JPSurv - A Tool to Analyze and Estimate Cancer Survival Trends

September 29, 2022

NCI Analytic Tools SEERies

Angela Mariotto, Ph.D.
Data Analytics Branch, DCCPS

Theresa Devasia, Ph.D.
Data Analytics Branch, DCCPS
Using WebEx and Webinar Logistics

- All lines will be in listen-only mode.
- Submit questions at any time using the Q&A or Chat Panel and select “All Panelists”.
- You may need to activate the appropriate box using the floating navigation panel. Found on the bottom of your screen.
- During the Live Demo- put your screen layout in “Full Screen” mode for a better viewing experience.
- Closed Captioning is available.
- This webinar is being recorded.
Speakers:

Angela Mariotto, Ph.D.
Chief
Data Analytics Branch
Surveillance Research Program

Theresa Devasia, Ph.D.
Mathematical Statistician
Data Analytics Branch
Surveillance Research Program
JPSurv: a web tool to estimate trends in survival

Angela Mariotto, PhD, NCI
Theresa Devasia, PhD, NCI

September 29, 2022
1. Part 1: PowerPoint presentation
   • Background
   • JoinPoint model for Survival: JPSurv
   • Non-Hodgkin Lymphoma application
   • Measures to summarize survival trend
   • Proportionality assumption: Chronic Myeloid Leukemia example
   • Discussion/Conclusions
   • Q&A

2. Part 2: JPSurv demo (Dr. Theresa Devasia)

3. Q&A
Sometimes the simplest questions are the hardest to answer!

NCI Director: Does this represent a significant change in the trend?

“\text{This is where things started getting really weird.}”

Courtesy of Rocky Feuer
Joinpoint

- Joinpoint is statistical software for the analysis of trends in rates (incidence or mortality) using joinpoint models, i.e., models like the figure where several different lines are connected together at the "joinpoints"

- Estimates the number and location of joinpoints, i.e., calendar years where trends changed

Why do we need a different joinpoint model for survival data?

- Survival has an extra dimension compared to rate (in addition to calendar year at diagnosis):
  - Time since diagnosis

- To answer questions such as
  - At which years at diagnosis there is significant changes in survival?
  - How much survival (or probabilities of cancer death) are changing annually between joinpoints?
  - Are the changes similar for different time since diagnosis?
Joinpoint model for survival: JPSurv

- Analyze trends in survival with respect to year of diagnosis
- JPSurv estimates the number and location of joinpoints, i.e. calendar years at diagnosis where the probabilities of dying of cancer (hazard) have shown change in trends
- It also summarizes trends between joinpoints
Joinpoint model for survival: JPSurv

- The joinpoint survival model is an extension of the proportional hazards (Cox) model for survival (1-3)
- It can be applied to both Relative Survival or Cause Specific Survival (1)

Joinpoint survival model

- Let \( x \) be calendar year of diagnosis and \( t \) time since diagnosis
- We assume that the hazard rate of dying at time \( t \) follows a proportional hazard model:

\[
\lambda(t \mid x) = \lambda_0(t) \exp\{h(x)\} = \exp\{\alpha_0(t) + h(x)\}
\]

Baseline hazard

\[
S(t \mid x) = S_0(t)^{\exp\{h(x)\}}
\]

Baseline survival

The joinpoint model: linear segments between joinpoints, describing trends with respect to year at diagnosis \( x \)
Joinpoint model $h(x)$ on calendar year $x$

- Let $K$ be the number of joinpoints and $t_1,\ldots, t_K$ the position of the joinpoints

\[ h(x) = \beta x + \sum_{j=1}^{K} \delta_k (x - t_j)^+ \]

\[ u^+ = \begin{cases} u, & u > 0 \\ 0, & u \leq 0 \end{cases} \]

- $K+1$ linear segments connected at the joinpoints at $t_1,\ldots, t_K$

- When there is no joinpoint ($K=0$), the model is a Cox proportional hazards model and the proportionality function is a linear function $\beta x$, i.e.

\[ h(x) = \beta x \]

- $\beta$ is the slope of the segment
Model estimation and selection: example 1975-2015 data

- For a fixed number of joinpoints \( K \) (up to 5) JPSurv fits a joinpoint model to each possible joinpoint location

