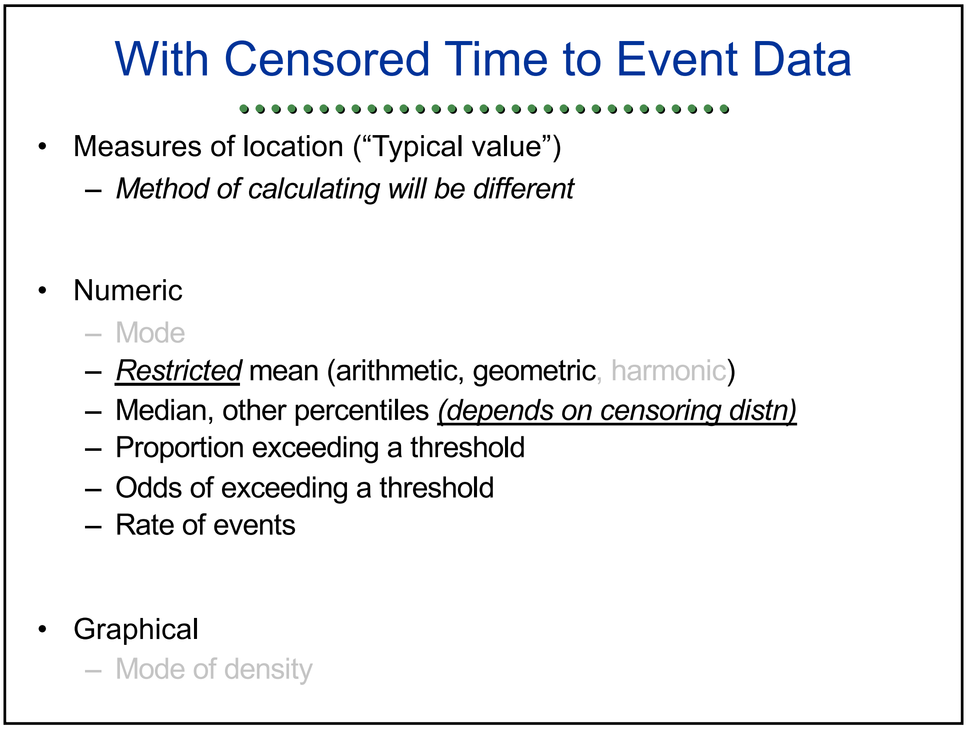

With Censored Time to Event Data

- Measures of location (“Typical value”)
  - *Method of calculating will be different*
- Numeric
  - Mode
  - *Restricted* mean (arithmetic, geometric, harmonic)
  - Median, other percentiles *(depends on censoring distn)*
  - Proportion exceeding a threshold
  - Odds of exceeding a threshold
  - Rate of events
- Graphical
  - Mode of density

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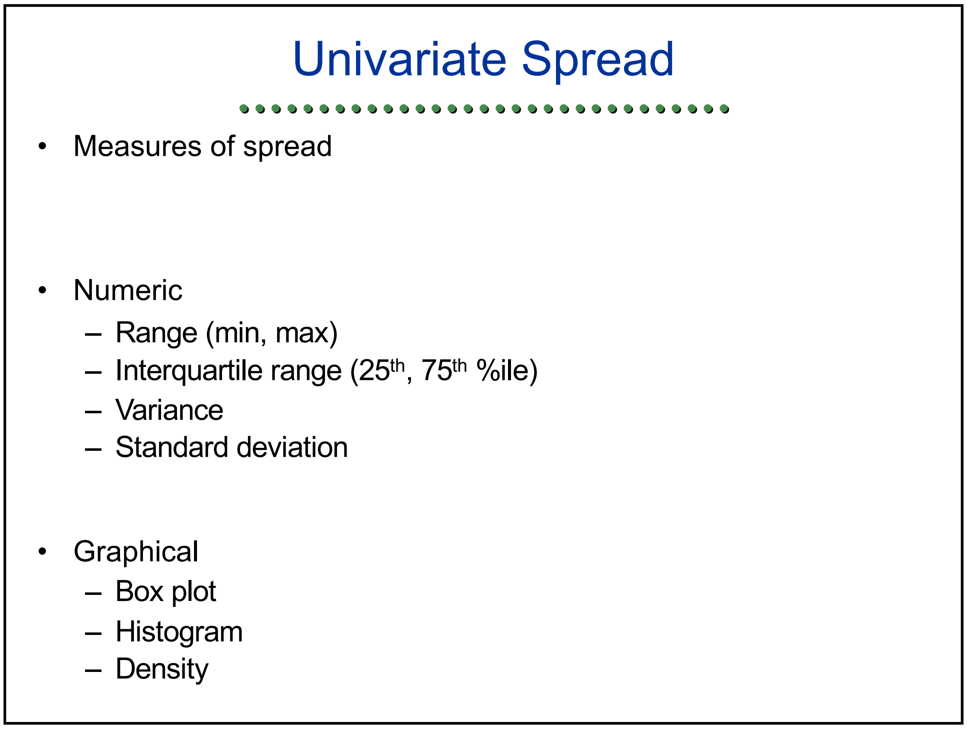

Univariate Spread

- Measures of spread

- Numeric
  - Range (min, max)
  - Interquartile range (25th, 75th %ile)
  - Variance
  - Standard deviation

- Graphical
  - Box plot
  - Histogram
  - Density

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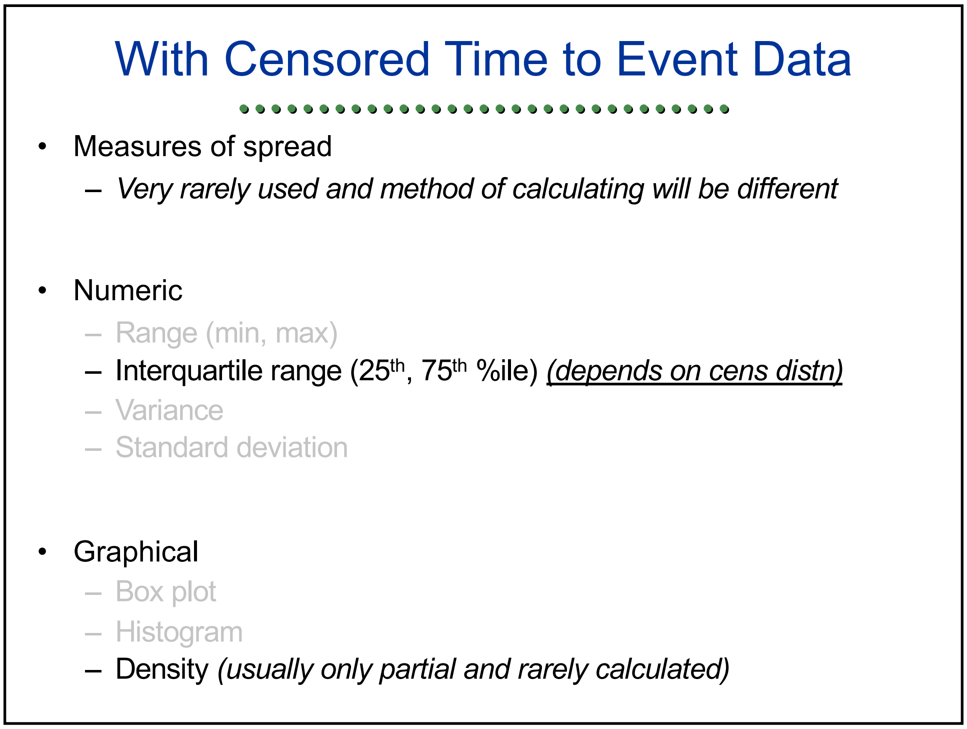

With Censored Time to Event Data

- Measures of spread
  - *Very rarely used and method of calculating will be different*

- Numeric
  - Range (min, max)
  - Interquartile range (25th, 75th %ile) *(depends on cens distn)*
  - Variance
  - Standard deviation

- Graphical
  - Box plot
  - Histogram
  - Density *(usually only partial and rarely calculated)*

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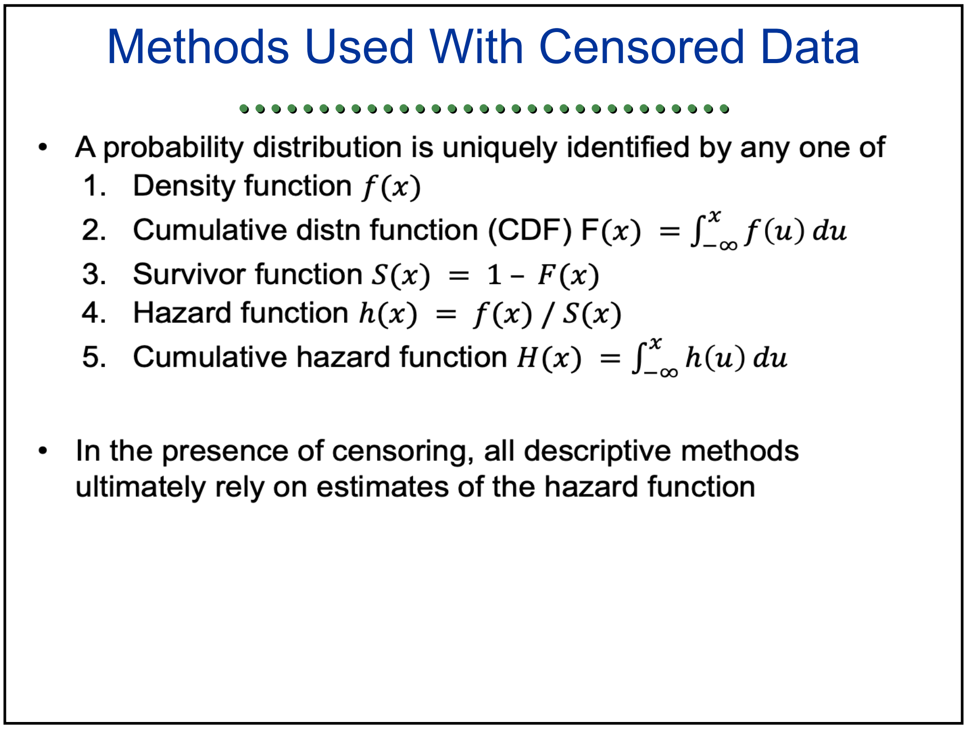

Methods Used With Censored Data

- A probability distribution is uniquely identified by any one of
  1. Density function $f(x)$
  2. Cumulative distn function (CDF) $\mathrm{F}(x) = \int_{-\infty}^{x} f(u)\, du$
  3. Survivor function $S(x) = 1 - F(x)$
  4. Hazard function $h(x) = f(x) \,/\, S(x)$
  5. Cumulative hazard function $H(x) = \int_{-\infty}^{x} h(u)\, du$

- In the presence of censoring, all descriptive methods ultimately rely on estimates of the hazard function

