Cancer Research Workshop
## Cancer Incidence and Death

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Estimated New Cases</th>
<th>Rank</th>
<th>Estimated Deaths</th>
<th>Rank</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bladder</td>
<td>68,810</td>
<td>6</td>
<td>14,100</td>
<td>8</td>
</tr>
<tr>
<td>Breast (Female -- Male)</td>
<td>182,460 -- 1,990</td>
<td>4</td>
<td>40,480 -- 450</td>
<td>3</td>
</tr>
<tr>
<td>Colon and Rectal (Combined)</td>
<td>148,810</td>
<td>5</td>
<td>49,960</td>
<td>2</td>
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<tr>
<td>Endometrial</td>
<td>40,100</td>
<td>11</td>
<td>7,470</td>
<td>11</td>
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<tr>
<td>Kidney (Renal Cell) Cancer</td>
<td>46,232</td>
<td>9</td>
<td>11,059</td>
<td>9</td>
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<tr>
<td>Leukemia (All)</td>
<td>44,270</td>
<td>10</td>
<td>21,710</td>
<td>6</td>
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<tr>
<td>Lung (Including Bronchus)</td>
<td>215,020</td>
<td>2</td>
<td>161,840</td>
<td>1</td>
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<tr>
<td>Melanoma</td>
<td>62,480</td>
<td>8</td>
<td>8,420</td>
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<tr>
<td>Non-Hodgkin Lymphoma</td>
<td>66,120</td>
<td>7</td>
<td>19,160</td>
<td>7</td>
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<tr>
<td>Pancreatic</td>
<td>37,680</td>
<td>12</td>
<td>34,290</td>
<td>4</td>
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<tr>
<td>Prostate</td>
<td>186,320</td>
<td>3</td>
<td>28,660</td>
<td>5</td>
</tr>
<tr>
<td>Skin (Nonmelanoma)</td>
<td>&gt;1,000,000</td>
<td>1</td>
<td>&lt;1,000</td>
<td>13</td>
</tr>
<tr>
<td>Thyroid</td>
<td>37,340</td>
<td>13</td>
<td>1,590</td>
<td>12</td>
</tr>
</tbody>
</table>
Breast Cancer Data Network
(similar network for African American and Asian)

Q: Peers Paper and Linda’s Presentation
Breast Cancer Screening Survey

1. What is your current age? 
   __________

2. Which race do you belong to? 

3. Are you Hispanic? 
   1. yes  2. no  9. unknown

4. When did you have your first period? 
   1. __________  9. unknown

5. Which state of menopause are you in? 
   1. premenopausal  2. perimenopausal  3. postmenopausal  9. unknown

6. If you choose 2 in the previous question, at what age was your menopause over? 
   1. __________  9. unknown

7. If you choose "postmenopausal" in question #5, what is the type of menopause? 
   1. surgical menopause  2. natural menopause  9. unknown

8. Did you ever give birth? 
   1. yes  2. no

9. What is your age of first live birth if you choose "yes" in 8? 
   1. __________  9. unknown

10. What is your weight in pounds? 
    1. __________  9. unknown

11. What is your height in feet? 
    1. __________  9. unknown

12. How would you describe your breast density? 
    1. almost entirely fat  2. scattered fibroglandular densities  3. heterogeneously dense  4. extremely dense  9. unknown or different measurement system

13. What is the number of first degree relatives (parents, brothers, sisters, or children) with breast cancer? 
    1. none  2. one  3. 2 or more  9. unknown

14. Are you receiving any hormone replacement therapy that is used to add more hormones to your body to counter the effects of menopause? 
    1. yes  2. no  9. unknown or not menopausal

15. Was the result of your last mammogram positive or negative? 
    1. false positive  2. negative  9. unknown

Classifier (Brain)

Screen

Decision

Strongly Recommend

Recommend

Optional
16. How often do you exercise weekly?
   1. never  2. sometimes  3. frequently

17. What is your smoking habit?
   1. never  2. light  3. medium  4. heavy  5. ever, but quit  9. does not apply

18. How would you describe your second-hand smoking environment?
   1. none  2. light  3. medium  4. heavy

19. Did you ever have breast procedure (biopsy, surgery, radiation)?
   1. yes  2. no  9. unknown

The questions below are for individuals who have breast tumor. You may stop here if you have never been diagnosed with breast tumor.