- Example: User chooses maximum number of joinpoints \( K=2 \)
  - \( K=0 \) → Fit one model with no joinpoint
  - \( K=1 \) → Fit models with 1 joinpoint at possible locations: 1978, ..., 2010
    - Advanced options provide control of the minimum number of years required between joinpoints (2 years), first (3 years) and last intervals (5 years)
  - \( K=2 \) → Fit models with combinations of 2 joinpoints (obeying restriction in Advanced Options)
Model estimation and selection

- For each fitted model JPSurv calculates:
  - Bayesian Information Criterion (BIC)
  - Akaike Information Criterion (AIC)
  - Log-likelihood

- **Selected model is the model that minimizes BIC**

- When maximum no. of joinpoints is large (>2) →
  - Long time to run all models
  - User is required to provide an e-mail to retrieve results
Example: Non-Hodgkin Lymphoma (NHL) Data

- Cancer patients diagnosed with NHL between 1975-2015
- Complete follow-up through 2016
- 10 years of follow-up

<table>
<thead>
<tr>
<th>Year</th>
<th>since diagnosis</th>
<th>Alive</th>
<th>Died</th>
<th>Lost</th>
<th>Interval</th>
<th>Cumul.</th>
<th>Interval</th>
<th>Cumul.</th>
<th>Interval</th>
<th>Cumul.</th>
<th>Relative (%)</th>
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<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>1975</td>
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<td>483</td>
<td>34</td>
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<td>...</td>
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</tr>
<tr>
<td>2015</td>
<td>&lt; 1 yr</td>
<td>5,081</td>
<td>876</td>
<td>76</td>
<td>82.6</td>
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<td>275</td>
<td>87</td>
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<td>97.7</td>
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<td>------</td>
</tr>
<tr>
<td>&lt; 1 yr</td>
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<td>71.4</td>
<td>69.9</td>
<td>...</td>
<td>81.2</td>
<td>81.9</td>
<td>84.4</td>
<td>84.0</td>
<td>84.5</td>
<td>83.8</td>
<td>84.3</td>
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<tr>
<td>1-&lt;2 yr</td>
<td>58.1</td>
<td>62.0</td>
<td>59.1</td>
<td>...</td>
<td>77.2</td>
<td>77.8</td>
<td>79.2</td>
<td>79.7</td>
<td>79.9</td>
<td>80.0</td>
<td>80.3</td>
</tr>
<tr>
<td>2-&lt;3 yr</td>
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<td>56.9</td>
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<td>74.8</td>
<td>75.4</td>
<td>76.5</td>
<td>77.6</td>
<td>77.7</td>
<td>77.9</td>
<td>78.1</td>
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<tr>
<td>3-&lt;4 yr</td>
<td>49.8</td>
<td>52.4</td>
<td>49.4</td>
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<td>72.9</td>
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<td>75.8</td>
<td>75.5</td>
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<tr>
<td>4-&lt;5 yr</td>
<td>46.0</td>
<td>47.9</td>
<td>46.3</td>
<td>...</td>
<td>70.8</td>
<td>71.7</td>
<td>73.2</td>
<td>74.4</td>
<td>74.5</td>
<td>74.6</td>
<td>75.4</td>
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<tr>
<td>5-&lt;6 yr</td>
<td>41.5</td>
<td>45.6</td>
<td>43.3</td>
<td>...</td>
<td>69.2</td>
<td>70.6</td>
<td>72.2</td>
<td>72.4</td>
<td>72.7</td>
<td>72.6</td>
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<tr>
<td>6-&lt;7 yr</td>
<td>39.0</td>
<td>42.6</td>
<td>40.8</td>
<td>...</td>
<td>67.7</td>
<td>69.2</td>
<td>70.6</td>
<td>71.4</td>
<td>71.6</td>
<td>71.6</td>
<td>71.6</td>
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<tr>
<td>7-&lt;8 yr</td>
<td>36.8</td>
<td>40.4</td>
<td>38.1</td>
<td>...</td>
<td>66.5</td>
<td>67.8</td>
<td>69.5</td>
<td>70.5</td>
<td>70.5</td>
<td>70.5</td>
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<tr>
<td>8-&lt;9 yr</td>
<td>35.2</td>
<td>38.2</td>
<td>35.9</td>
<td>...</td>
<td>65.5</td>
<td>66.6</td>
<td>68.4</td>
<td>68.4</td>
<td>68.4</td>
<td>68.4</td>
<td>68.4</td>
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<tr>
<td>9-&lt;10 yr</td>
<td>33.6</td>
<td>36.2</td>
<td>34.6</td>
<td>...</td>
<td>64.1</td>
<td>65.6</td>
<td>65.6</td>
<td>65.6</td>
<td>65.6</td>
<td>65.6</td>
<td>65.6</td>
</tr>
</tbody>
</table>
Specifying Data and Parameters in JPSurv