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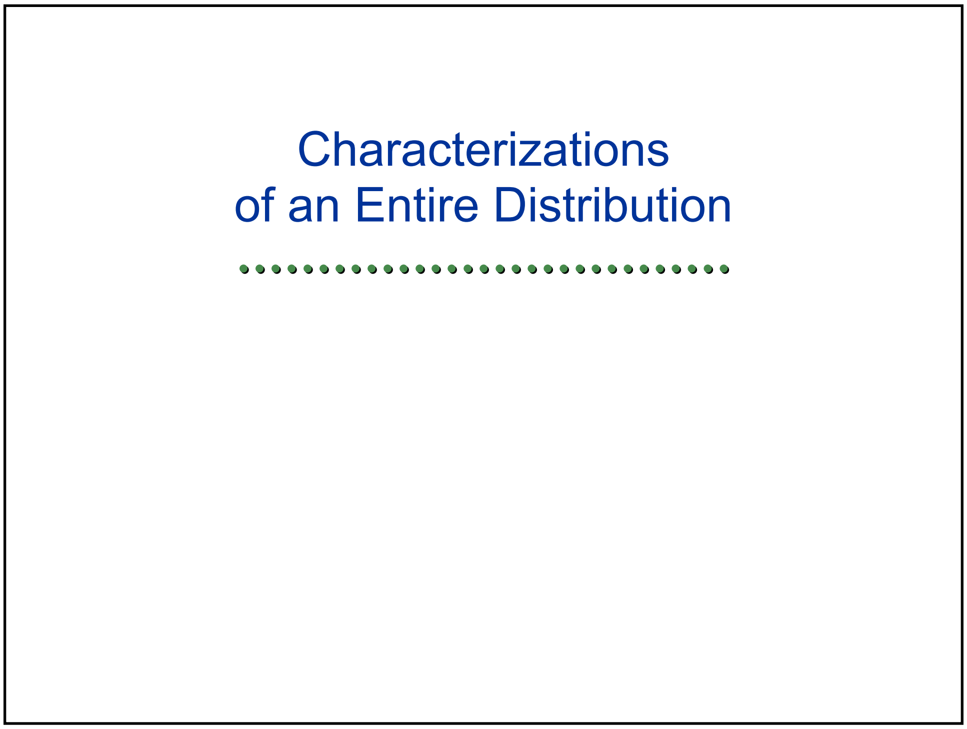

Characterizations of an Entire Distribution

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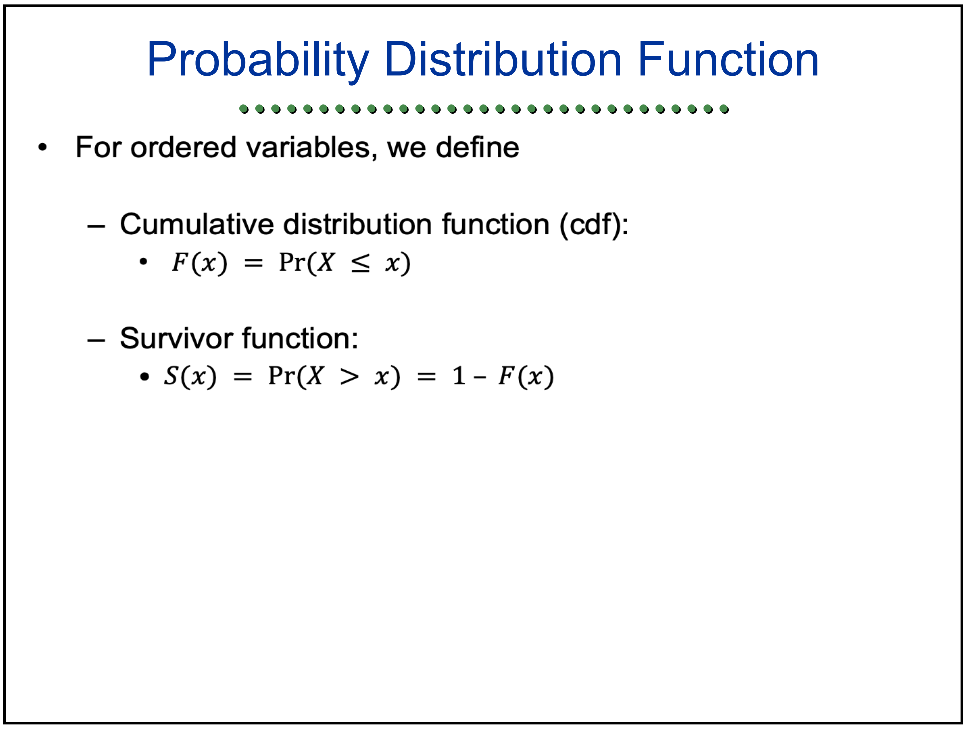

Probability Distribution Function

- For ordered variables, we define
  - Cumulative distribution function (cdf):
    - $F(x) = \Pr(X \leq x)$
  - Survivor function:
    - $S(x) = \Pr(X > x) = 1 - F(x)$

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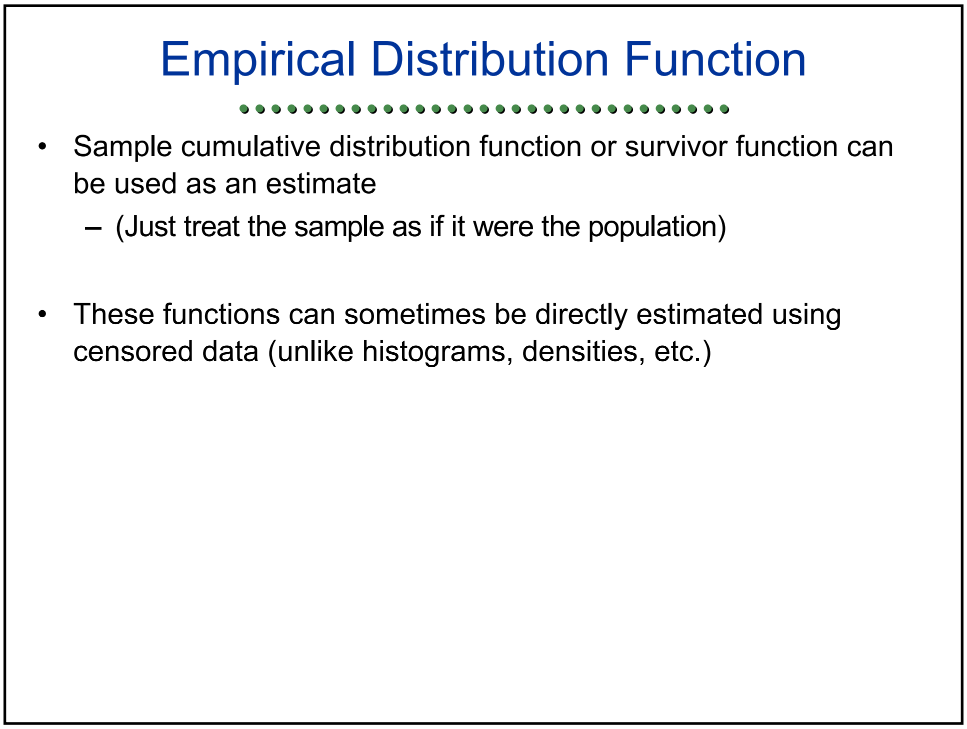

Empirical Distribution Function

- Sample cumulative distribution function or survivor function can be used as an estimate
  - (Just treat the sample as if it were the population)
- These functions can sometimes be directly estimated using censored data (unlike histograms, densities, etc.)

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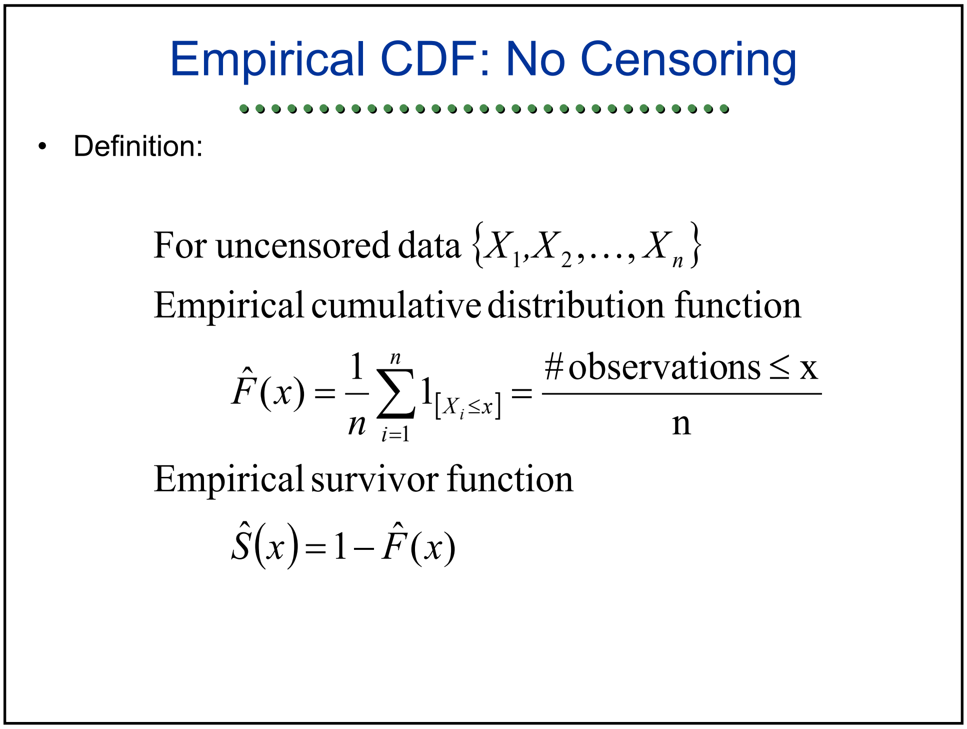

Empirical CDF: No Censoring

- Definition:

For uncensored data $\{X_1, X_2, \ldots, X_n\}$

Empirical cumulative distribution function

$$\hat{F}(x) = \frac{1}{n}\sum_{i=1}^{n} 1_{[X_i \le x]} = \frac{\#\text{observations} \le \text{x}}{\text{n}}$$

Empirical survivor function

$$\hat{S}(x) = 1 - \hat{F}(x)$$

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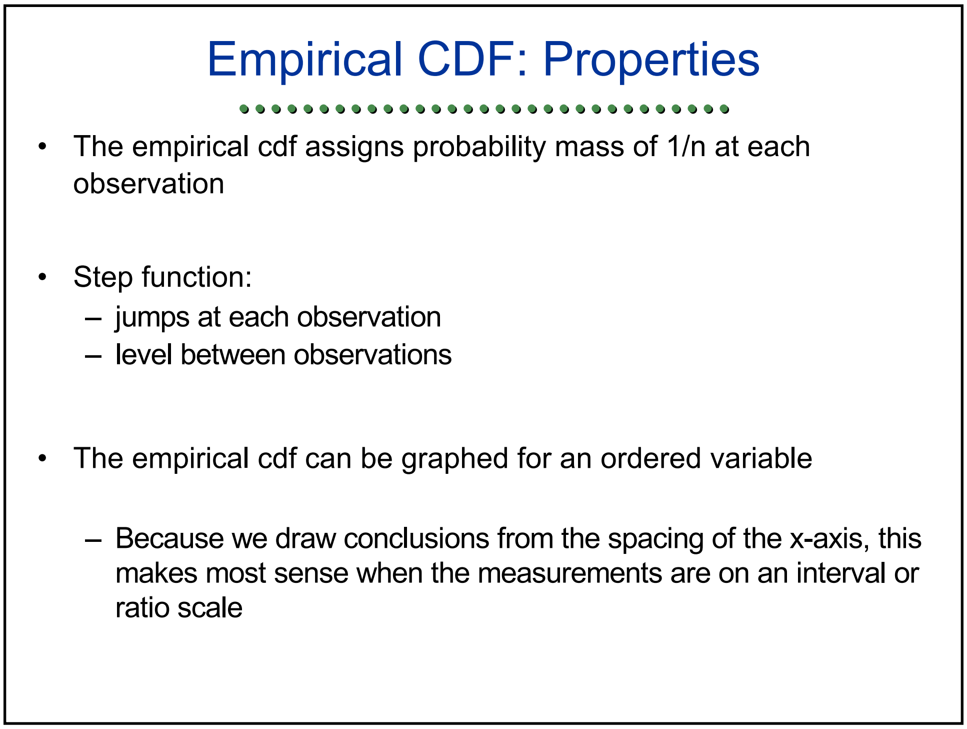