20. How often do you have breast mammogram check?
   1. every 3 months  2. every 6 months  3. every year
   4. every 1.5 years  5. every 2 years  9. unknown

21. What type is the breast tumor?
   1. benign  2. carcinoma in situ (non-invasive)  3. malignant (invasive)  9. unknown

22. At what stage was your breast cancer when it was diagnosed?
   1. stage 1  2. stage 2  3. stage 3  4. stage 4  9. unknown

23. What was the size of your primary tumor?
   1. ______cm  9. unknown

24. What kind of treatments did you receive, please choose all that apply?

<table>
<thead>
<tr>
<th>treatment</th>
<th>surgery</th>
<th>chemotherapy</th>
<th>radiation</th>
<th>Targeted-drug therapy</th>
<th>Hormone therapy</th>
<th>unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes/No</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

25. If you experienced reoccurrence of breast cancer, after how many years did you have the reoccurrence?
   ______ years
Linda’s Tumor growth model

- Growth model assumptions
  - Exponential growth
  - Tumors are spherical
  - Growth rate depends on age
  - Doubling times for a given age follow a lognormal distribution
Growth equations

Quasi-exponential growth

\[
\frac{dV(t)}{dt} = \frac{\ln 2}{\tau_d(t)} \cdot V(t)
\]

\(t\) is age in years

\(V\) is tumor volume

Doubling time increases with age

Assume doubling time is lognormally distributed

\[
\ln(\tau_d(t)) = \mu(t) + \sigma \cdot \xi_d
\]

\(\mu\) is the mean of log of doubling time distribution

\(\sigma\) is the spread of log of doubling time distribution

\(\xi_d\) is a random draw for each person (normally distributed)

Assume that the mean of the log of doubling time distribution depends linearly on age (based on data from Peer et al. 1993)

Parameter for spread calibrated to fit mammogram yield data
Doubling Time

Doubling Time: The time it takes for a tumor to double in volume. It depends on two assumptions: how the volume is calculated and the way tumor grows.

Tumor Growth Assumption
1. Exponential Growth
2. Linear Growth
3. Quadratic Growth

Tumor Volume Assumption
1. \[ V = \frac{4}{3} \cdot \pi \cdot r^3 \quad r = a/2 \]
2. \[ V = \frac{4}{3} \cdot \pi \cdot r^3 \quad r = \frac{2a + b}{12} \]
3. \[ V = \frac{4}{3} \cdot \pi \cdot \left(\frac{a}{2}\right)^2 \cdot \left(\frac{b}{2}\right) \]
4. \[ V = \frac{4}{3} \cdot \pi \cdot \frac{1}{2}a \cdot \frac{1}{2}b \cdot \frac{1}{2} \cdot \left(\frac{1}{2}a + \frac{1}{2}b\right) \]

1. \[ f(t) = 42 \cdot e^{-0.015254t} \]
2. \[ f(t) = 22.67865 - 0.05925 \cdot t \]
   \[ f(t) = 45.014257 - 0.764531 \cdot t + 0.00547 \cdot t^2 \]
3. \[ f(t) = 1.208443 \cdot e^{0.033947t} \]
Chunling’s Outline

- Nonparametric and parametric analysis of treatment effectiveness of breast cancer
- Statistical modeling of relapse time of breast cancer with different treatments
- Markov modeling of breast cancer states
- Statistical analysis of lung cancer mortality time
- Sensitivity analysis of breast cancer
Yong’s Outline

- Probabilistic comparison of survival analysis models using simulation and cancer data
- Identify attributable variables and interactions in breast cancer
- Statistical modeling of breast cancer using differential equations
- Power law process in cancer analysis
Bong-Jin’s Outline

- Understanding CPS-II and SEER Databases
- Regional Behavior
- Data Manipulation
- Parametric and Nonparametric Analysis
Power Law Process

- Power law process (PLP) also named non-homogeneous poisson process (NHPP) as well as weibull process (WP). [4]. PLP has been used in many applications.

\[ P[(N(b)) - N(a)] = k = \frac{e^{-\lambda_{a,b}} (\lambda_{a,b})^k}{k!} \quad k = 0,1,... \]

- NHPP has the intensity function:
- \( V(t) \) has been very successfully used in reliability analysis \( v(t)=f(\beta) \)

\[ v(t) = \left( \frac{\beta}{\alpha} \right) \left( \frac{t}{\alpha} \right)^{\beta-1}, \quad \text{for } \alpha > 0, \beta > 0, t > 0. \]
Power Law Process

1) if the parameter beta is greater than one, then the tumor size increase means the survival rate decreased.

2) If beta is less than one in survival analysis, then the tumor size decrease which means the survival time increase.