- Selecting the cohort
- Specifying the calendar years and follow-up time to fit the model
- Max. # JP to test
- E-mail to retrieve results
- Controls restriction on Joinpoints
- Run

- Data
- Year of Diagnosis
  - Year of diagnosis 1975+
- Year of Diagnosis Range:
  - 1975 to 2015
- Max. No. of Years from Diagnosis (follow-up) to include:
  - <= 10
- Site recode NHL and CML:
  - Non-Hodgkin Lymphoma
  - Chronic Myeloid Leukemia
- Maximum Joinpoints: 5
- Multiple Cohorts or single cohort with maximum Joinpoints greater than 2 will require additional computing time. When computation is completed, a notification will be sent to the e-mail entered above.
- E-mail: mariotta@mail.nih.gov

- Advanced Options

- Dictionary File: NHL_CML_1.dic
- Data File: NHL_CML_1.txt
- Data Type: Relative Survival in Percents
Provides more stable survival projections not dependent on fluctuations at the last calendar years.
Non-Hodgkin Lymphoma - Testing up to 5 Joinpoints

<table>
<thead>
<tr>
<th>Model #</th>
<th>Number of Joinpoints</th>
<th>Location</th>
<th>Bayesian Information Criterion (BIC)</th>
<th>Akaike Information Criterion (AIC)</th>
<th>Log Likelihood</th>
<th>Converged</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>None</td>
<td>1542.01</td>
<td>1414.55</td>
<td>-696.27</td>
<td>Yes</td>
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<tr>
<td>2</td>
<td>1</td>
<td>1991</td>
<td>1123.45</td>
<td>984.40</td>
<td>-480.20</td>
<td>Yes</td>
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<tr>
<td>3</td>
<td>2</td>
<td>1995, 2002</td>
<td>984.96</td>
<td>834.33</td>
<td>-404.16</td>
<td>Yes</td>
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<tr>
<td>4</td>
<td>3</td>
<td>1983, 1994, 2003</td>
<td>983.27</td>
<td>821.04</td>
<td>-396.52</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Survival vs. Year at Diagnosis

Relative Survival by Diagnosis Year
Survival vs. Time Since Diagnosis

Relative Survival by Year Since Diagnosis for Selected Diagnosis Year
How do we summarize survival trends between joinpoints?
Trends in Joinpoint Model for Analysis of Rates

- Annual Percent Change (APC) is used to describe trends between joinpoints
- Interpretation: if the APC is 1%, and the rate in 1990 is 50 per 100,000
  - In 1991 the rate is $50 \times 1.01 = 50.5$ per 100,000
  - In 1992 the rate is $50.5 \times 1.01 = 51.005$ per 100,000
Two summary trend measures in JPSurv

- Probability of Cancer Death Scale
  - Annual Percent Change in the Probability of Cancer Death\(^1\): APC\(_D\)

- Cumulative Survival Scale
  - Motivation for developing a measure in the survival scale is because prognosis is usually reported as cumulative survival
  - Average Absolute Change in Survival\(^2\): AAC\(_S\)

Annual Percent Change in the Probability of Cancer Death (APC_D)

- $P(i,y)$: Conditional probability of dying of cancer in interval $i$ given alive at the beginning of the interval, for patients diagnosed in year $y$

- *Example* $i=1$ and $y=1996$

\[
APC\_D = 100 \times \frac{P(1,1996) - P(1,1995)}{P(1,1995)} = 100 \times \{\exp(\beta) - 1\}
\]

- It does not depend on interval $i$ nor the calendar year $y$ at the joinpoint segment but only on the $\beta$ the coefficient in the joinpoint segment

1. Yu et al. JRSS-A 2009;172:405-25
Numbers are the Annual Percent Change in the Probabilities of Cancer Death

- Largest decrease in the Prob of cancer death occurred between 1995-2003: 6.64% annual percentage decrease
- The estimate is independent of the interval
Interpretation for the trends between 1995-2003
Annual Percent Change in the Probabilities of Cancer Death