Empirical CDF: Properties

- The empirical cdf assigns probability mass of 1/n at each observation
- Step function:
  - jumps at each observation
  - level between observations
- The empirical cdf can be graphed for an ordered variable
  - Because we draw conclusions from the spacing of the x-axis, this makes most sense when the measurements are on an interval or ratio scale

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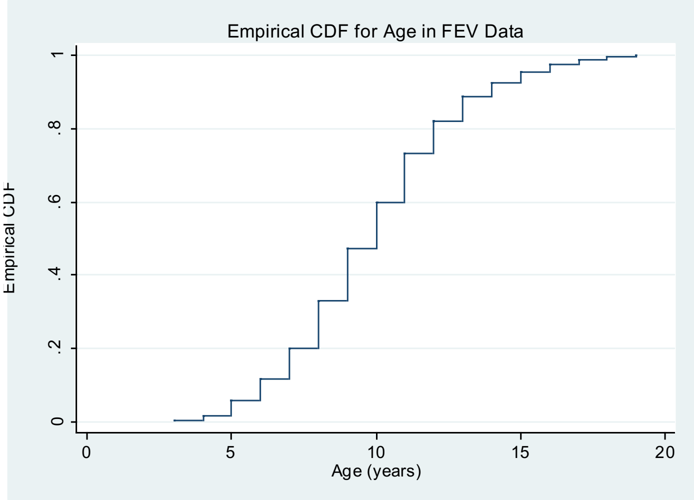
Ex: Age CDF (FEV data)

- From an observational dataset exploring associations between smoking and lung function in children



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Survivor Curves

- In biomedicine, we typically look at the “survivor” curves for times to an event, rather than the CDF
- Note that we can “see” many common sample statistics from a plot of any survival curve
- (With censored data, we will use the Kaplan-Meier estimate, rather than the empirical CDF, to obtain the survival curve)

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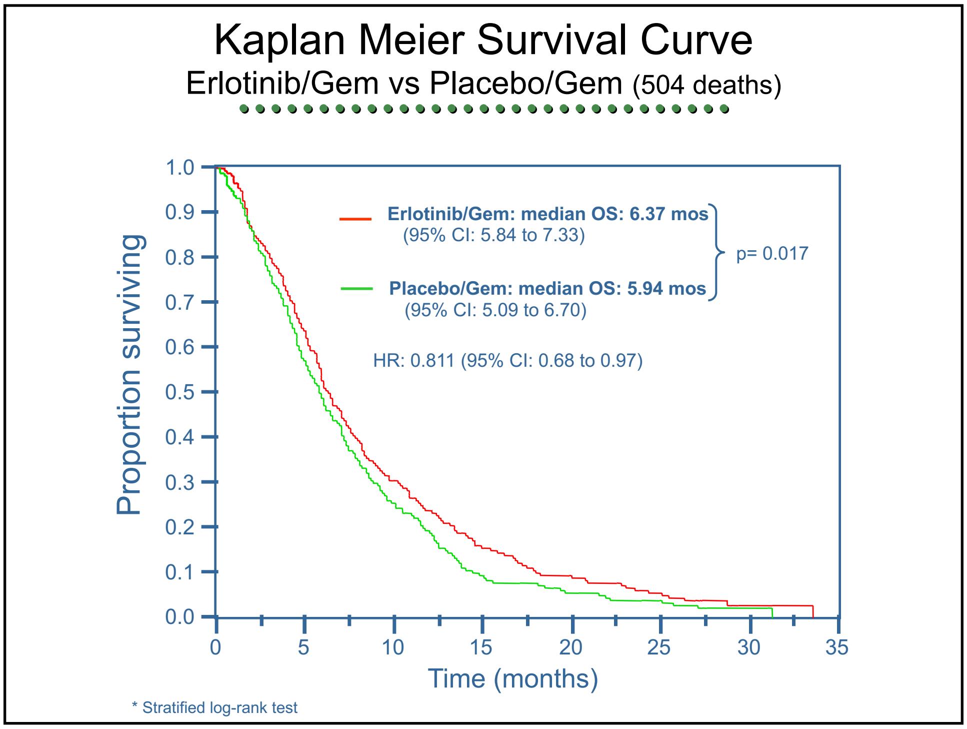

Kaplan Meier Survival Curve

Erlotinib/Gem vs Placebo/Gem (504 deaths)

Erlotinib/Gem: median OS: 6.37 mos (95% CI: 5.84 to 7.33)

Placebo/Gem: median OS: 5.94 mos (95% CI: 5.09 to 6.70)

p= 0.017

HR: 0.811 (95% CI: 0.68 to 0.97)

* Stratified log-rank test

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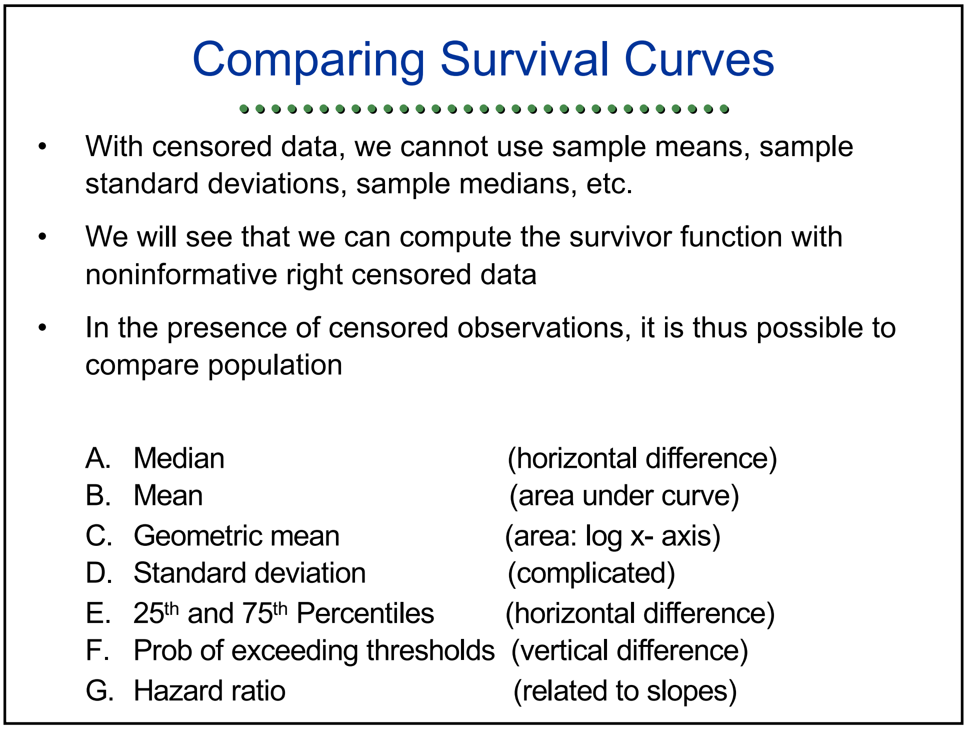

Comparing Survival Curves

- With censored data, we cannot use sample means, sample standard deviations, sample medians, etc.
- We will see that we can compute the survivor function with noninformative right censored data
- In the presence of censored observations, it is thus possible to compare population

A.	Median	(horizontal difference)
B.	Mean	(area under curve)
C.	Geometric mean	(area: log x- axis)
D.	Standard deviation	(complicated)
E.	25th and 75th Percentiles	(horizontal difference)
F.	Prob of exceeding thresholds	(vertical difference)
G.	Hazard ratio	(related to slopes)

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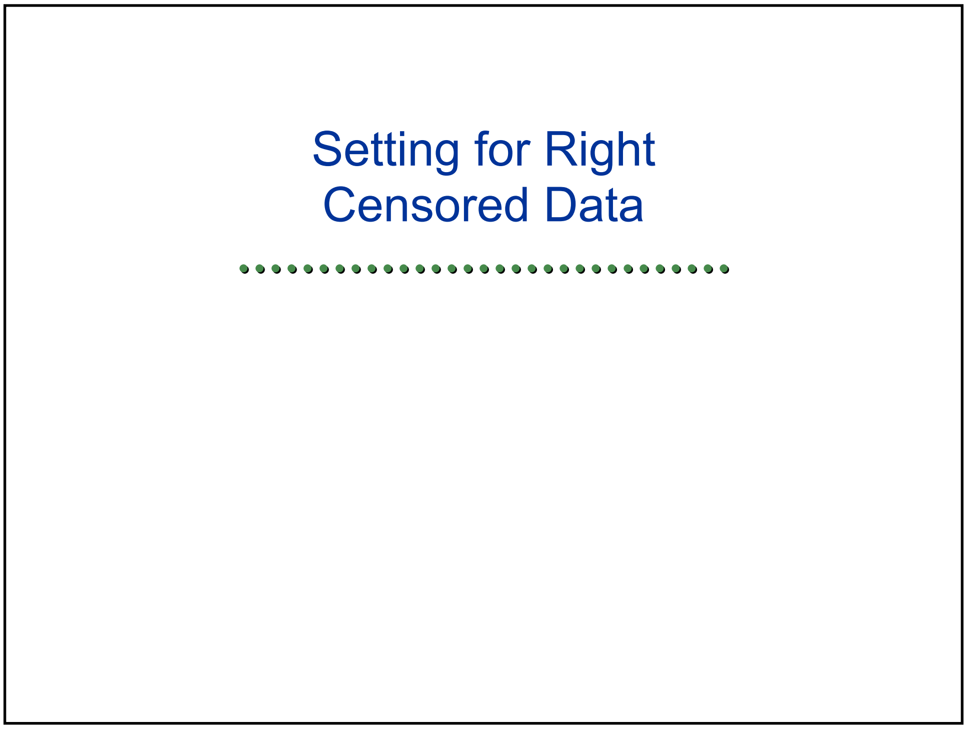

Setting for Right Censored Data

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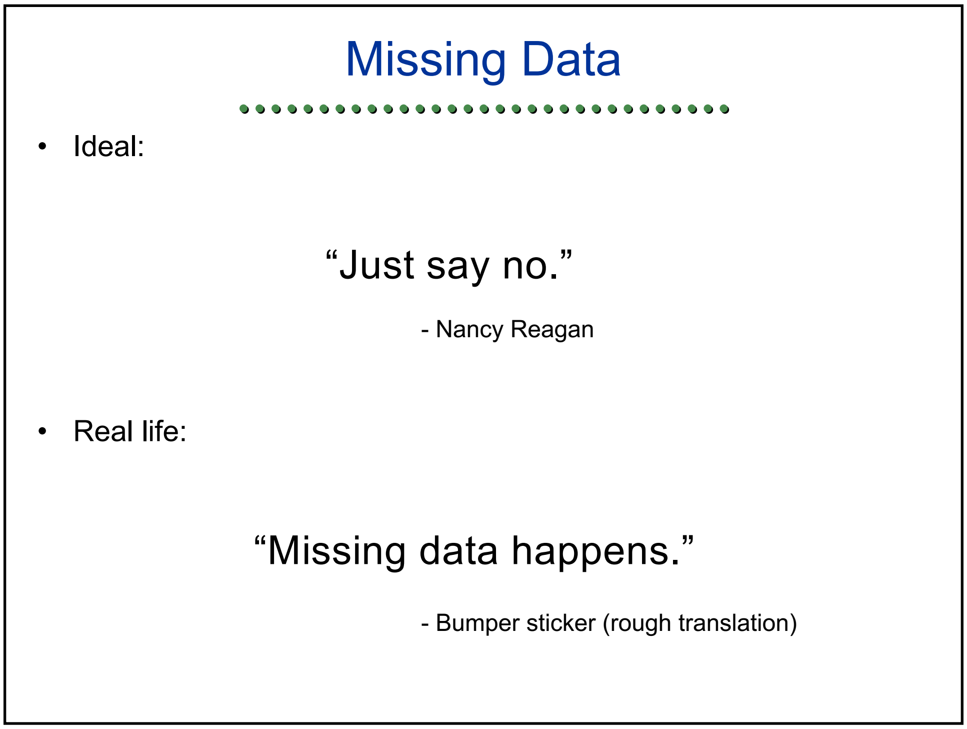

Missing Data

- Ideal:

“Just say no.”