3) If beta equals to one then the tumor size is constant and the NHPP will become homogenous passion process (HPP).
Time Series Analysis of Breast Cancer Tumors Stages 1 and 2

- **Stage 1**
  - ARIMA \((3,1,2)\)
  \[
  \Delta T_{S_t} = -1.6808\Delta T_{S_{t-1}} - 1.0923\Delta T_{S_{t-2}} - 0.1305\Delta T_{S_{t-3}} + 1.1878\varepsilon_{t-1} + \varepsilon_{t-2}
  \]

- **Stage 2**
  - ARIMA \((1,1,3)\)
  \[
  \Delta T_{S_t} = 0.9868\Delta T_{S_{t-1}} - 1.9024\varepsilon_{t-1} + 0.9649\varepsilon_{t-2} - 0.0219\varepsilon_{t-3}
  \]
## Residual Analysis

<table>
<thead>
<tr>
<th>Stage 1</th>
<th>Stage 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>-0.11173</td>
<td>-0.28049</td>
</tr>
<tr>
<td>-0.07082</td>
<td>1.84478</td>
</tr>
<tr>
<td>0.09238</td>
<td>1.26321</td>
</tr>
<tr>
<td>0.094</td>
<td>1.67586</td>
</tr>
<tr>
<td>-0.1189</td>
<td>-0.58496</td>
</tr>
<tr>
<td>0.1284</td>
<td>-1.02263</td>
</tr>
<tr>
<td>0.01277</td>
<td>-0.48973</td>
</tr>
<tr>
<td>0.25898</td>
<td>-0.31764</td>
</tr>
<tr>
<td>-0.10868</td>
<td>0.16721</td>
</tr>
<tr>
<td>0.17586</td>
<td>-0.44447</td>
</tr>
<tr>
<td>0.20695</td>
<td>-0.29586</td>
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<tr>
<td>0.26066</td>
<td>-0.57591</td>
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<tr>
<td>-0.05438</td>
<td>0.79763</td>
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<tr>
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<td>0.88955</td>
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<tr>
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<td>1.61346</td>
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<tr>
<td>-0.61654</td>
<td>2.30179</td>
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<tr>
<td>0.90261</td>
<td>-2.82097</td>
</tr>
<tr>
<td>-0.30981</td>
<td>-0.32845</td>
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</table>
## Validation Statistics

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>Variance</th>
<th>Standard Deviation</th>
<th>Standard Error</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>0.130659</td>
<td>0.118866</td>
<td>0.344768962</td>
<td>0.068953792</td>
</tr>
<tr>
<td>Stage 2</td>
<td>0.353634</td>
<td>1.585643</td>
<td>1.259223273</td>
<td>0.251844655</td>
</tr>
</tbody>
</table>
Determine if Parametric analysis is applicable with respect to Ductal vs. Lobular carcinoma. In other words is it possible that we can identify probability distribution with respect to size of tumor in Ductal vs. Lobular.

- Is the probability distribution same or different?
  - If there is a difference then we can characterize the behavior of the size of the tumor between the two different types.
  - 1st option is use Parametric analysis as it has been shown to be the best analysis in terms of survival curves. However, if Parametric analysis is not applicable we will proceed with Non-Parametric analysis.

Determine if there is any significance difference in True Mean between Ductal vs. Lobular. That is, is the True Mean of the tumor size in these two cancers the same or different? If the assumption is that they are same then accept the hypothesis. However, if they are different which one is relatively has a higher value in terms of Tumor size.

Determine if there is True Mean differences between various races in Ductal vs. Lobular.
- Caucasians vs. African Americans
- African American vs. Asians
- Caucasians vs. Asians
Utilize Markovian analysis to project the future with respect to various attributable variables.
- Perform Markovian analysis of the four Stages of Ductal carcinoma subject to various treatments with Stages I – IV.
- Perform Markovian analysis of the four Stages of Lobular carcinoma subject to various treatments with Stage I – IV.

Using this data should be able to look at survival curve, i.e. is the survival curve smaller in a given larger tumor size from Stage I. Determine the same questions for all the Stages in Ductal and Lobular.

In Ductal identify attributable variables including any interactions even Non-linear ones.
- We will make a model so that given a patient be able to come up with a value to estimate the growth rate of the tumor.
- The objective here will be utilizing this model in a screening purpose so that there is will be ranking of the attributable variables with respect to the tumor growth.

The same identification process will be done with respect to Lobular carcinoma.

Given that 3c and 3d data, determine if these variables are the same or different. This given insight into basic questions into breast cancer. These interactions will dictate the basic differences between Ductal vs. Lobular.