- APC_D = -6.64% and P(1,1995)=27.9%
  - then
  - P(1, 1996)=27.9% x 0.9336 = 26.0%
  - P(1, 1997)=26.0% x 0.9336 = 24.3%
  - ......  
  - P(1,2003)=P(1,2002) x 0.9336 =16.3%
if the APC_D is -6.64%

and the annual prob. of cancer death in the 5 year after diagnosis in 1995 is P(5,1995)=5.0% then

- P(5, 1996)=5.0% x 0.9336 = 4.7%
- P(5, 1997)=4.7% x 0.9336 = 4.4%
- ......
- P(5,2003)=P(5,2002) x 0.9336 =2.9%

The annual probability of dying of cancer is decreasing by 6.64% for each subsequent year of diagnosis.
Average Absolute Change in Survival (AAC_S)

- \( S(i,y) \) : i-year Cumulative Survival for patients diagnosed in year \( y \)
- Average of \( \{S(j,y+1)-S(j,y)\} \) over calendar years \( y \) in the joinpoint segment
- Example \( i=1 \) and segment 1995 to 2003, 8 years

\[
AAC_S(1) = \sum_{y=1995}^{2003} \frac{S(1,y+1)-S(1,y)}{8}
\]

- Measured in survival “percentage points (pp)”
- Depends on time since diagnosis and is averaged on the calendar years at the segment

Largest increases in relative survival (RS) occurred between 1995-2003:
1.33 percentage points (pp) in 1-year RS, 2 pp in 5-year RS and 2.27 pp in 10-year RS
Interpretation for the trends between 1995-2003
Average Absolute Change in Survival (AAC_S)

- The AAC_S(1) is 1.33 survival percentage points for the 1-year survival trends
- The 1-year relative survival in 1995 is S(1,1995)=72.1%
  - S(1, 1996)=72.1% + 1.33% = 73.5%
  - S(1, 1997)=73.5% + 1.33% = 74.8%
  - ......
  - P(1,2003)=P(1,2002) + 1.33% =82.8%
The AAC_S(5) is 2.00 survival percentage points for the 5-year survival trends.

The 5-year relative survival in 1995 is $S(5,1995)=54.3\%$

- $S(5, 1996)=72.1\% + 2.00\% = 56.3\%$
- $S(5, 1997)=73.5\% + 2.00\% = 58.3\%$
- ......
- $S(5,2003)=S(5,2002) + 2.00\% =70.3\%$

The 5-year cancer survival is increasing on average 2 percentage points for each subsequent year of diagnosis.
<table>
<thead>
<tr>
<th>Interpretation</th>
<th>AAC_S: Average Absolute Change in Survival</th>
<th>APC_D: Annual Percent Change in the Conditional Probability of Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>AAC_S(5)=2%:</td>
<td>The 5-year cancer survival is increasing on average 2 percentage points for each subsequent year of diagnosis</td>
<td>APC_D=-2%: The annual probability of dying of cancer is decreasing by 2% for each subsequent year of diagnosis. This measure is similar to APC</td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td>No</td>
</tr>
<tr>
<td>AAC_S(1) ≠ AAC_S(5)</td>
<td></td>
<td>APC_D is the same for 0-1 year, 1-2 years, ... from diagnosis.</td>
</tr>
</tbody>
</table>

**Motivation/Summary**

- More clear interpretation in terms of cumulative survival (prognosis)
- Vary by time since diagnosis
- More challenging prognosis interpretation
- Do not vary by time versus
- More elegant mathematical derivation
Notes about trend survival measures

- The standard errors for trends measures are obtained using the delta method.
- The trend measures in the probability of death (APC_D) and survival have opposite signs.
  - Increasing survival: APC_D is negative vs AAC_S is positive.
  - Decreasing survival: APC_D is positive vs AAC_S is negative.
Proportionality assumption: Example of survival for patients diagnosed with Chronic Myeloid Leukemia
Proportionality assumption

- JPsurv assumes that the probabilities of cancer death (hazard) by time since diagnosis are proportional (in the log scale)
  - Changes are “similar” in the first versus later years after diagnosis
- Works well for most cancer sites and applications
- In some exception cancer sites proportionality assumption does not hold: Example Chronic Myeloid Leukemia\(^1\)

**Proportionality Assumption**

- If \( t \) is time since diagnosis and \( y \) is the year at diagnosis a proportional survival model is:

\[
S(t \mid y) = S_0(t)^{\exp[h(y)]}
\]