- Nancy Reagan

- Real life:

“Missing data happens.”

- Bumper sticker (rough translation)

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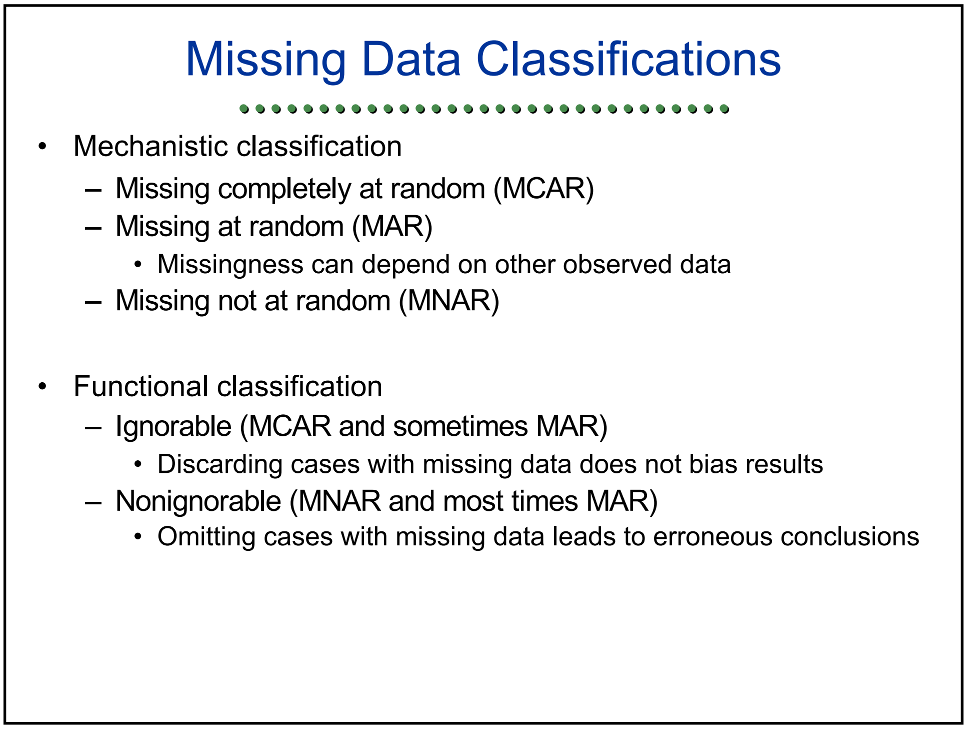

Missing Data Classifications

- Mechanistic classification
  - Missing completely at random (MCAR)
  - Missing at random (MAR)
    - Missingness can depend on other observed data
  - Missing not at random (MNAR)

- Functional classification
  - Ignorable (MCAR and sometimes MAR)
    - Discarding cases with missing data does not bias results
  - Nonignorable (MNAR and most times MAR)
    - Omitting cases with missing data leads to erroneous conclusions

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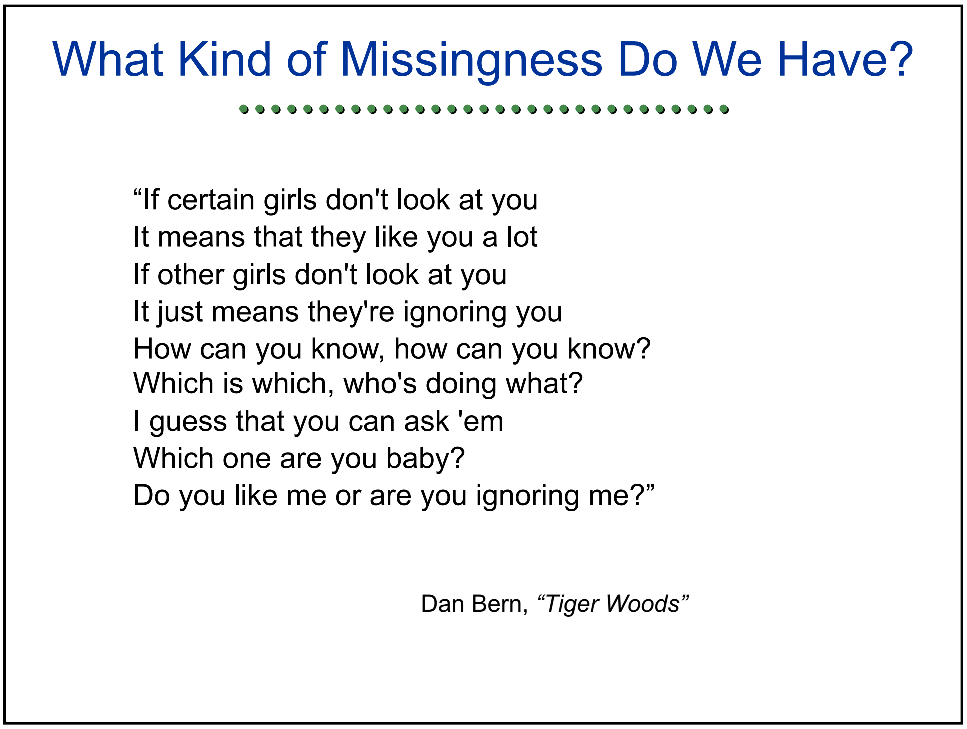

What Kind of Missingness Do We Have?

“If certain girls don't look at you
It means that they like you a lot
If other girls don't look at you
It just means they're ignoring you
How can you know, how can you know?
Which is which, who's doing what?
I guess that you can ask 'em
Which one are you baby?
Do you like me or are you ignoring me?”

Dan Bern, *“Tiger Woods”*

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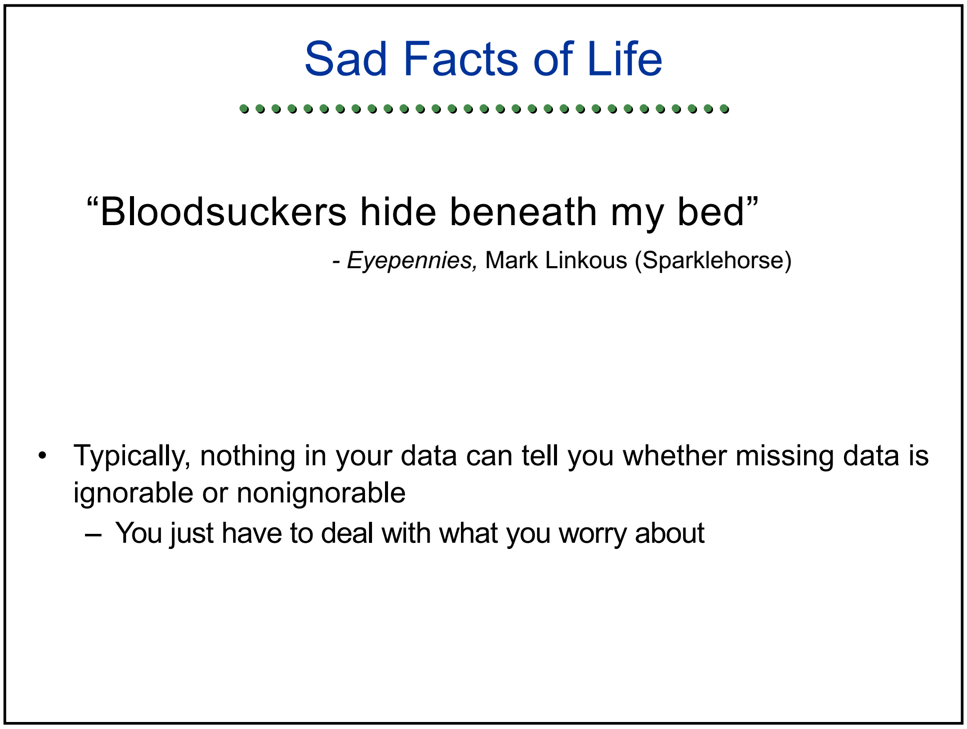

Sad Facts of Life

> "Bloodsuckers hide beneath my bed"
>
> \- *Eyepennies,* Mark Linkous (Sparklehorse)

- Typically, nothing in your data can tell you whether missing data is ignorable or nonignorable
  - You just have to deal with what you worry about

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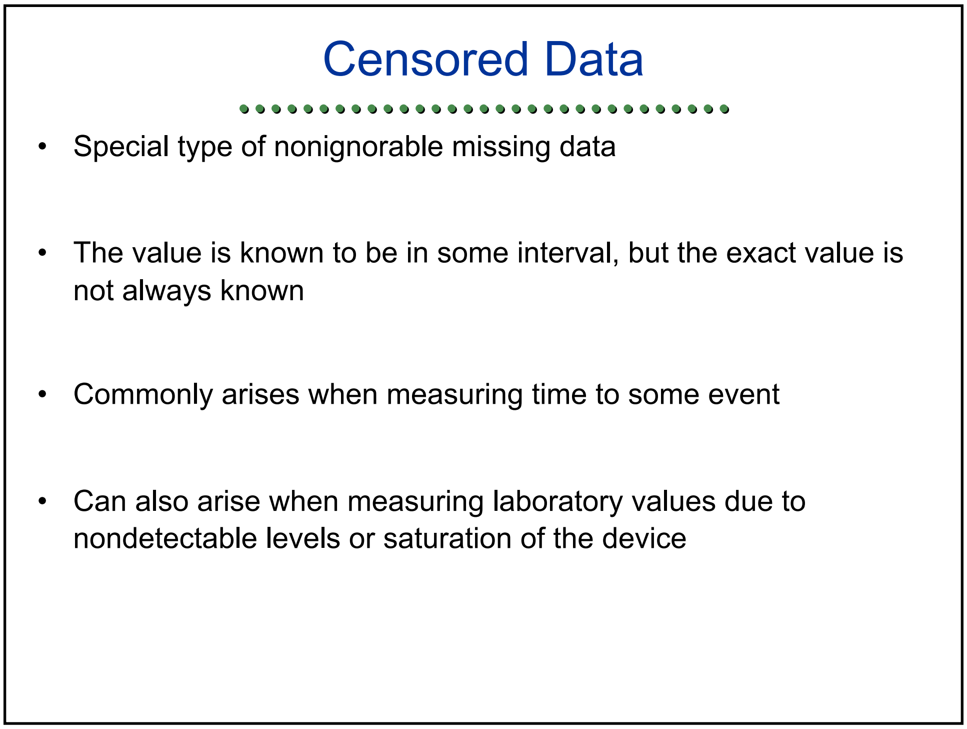

Censored Data

- Special type of nonignorable missing data
- The value is known to be in some interval, but the exact value is not always known
- Commonly arises when measuring time to some event
- Can also arise when measuring laboratory values due to nondetectable levels or saturation of the device