The model will continue once the different attributable risks are identified and ranked to determine the differences between the Stages I – IV in both Ductal and Lobular.
- Determine if the rank changes between the two cancers.
- This will give insight into why a person is in Stage I vs. Stage II vs. Stage III vs. Stage IV.
- If there are no significant changes then should be able to combine both of the cancers to improve statistical analysis.
Perform complete analysis (Parametric or Non-parametric from above) of Stage I of Ductal vs. Stage I of Lobular. Similar question will be described from above.
- Tumor size: same analysis as in 1a and 1b.
- Race: same analysis as in 1C.
- Survival time between the two cancers
- Broadly we will look at these differences to decipher if same or different. If same accept or reject the assumption that there are no differences among the two cancers. If indeed there are differences, which one (Ductal or Lobular) has higher value in terms of Tumor size, Race, and Survival time in Stage I?

Perform complete analysis of Stage II of Ductal vs. Stage II of Lobular.
- Tumor size
- Race
- Survival time

Perform complete analysis of Stage III of Ductal vs. Stage III of Lobular carcinoma.
- Tumor size
- Race
- Survival time

Perform complete analysis of Stage IV of Ductal vs. Stage IV of Lobular carcinoma.
- Tumor size
- Race
- Survival time
Q: Partition of Data
Smoking Data Analysis

Three Dimensional Survival Analysis of Mortality Time $S(t; CPD, t_d)$
Smoking Data Variables

- CPD= Cigarette per day
- Duration= # of years
- Total=CPD x Duration x 365

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<tr>
<th>CPD</th>
<th>Duration</th>
<th>Total</th>
</tr>
</thead>
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<tr>
<td>3</td>
<td>29</td>
<td>31755</td>
</tr>
<tr>
<td>5</td>
<td>32</td>
<td>58400</td>
</tr>
<tr>
<td>40</td>
<td>37</td>
<td>540200</td>
</tr>
<tr>
<td>40</td>
<td>18</td>
<td>262800</td>
</tr>
<tr>
<td>40</td>
<td>40</td>
<td>584000</td>
</tr>
<tr>
<td>19</td>
<td>50</td>
<td>346750</td>
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<td>44</td>
<td>401500</td>
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<td>13</td>
<td>15</td>
<td>71175</td>
</tr>
<tr>
<td>10</td>
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<td>43800</td>
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</table>
## Data Summary and Correlation Coefficient

<table>
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<tr>
<th>Variable</th>
<th>N</th>
<th>Mean</th>
<th>SD</th>
<th>Min</th>
<th>Max</th>
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<tbody>
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<td>14.29450</td>
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<tr>
<td>Duration</td>
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<td>11.87847</td>
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<tr>
<td>Total</td>
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<td>1460000</td>
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</table>

<table>
<thead>
<tr>
<th></th>
<th>CPD</th>
<th>Duration</th>
<th>Total</th>
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</thead>
<tbody>
<tr>
<td>CPD</td>
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<td>0.24122</td>
<td>0.86877</td>
</tr>
<tr>
<td>Duration</td>
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<td>0.60588</td>
</tr>
<tr>
<td>Total</td>
<td>0.86877</td>
<td>0.60588</td>
<td>1.00</td>
</tr>
</tbody>
</table>
Objective

We are interested in finding a bivariate distribution which describes the duration and the total number of cigarettes consumed.
Preliminary Observation: Both duration and total number of cigarettes satisfy the Johnson distribution.

\[
f(x) = \frac{\delta}{\lambda \sqrt{2 \pi z (1-z)}} \exp \left( -\frac{1}{2} \left( \gamma + \delta \ln \left( \frac{z}{1-z} \right) \right)^2 \right)
\]

\[
z \equiv \frac{x - \xi}{\lambda}
\]

\[
\xi \leq x \leq \xi + \lambda
\]
Total Cigarettes

\[ \gamma = 3.5404, \delta = 1.8153, \lambda = 3129800, \xi = -159270 \]
\[ \gamma = -0.63955, \delta = 1.5516, \lambda = 83.065, \xi = -18.794 \]
Goodness of Fit Test