- Which translate into a proportional survival model at the log scale

\[
\log[S(t \mid y)] = \exp[h(y)] + \log[S_0(t)]
\]

Proportionality constant depends on year of diagnosis \( y \)
Common baseline survival (depends on time since diagnosis \( t \))
# Model Selection Using up to 10 years Survival Data

## Cohort: Chronic Myeloid Leukemia

<table>
<thead>
<tr>
<th>Model #</th>
<th>Number of Joinpoints</th>
<th>Location</th>
<th>Bayesian Information Criterion (BIC)</th>
<th>Akaike Information Criterion (AIC)</th>
<th>Log Likelihood</th>
<th>Converged</th>
</tr>
</thead>
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<td>959.84</td>
<td>823.78</td>
<td>-396.89</td>
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</table>
Indication that the model does not fit well the 1-year relative survival
Modeled conditional probability of cancer death (CPCD)

- 1-year overestimated before 1995 and underestimated after
- 5-year underestimated before 1995 and overestimated after
B: 2 Year of follow-up data - 2 JP in 1999 & 2010

Figure 3.
Observed (dots) and modeled (lines) annual probabilities of dying of cancer in the 0–1 and 1–2 annual intervals since diagnosis by year of diagnosis, for patients diagnosed with CML. The figures correspond to models using up to 2 years of follow-up (A and B) and 5 years of follow-up (C). B is the final model using the BIC criteria while A is the final model using the AIC criteria. The dashed lines are projections beyond available data. JP, joinpoints.
Interpretation for the Chronic Myeloid Leukemia example

- The Jpsurv model did not fit the data well
  - Probability of cancer death did not decrease proportionally for all years since diagnosis
  - The modeled 1-year survival overestimated observed survival after 1995
  - Restricting the data to 2 years of follow-up, improved the fit
- Suggests larger improvements in the chances of surviving CML for patients who had already survived 3+ years compared with the initial years after diagnosis after 1995
- The first tyrosine kinase inhibitor (TKI), Imatinib, was approved by the FDA in 2000 to treat patients with CML
Relaxing proportionality assumption in JPSurv

- Work in progress

- We will be implementing a more flexible joinpoint model in JPSurv that relax (somewhat) the proportionality assumption of year at diagnosis effect.

- The new model will identify the best cut-point for time since diagnosis, e.g. 2 years from diagnosis and allow for two different joinpoint survival models:
  - A JPSurv model for the 0-<2 time since diagnosis
  - A PSurv model for the 2-<5 time since diagnosis
Discussion/Conclusions
Opportunities

- JPSurv webtool provides a suite of estimates and graphs for analyzing cancer survival trends
- Can be used with both relative survival and cause-specific survival
- Easier to use with data exported from SEER*Stat.
  - Improving the CSV functionality to read other survival data
- Trend measures available for trends of probability of cancer death and cumulative survival measures
- Can be used to **project** survival beyond the observed data, both in future calendar years as well as time since diagnosis.
  - Particularly useful in prevalence projections
Opportunities

- Different statistics to select best model are available: BIC, AIC and log-likelihood
  - BIC is the default and provide more parsimonious models

- Advanced options provide control of the minimum number of years required between joinpoints, first and last intervals and the number of years for projections
  - Last interval important for projections

- Graphs, trend measures and results are available and can be displayed for all tested models
Challenges

- The model and trend survival measures presents some challenges in understanding and interpretation
  - Trends in survival and probability of cancer death (hazard) measures
  - Two time scales: time since diagnosis and calendar year
- Assumes proportionality by time since diagnosis
  - Graphical display provides way of checking assumption
Summary

- The JPSurv webtool provides a suite of estimates for analyzing trends in cancer survival that complement traditional descriptive survival analyses.

- Caution should still be used when interpreting survival trends for those cancer sites for which screening or early detection have been widely disseminated in the population:
  - Survival increases may reflect biases (overdiagnosis, lead time and length biases) rather than real improvements.
  - Looking at incidence and mortality trends (1,2) can help in the interpretation of survival trends.

References


Thank you! Questions?
Live Demonstration

Theresa Devasia

NCI Analytic Tools SEERies
Q&A Discussion
Upcoming Webinar:

Geospatial Tools

Thursday, October 20 at 1:00-3:00 pm ET

Zaria Tatalovich, Ph.D.
Geospatial Scientist
DCCPS, NCI