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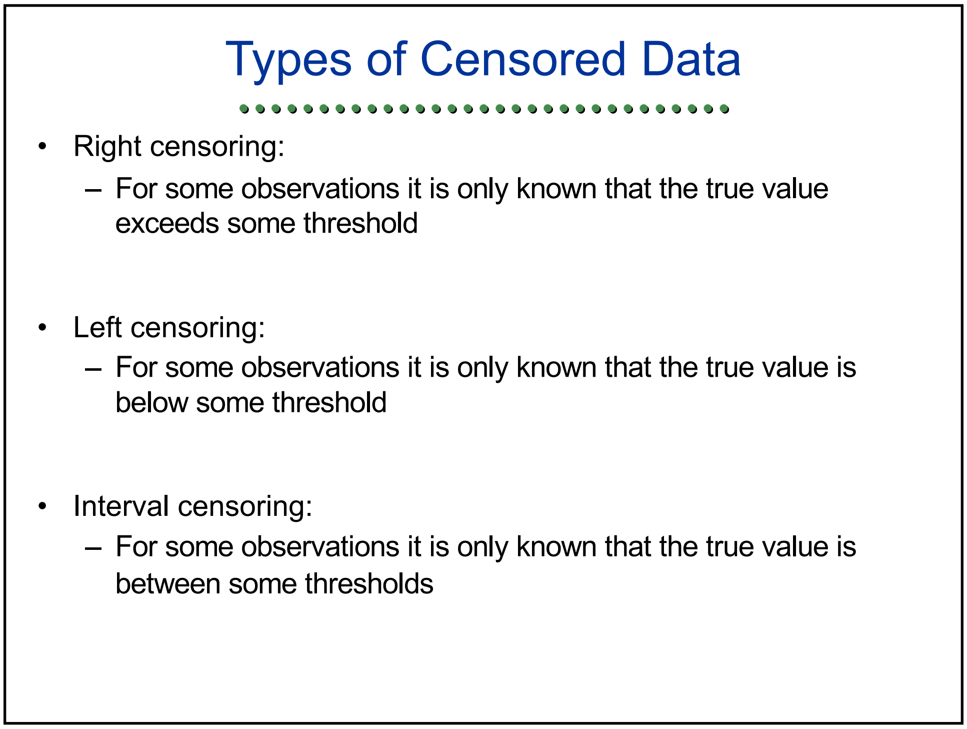

Types of Censored Data

- 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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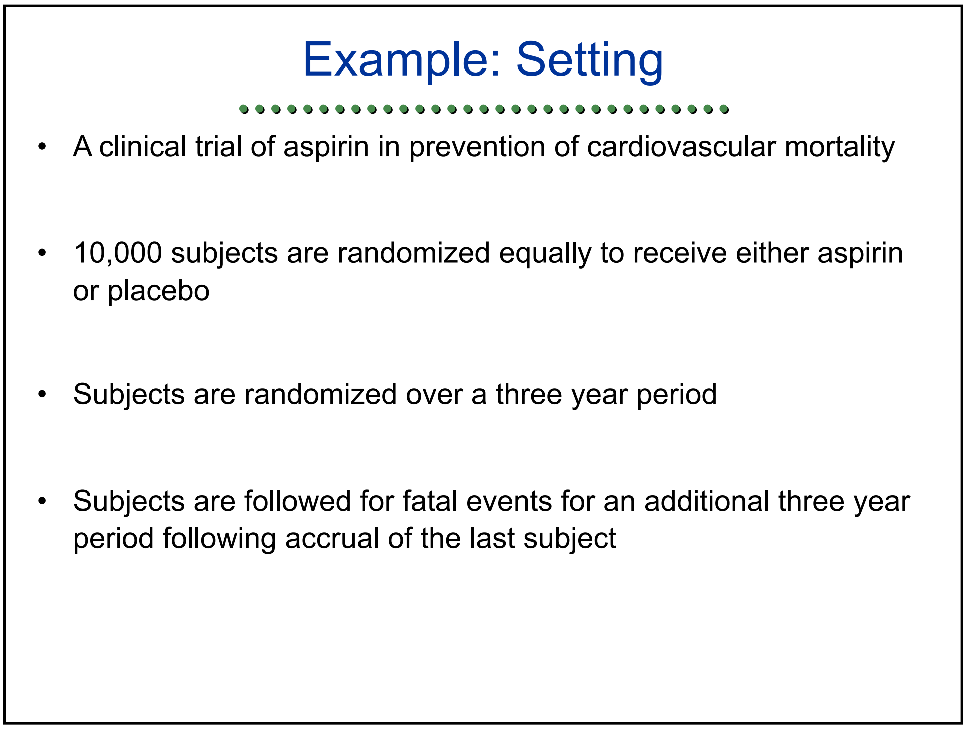

Example: Setting

- A clinical trial of aspirin in prevention of cardiovascular mortality
- 10,000 subjects are randomized equally to receive either aspirin or placebo
- Subjects are randomized over a three year period
- Subjects are followed for fatal events for an additional three year period following accrual of the last subject

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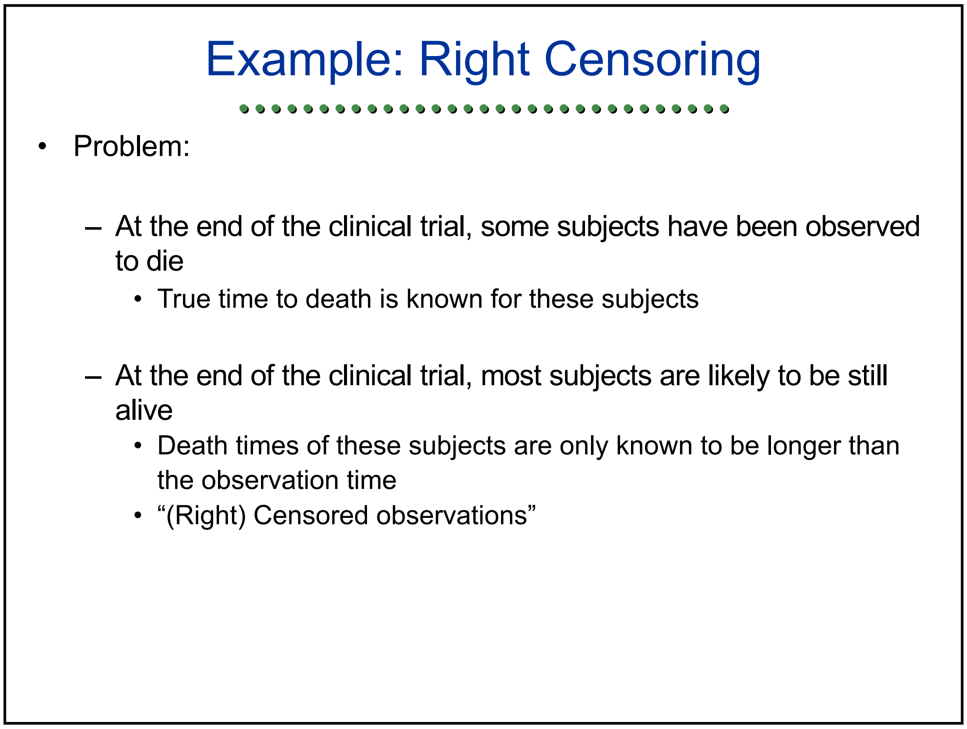

Example: Right Censoring

- Problem:
  - At the end of the clinical trial, some subjects have been observed to die
    - True time to death is known for these subjects
  - At the end of the clinical trial, most subjects are likely to be still alive
    - Death times of these subjects are only known to be longer than the observation time
    - “(Right) Censored observations”

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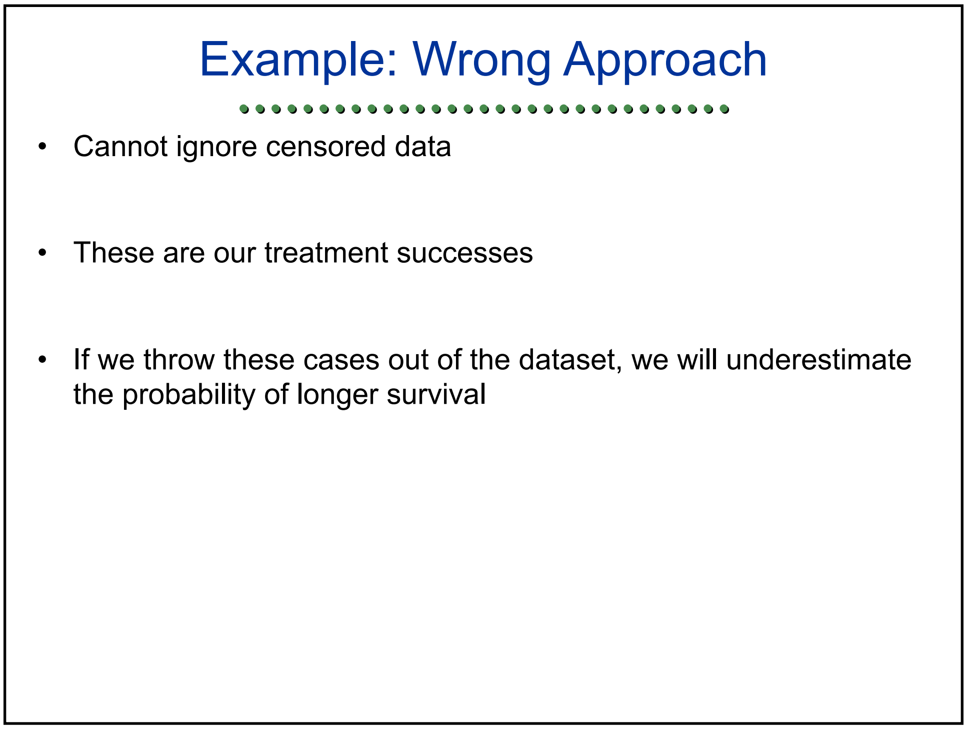

Example: Wrong Approach

- Cannot ignore censored data
- These are our treatment successes
- If we throw these cases out of the dataset, we will underestimate the probability of longer survival

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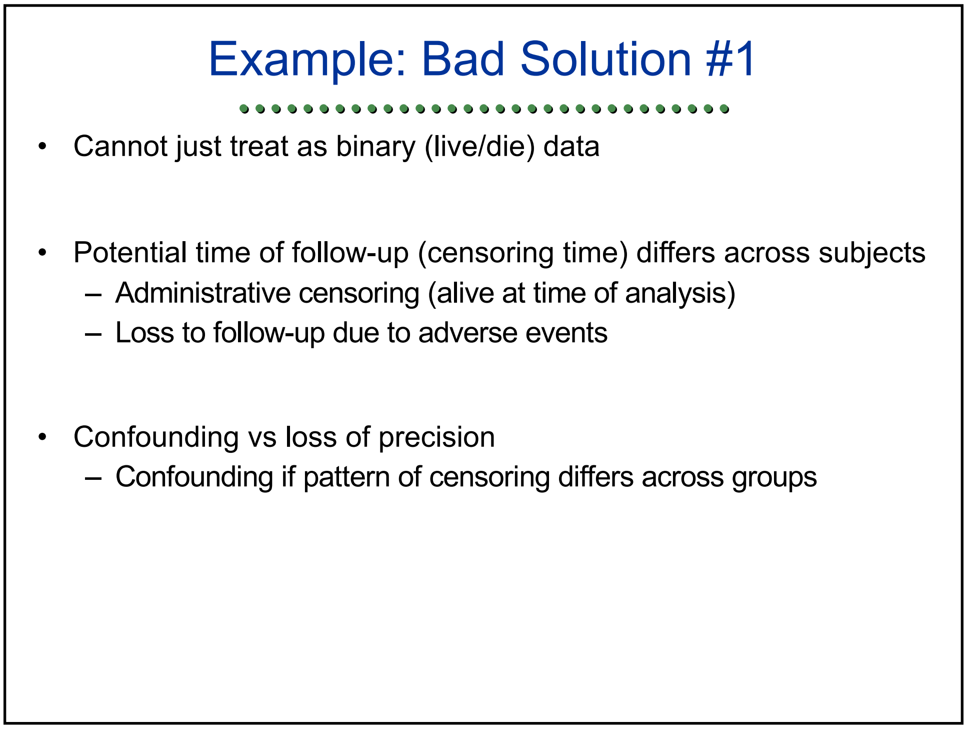