- If Duration and Total has bivariate Johnson’s distribution
- \((Z_1,Z_2)\) must have bivariate standard normal distribution where

\[
Z_1 = \gamma_1 + \delta_1 \log \left[ \frac{\text{Duration} - a_1}{b_1 - \text{Duration}} \right]
\]

\[
Z_2 = \gamma_2 + \delta_2 \log \left[ \frac{\text{Total} - a_2}{b_2 - \text{Total}} \right]
\]
<table>
<thead>
<tr>
<th>Z1</th>
<th>Z2</th>
</tr>
</thead>
<tbody>
<tr>
<td>-1.42144</td>
<td>-0.16811</td>
</tr>
<tr>
<td>-1.16787</td>
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<tr>
<td>1.279517</td>
<td>0.471151</td>
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<tr>
<td>0.166311</td>
<td>-0.99515</td>
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<tr>
<td>1.422787</td>
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<tr>
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<tr>
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<tr>
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<tr>
<td>2.120661</td>
<td>0.824691</td>
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<tr>
<td>0.568362</td>
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<tr>
<td>0.237858</td>
<td>-0.91964</td>
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<td>0.129752</td>
<td>0.304699</td>
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<tr>
<td>1.230353</td>
<td>-1.22458</td>
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<tr>
<td>-1.59476</td>
<td>0.918576</td>
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<tr>
<td>-0.26983</td>
<td>0.06427</td>
</tr>
<tr>
<td>1.279517</td>
<td>1.46054</td>
</tr>
</tbody>
</table>
Distribution of Z1

Probability Density Function

Normal (0.97084; 0.04065)
Distribution of Z2

\[ \sigma = 1.004 \]

\[ \mu = 0.00136 \]
Preliminary Conclusion

- Marginal normality was investigated by calculating the Kolmogorov-Smirnov (KS), the Anderson-Darling (AD) and Shapiro-Wilks (SW) test for each component.

- Thus a viable candidate for modeling smoking data is bivariate Johnson’s distribution.
Colon Cancer Data Network

- **WOMEN (216,582)**
  - **WHITE (185,535)**
    - **SQUAMOUS (559)**
      - **MUCINOUS (17789)**
    - **ADENOCARCINOMA (121,584)**
      - **OTHER (63392)**
    - **OTHER (6984)**
  - **BLACK (18,727)**
    - **SQUAMOUS (81)**
      - **MUCINOUS (1679)**
    - **ADENOCARCINOMA (11,662)**
      - **SIGNET (107)**
    - **OTHER (3080)**
  - **ASIAN (9,987)**
    - **SQUAMOUS (04)**
      - **MUCINOUS (655)**
    - **ADENOCARCINOMA (6903)**
      - **SIGNET (54)**
  - **OTHER (2333)**
Find the true mean of the tumor size with respect to each race (i.e., Whites, Blacks, and Asians) for males. If they are same then analysis will be done one entity. If the true means are different for the different races then rank them and all the analysis will be done separately from this point onwards.

- The same will be done for females.

- Compare the various combinations of races for comparison i.e., Whites vs. Blacks, whites vs. Asians, and Blacks vs. Asians. If we accept that there are no differences between the races that hypothesis will be tested and reported in all levels of the analysis.

- Find the true mean of the tumor size with respect to males at the level of Astrocytoma, Other Glioma, Ependymoma, and Medulloblastoma & Other PNET.

- Find the true mean of the tumor size with respect to females at the level of Astrocytoma, Other Glioma, Ependymoma, and Medulloblastoma & Other PNET.

- Test the hypothesis that these are different and if different which is larger in comparing male vs. females.

- At the level of Astrocytoma

- The mean survival times of males in Low Grade Astrocytoma vs. Glioblastoma & Anaplastic Astrocytoma vs. Astrocytoma NOS. Do the same for females.

- Test the hypothesis is the survival time in males with respect to surgery vs. no surgery vs. other treatments the same for Low Grade Astrocytoma. Do the same for Glioblastoma & Anaplastic Astrocytoma vs. Astrocytoma NOS. Repeat the same set of analysis with respect to females.

- In all above cases display survival curves in males and females for Low Grade Astrocytoma for surgery, no surgery, and other treatments. Do the same for Glioblastoma & Anaplastic Astrocytoma vs. Astrocytoma NOS.

- At the level Other Glioma

- Find any significant differences between Glioma and Astrocytoma in males. Repeat the analysis for females.

- Find the mean survival times with respect to various treatments, i.e. surgery vs. no surgery vs. other treatment in males followed by females for Other Glioma.

- Test the hypothesis that survival curve for surgery would be better, worse, or same to survival curves for no surgery vs. other treatments in males. Repeat the same analysis with females.

- At the level of Ependymoma

- i. Find any significant statistical differences between Ependymoma, Glioma, and Astrocytoma in males. Repeat the analysis for females.

- ii. Find the mean survival times with respect to surgery vs. no surgery vs. other treatment in males followed by females for Ependymoma.

- iii. Determine if survival curve for surgery would be better, worse, or same to survival curves for no surgery vs. other treatments in males. Repeat the same analysis with females for Ependymoma.

- d. Same analysis will be performed for Medulloblastoma.