Example: Bad Solution #1

- Cannot just treat as binary (live/die) data
- Potential time of follow-up (censoring time) differs across subjects
  - Administrative censoring (alive at time of analysis)
  - Loss to follow-up due to adverse events
- Confounding vs loss of precision
  - Confounding if pattern of censoring differs across groups

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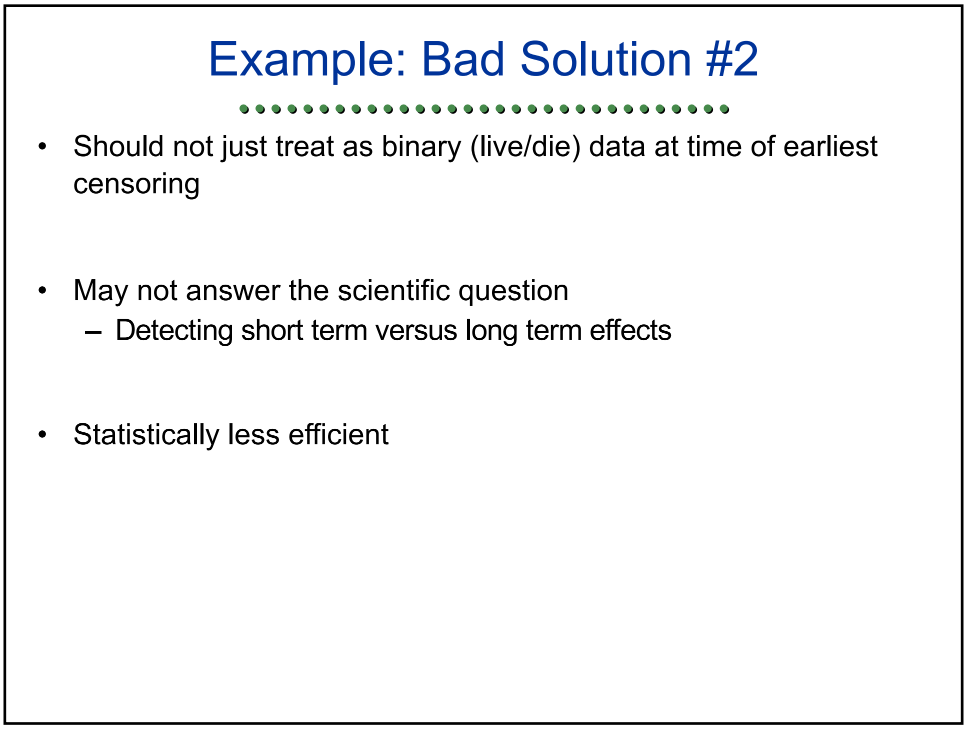

Example: Bad Solution #2

- Should not just treat as binary (live/die) data at time of earliest censoring
- May not answer the scientific question
  - Detecting short term versus long term effects
- Statistically less efficient

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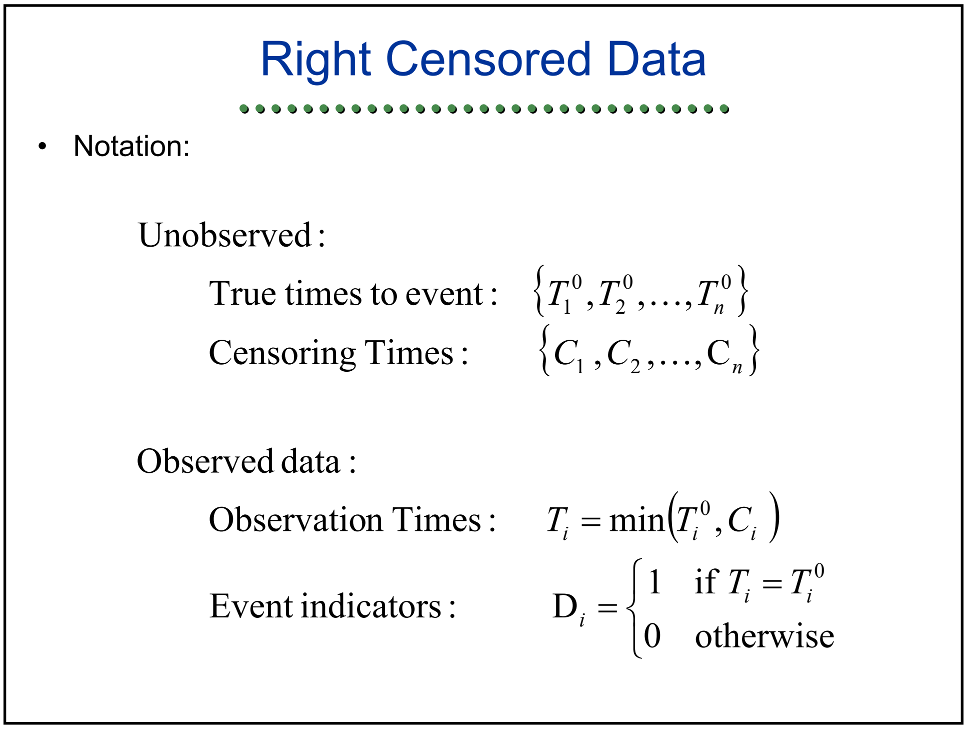

Right Censored Data

- Notation:

Unobserved:

True times to event: $\left\{T_1^0, T_2^0, \ldots, T_n^0\right\}$

Censoring Times: $\left\{C_1, C_2, \ldots, \mathrm{C}_n\right\}$

Observed data:

Observation Times: $T_i = \min\left(T_i^0, C_i\right)$

Event indicators: $\mathrm{D}_i = \begin{cases} 1 & \text{if } T_i = T_i^0 \\ 0 & \text{otherwise} \end{cases}$

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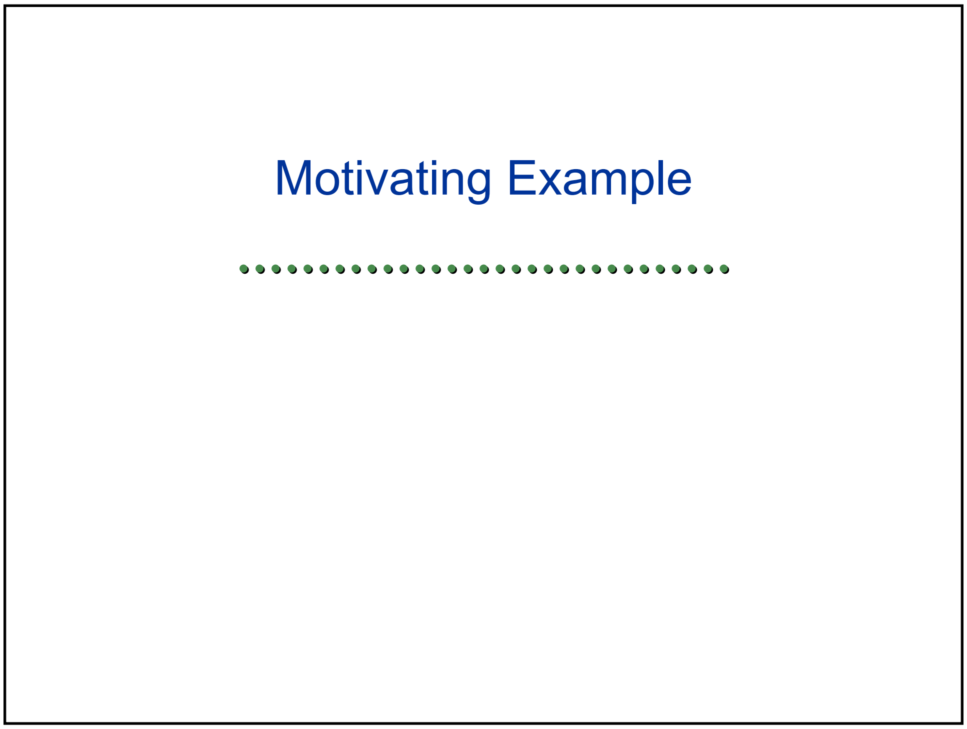

Motivating Example

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Motivating Example

- Hypothetical study of subject survival
- Subjects accrued to study and followed until time of analysis
- Study done at three centers, which started the studies in three successive years
- Censoring time thus differs across centers

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Data by Date (Real Time)

```
Staggered study entry by site
                          Accrual Group
Year                    A       B       C

2010   On study       100      --      --
           Died        43
      Surviving        57

2011   On study        57     100      --
           Died        27      53
      Surviving        30      47

2012   On study        30      47     100
           Died        13      22      55
      Surviving        17      25      45
```

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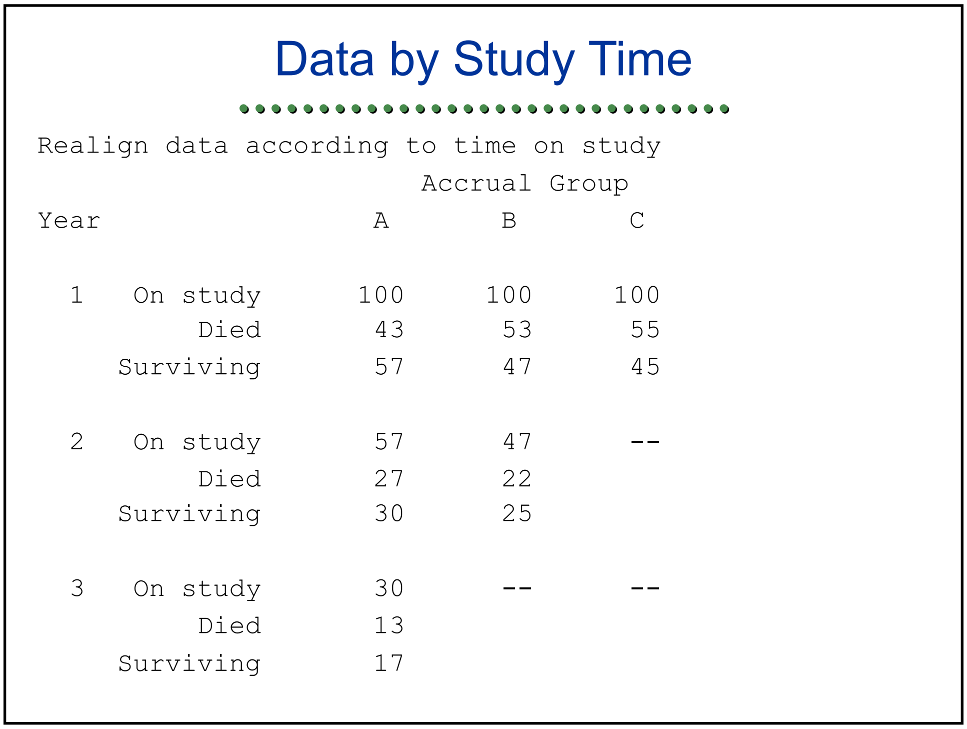

Data by Study Time

```
Realign data according to time on study
                                Accrual Group
Year                     A         B         C


  1    On study        100       100       100
            Died        43        53        55
       Surviving        57        47        45

  2    On study         57        47        --
            Died        27        22
       Surviving        30        25

  3    On study         30        --        --
            Died        13
       Surviving        17
```

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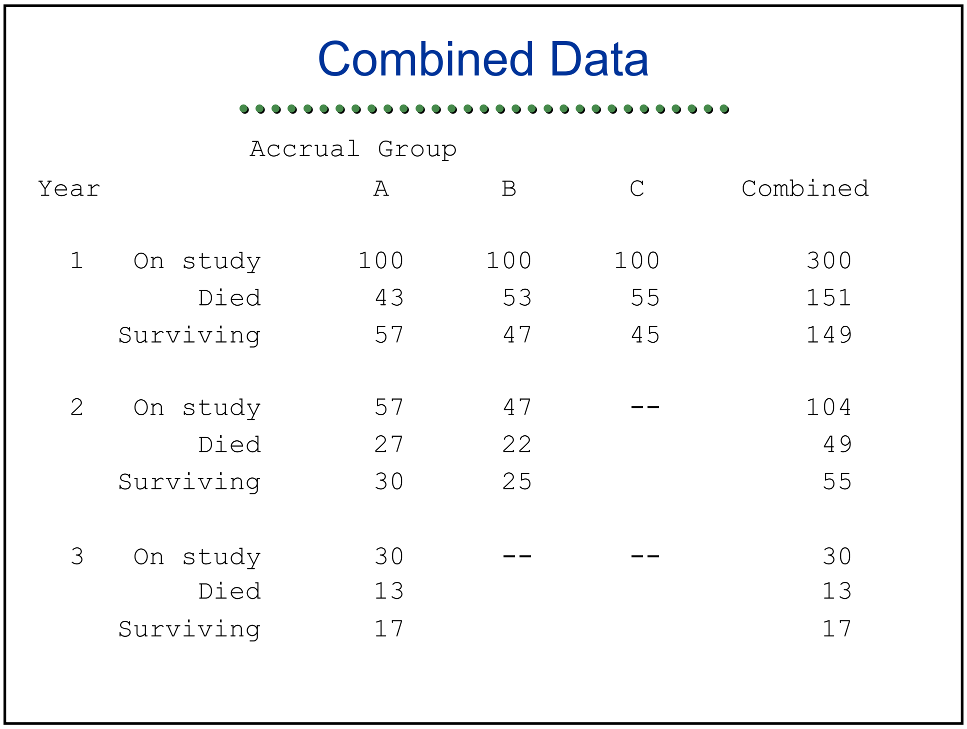

Combined Data

```
                 Accrual Group
Year                     A         B         C       Combined

  1    On study        100       100       100           300
            Died        43        53        55           151
       Surviving        57        47        45           149

  2    On study         57        47        --           104
            Died        27        22                      49
       Surviving        30        25                      55

  3    On study         30        --        --            30
            Died        13                                  13
       Surviving        17                                  17
```

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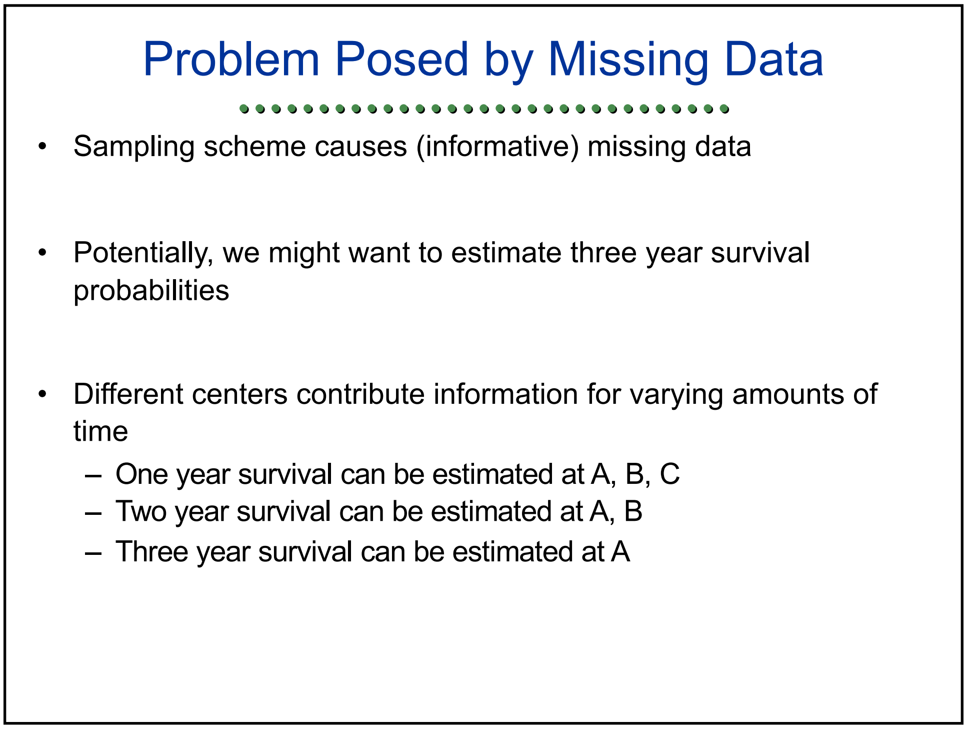

Problem Posed by Missing Data

- Sampling scheme causes (informative) missing data
- Potentially, we might want to estimate three year survival probabilities
- Different centers contribute information for varying amounts of time
  - One year survival can be estimated at A, B, C
  - Two year survival can be estimated at A, B
  - Three year survival can be estimated at A

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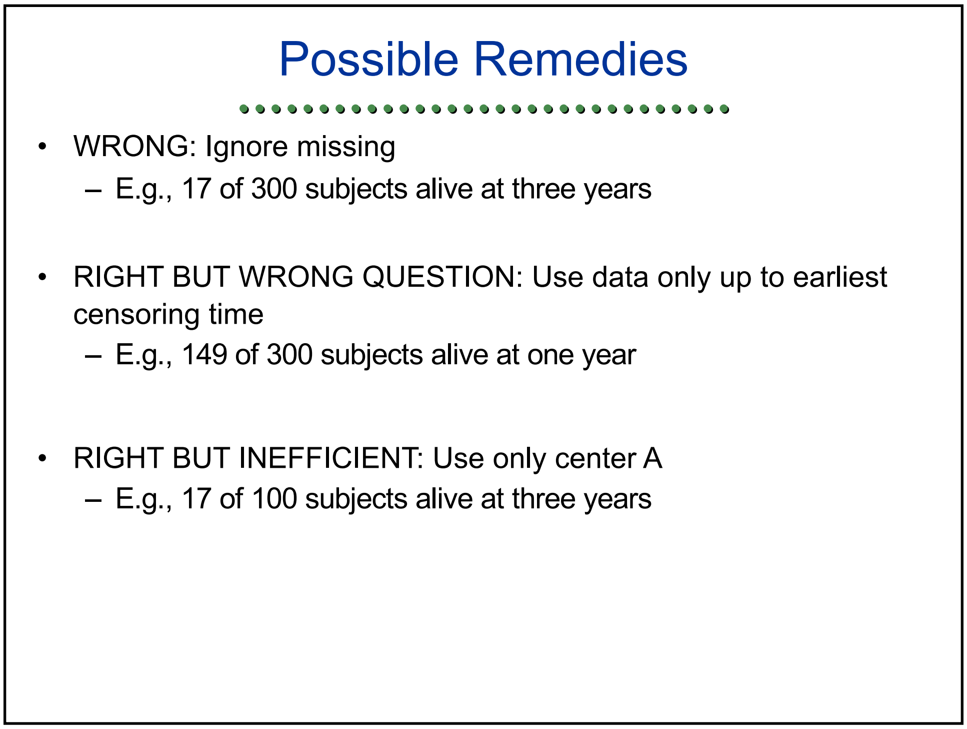

Possible Remedies

- WRONG: Ignore missing
  - E.g., 17 of 300 subjects alive at three years
- RIGHT BUT WRONG QUESTION: Use data only up to earliest censoring time
  - E.g., 149 of 300 subjects alive at one year
- RIGHT BUT INEFFICIENT: Use only center A
  - E.g., 17 of 100 subjects alive at three years

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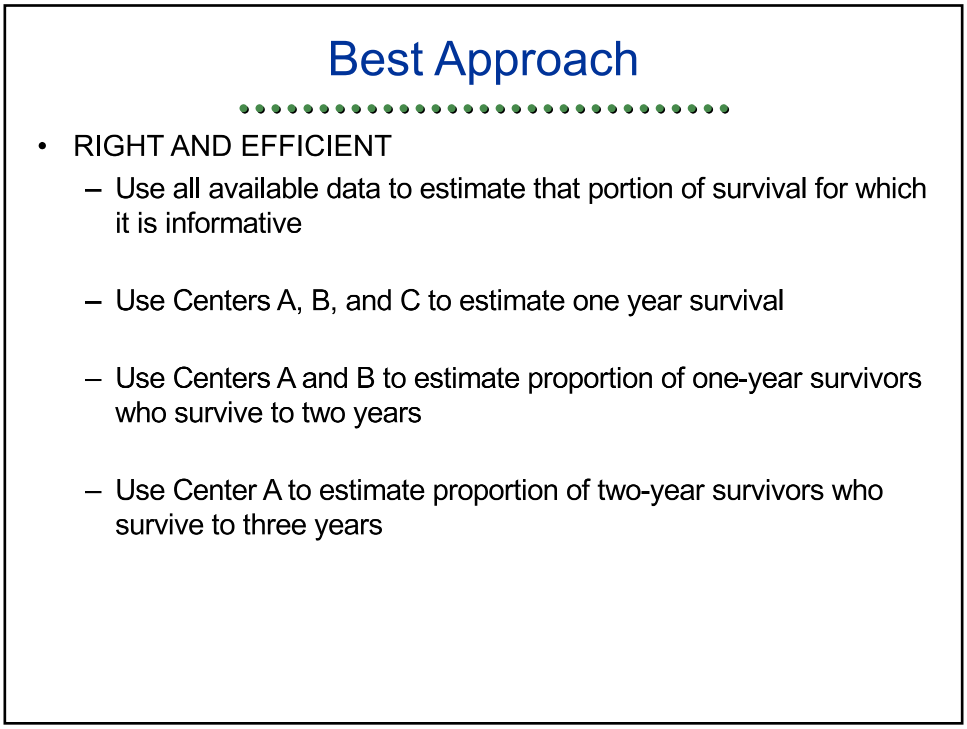

Best Approach

- RIGHT AND EFFICIENT
  - Use all available data to estimate that portion of survival for which it is informative
  - Use Centers A, B, and C to estimate one year survival
  - Use Centers A and B to estimate proportion of one-year survivors who survive to two years
  - Use Center A to estimate proportion of two-year survivors who survive to three years

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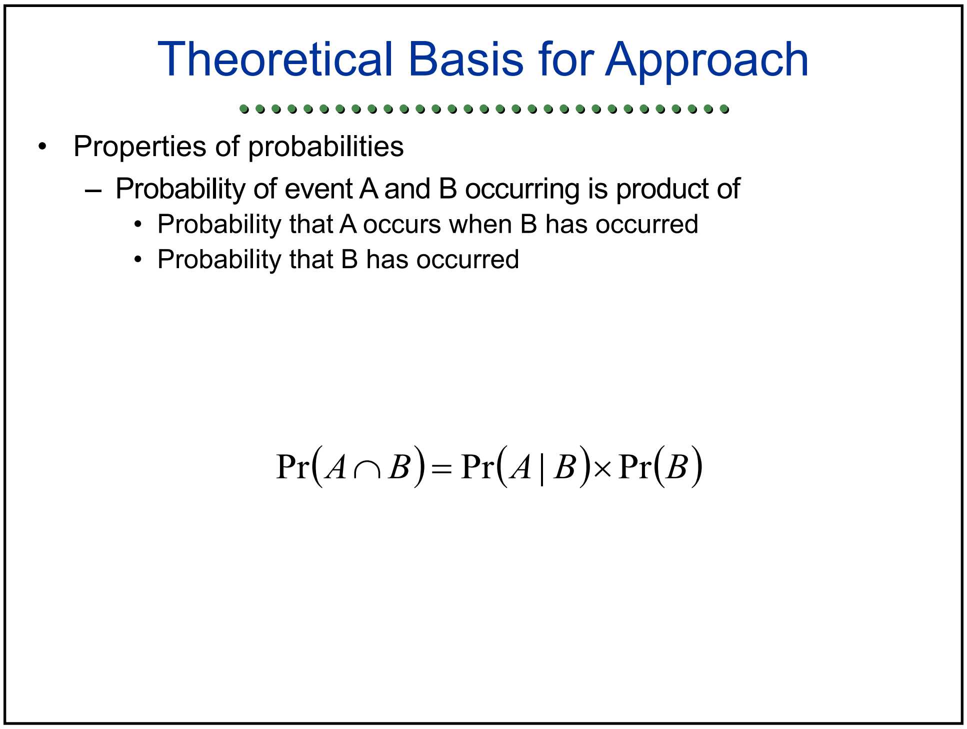

Theoretical Basis for Approach

- Properties of probabilities
  - Probability of event A and B occurring is product of
    - Probability that A occurs when B has occurred
    - Probability that B has occurred

$$\Pr\left(A \cap B\right) = \Pr\left(A \mid B\right) \times \Pr\left(B\right)$$

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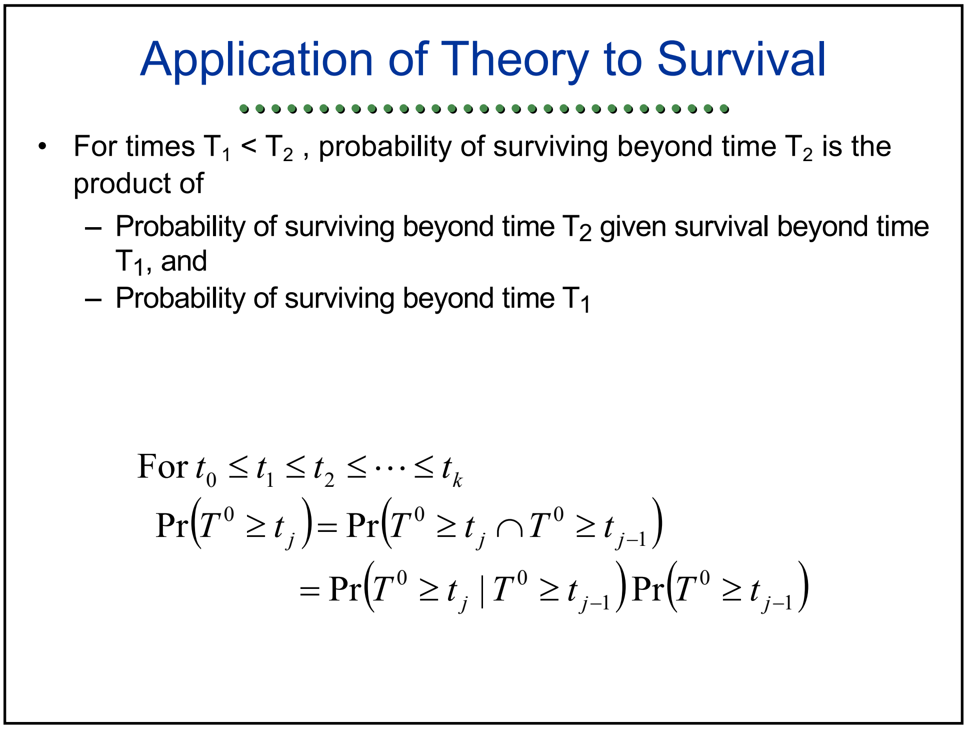

Application of Theory to Survival

- For times $T_1 < T_2$, probability of surviving beyond time T_2 is the product of
  - Probability of surviving beyond time T_2 given survival beyond time T_1, and
  - Probability of surviving beyond time T_1

$$\text{For } t_0 \le t_1 \le t_2 \le \cdots \le t_k$$

$$\begin{aligned}\Pr\left(T^0 \ge t_j\right) &= \Pr\left(T^0 \ge t_j \cap T^0 \ge t_{j-1}\right)\\ &= \Pr\left(T^0 \ge t_j \mid T^0 \ge t_{j-1}\right)\Pr\left(T^0 \ge t_{j-1}\right)\end{aligned}$$

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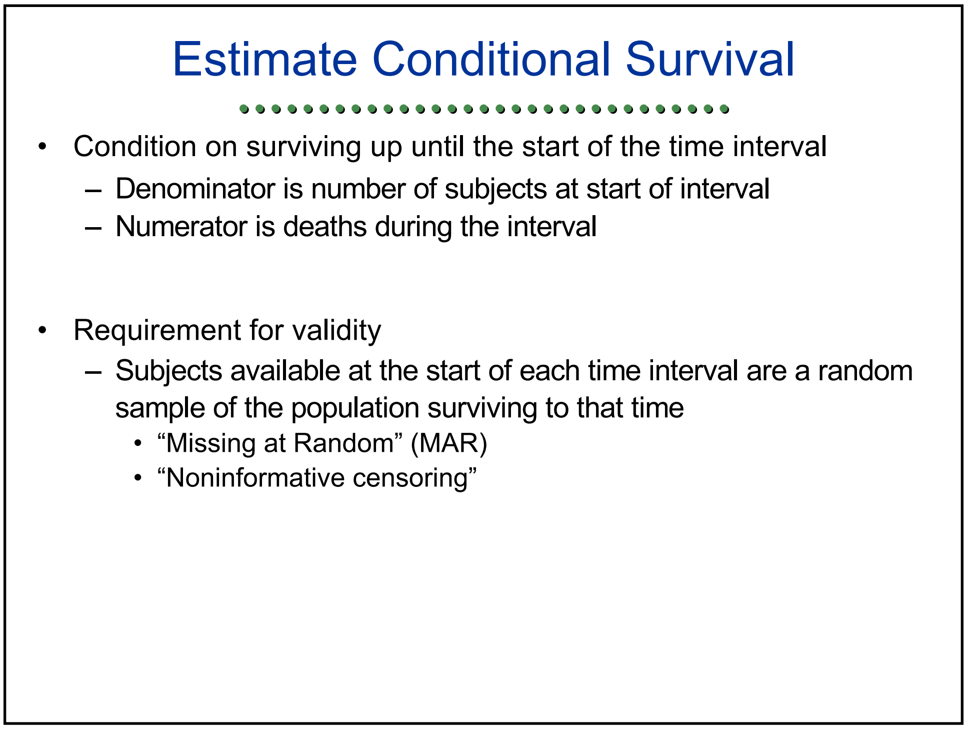

Estimate Conditional Survival

- Condition on surviving up until the start of the time interval
  - Denominator is number of subjects at start of interval
  - Numerator is deaths during the interval

- Requirement for validity
  - Subjects available at the start of each time interval are a random sample of the population surviving to that time
    - “Missing at Random” (MAR)
    - “Noninformative censoring”

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Estimate Survival Probability

- Estimate probability of survival at the endpoint of each time interval

- Multiply the conditional probabilities for all intervals prior to the time point of interest

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Application to Example

- Within interval conditional probabilities
  - Use A, B, C to estimate $Pr\ (T^0 \geq 1)$
  - Use A, B to estimate $Pr\ (T^0 \geq 2 \mid T^0 \geq 1)$
  - Use A to estimate $Pr\ (T^0 \geq 3 \mid T^0 \geq 2)$

- Multiply to obtain unconditional cumulative survival
  - $Pr\ (T^0 \geq 1)$
  - $Pr\ (T^0 \geq 2) = Pr\ (T^0 \geq 2 \mid T^0 \geq 1)\ \ Pr\ (T^0 \geq 1)$
  - $Pr\ (T^0 \geq 3) = Pr\ (T^0 \geq 3 \mid T^0 \geq 2)\ \ Pr(T^0 \geq 2)$

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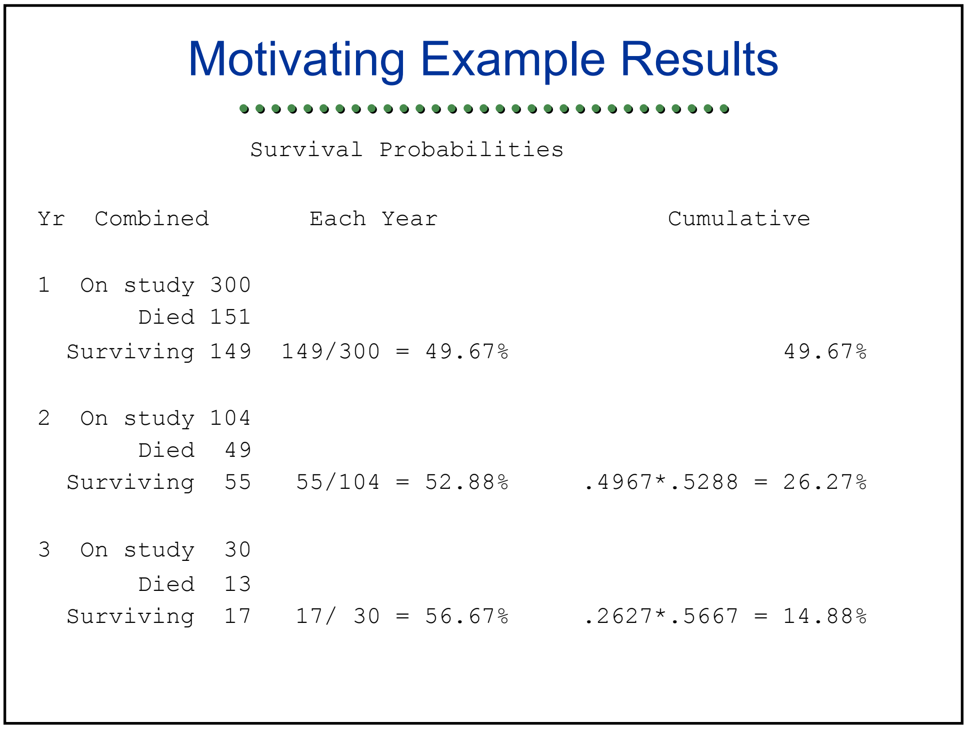

Motivating Example Results

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                Survival Probabilities

Yr  Combined       Each Year                Cumulative

1  On study 300
        Died 151
  Surviving 149  149/300 = 49.67%                      49.67%

2  On study 104
        Died  49
  Surviving  55   55/104 = 52.88%     .4967*.5288 = 26.27%

3  On study  30
        Died  13
  Surviving  17   17/ 30 = 56.67%     .2627*.5667 = 14.88%
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