An Overview of Survival Statistics in SEER*Stat

SEER’s mission is to provide information on cancer statistics in an effort to reduce the burden of cancer among the U.S. Population.

SEER collects data on cancer cases from various locations and sources throughout the United States.
- Data collection began in 1973 with a limited amount of registries and continues to expand to include even more areas and demographics today.
- There are currently 18 SEER registries which covers 28% of the US population with data for cases diagnosed in 2000 and later.

SEER: Surveillance, Epidemiology, and End Results Program
- Surveillance: collection and analysis of information on new cancer cases, extent of disease, screening tests, treatment, survival, and cancer deaths
- Epidemiology: study of the distribution and determinants of disease
- End Results: actively follow patients throughout their lifetime to provide a comprehensive source of survival data. > 95% of patients have a current date of last contact (known alive or known to have died).
Possibilities After Cancer Diagnoses

End-of study
(e.g. 5-year survival)

- Died from cancer
- Died from other cause
- Lost to follow-up
- Alive

Time since diagnosis

= End of observation (censored)

What makes population-based cancer survival using registry data unique?

- Patients are enrolled at the registry after being diagnosed with cancer; patients are actively followed for vital status and cause of death.
- Unlike a clinical trial (detailed review of the medical record to ascertain the cause of death), registries depend on death certificates to obtain cause of death information.
- Cause of death information obtained from the death certificates may not be reliable (misclassification errors) or may not be available for some of the registries.
- Survival by treatment can be biased. Treatment decisions are influenced by prognosis and comorbidities.
Types of Questions NCI Receives Concerning Survival

- **Policy Maker**: How the cancer survival benefit of a successful clinical trial is translated into the population?
- **Science Writer**: How has survival of prostate cancer changed over time? How do you expect it to change in the future?
- **Congressperson**: What is the most recent estimate of 5-year survival for breast cancer? How does it differ by race/ethnicity?
- **Researcher**: What is the impact of coexisting cardiovascular disease on survival of patients with localized breast cancer?
- **Patient**: I have just been diagnosed with ovarian cancer. What are my chances of surviving this cancer?
- **Cancer Survivor**: I have survived five years after diagnosis with colorectal cancer. What is the possibility that I am cured?

Types of Survival Measures

**ESTIMATION AND INTERPRETATION**
SEER*Stat Cancer Survival Measures

- **Observed survival**
  - Probability of surviving all causes of death

- **Net Survival**
  - Probability of surviving cancer in the absence of other causes of death

- **Crude Probability of death**
  - Probability of dying of cancer and other causes in the presence of competing risks

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**Net Survival**

- Provides a cancer progress measure that is not affected by changes in other-cause mortality
  - Measures of how quickly progress in clinical research is transferred into clinical practice
  - Compares survival experience between different population groups, e.g., race and socioeconomic status
    - Caution with biases (earlier diagnosis, over-diagnosis or later death)
- Measure of "biological cure" by identifying when the net survival curve levels off, i.e., an individual is no longer at risk of dying from the cancer
- Methods for calculating net survival:
  - Relative survival
  - Cause-specific survival
Net Survival: measuring **cancer** prognosis

**RELATIVE VS. CAUSE-SPECIFIC**

<table>
<thead>
<tr>
<th>How might we measure the prognosis of cancer patients?</th>
</tr>
</thead>
<tbody>
<tr>
<td>➢ <strong>Total mortality (among cancer patients)</strong></td>
</tr>
<tr>
<td>* All cause survival/observed survival (event is death)</td>
</tr>
<tr>
<td>➢ <strong>Interest</strong> is typically in survival associated with a diagnosis <strong>of</strong> cancer (not affected by the chances of dying of other causes):</td>
</tr>
<tr>
<td>➢ <strong>Net Survival</strong></td>
</tr>
<tr>
<td>* Cancer-specific survival: uses cause of death information</td>
</tr>
<tr>
<td>* Relative survival: is an alternative method that does not use cause of death information</td>
</tr>
</tbody>
</table>
Survival measures for prognosis

- Relative survival is extremely valuable in research and for monitoring and comparing cancer survival
- But… How useful is it for patients?
- Patients do not live in this hypothetical world
- Treatment decisions are made in the “real world”, which includes risk of dying of other causes
- To calculate “real world” probabilities we need to take into account the risk of dying of other causes and borrow ideas from competing risks theory

Example: Cumulative Probability of Death in Men and Women Age 70+ Diagnosed with Localized Colorectal Cancer, 1985 – 2001, SEER 9

- Net probability of death (100 - relative survival)
- Crude probability of death, other
- Crude probability of death, cancer

Total Cumulative Mortality = (100 - observed Survival)

- Net probability of death (100 - relative survival) in the range of 22.2%
- Crude probability of death, other in the range of 84.5%
- Crude probability of death, cancer in the range of 15.5%
Relative Survival

- Does not use cause of death information.
- Measure of excess mortality experienced by cancer patients.

**Observed survival** is the probability of surviving from all causes of death for a group of cancer patients under study.

**Expected survival** is the survival probability of a population similar to the patient group but free of the cancer under study.

- For details, see SRP technical notes by Cho et. al (2011)
**Expected Survival**

- Estimated from US life tables matched by age, sex, calendar time, and race (sometimes SES, geography) to the cancer patient cohort
- Assumes that life tables are representative of patients’ other-cause survival (represent background mortality in the absence of cancer)
- There are different methods to estimate expected survival. The most common methods are:
  - Ederer I, Ederer II, Hakulinen and Pohar-Perme
    - Methods differ regarding how long each individual is considered to be at risk for the purpose of estimating expected survival.

**Methods to Estimate Expected Survival in SEER*Stat**

- **Ederer I (Ederer et al. 1961)**
  Calculates the expected survival rates assuming each patient would be a member of the general population from diagnosis to entire follow-up.
  Matched individuals are considered to be at risk indefinitely.

- **Ederer II (Ederer and Heise 1959, current default, CSR)**
  Calculates the expected survival rates for patients under observation at each point of follow-up.
  Matched individuals are considered to be at risk until the corresponding cancer patient dies or is censored - adjusts for actual (rather than potential) follow-up times.

- Hakulinen (Hakulinen 1982)
  Matched individuals are considered to be at risk until the corresponding patient is censored. If a cancer patients dies, the matched individual is assumed to be at risk until the closing date of the study.

- Pohar Preme method (Perme et al. 2012, available in the future)
SEER*Stat expected survival tables are available by:

- Race: white, black, other (American Indian/Alaska Native, Asian/Pacific Islander)
- Ages: 0-99 years (previously 119)
- Individual years are interpolated from U.S. Decennial Life Tables from the National Center for Health Statistics (NCHS) for 1970, 1980, 1990, and 2000.
- For 2000+, NCHS annual life tables are used.
- Life tables for “Other” race are calculated using the standard life table methods
- Calculation using state life tables and SES will be available in the future

Relative survival estimates using any of the expected survival methods available are very similar in most situations.

- For cancer sites diagnosed at a wide range of ages, there might be small differences at longer follow-up times.

It is challenging to estimate relative survival rates for population subgroups:

- Lack of “appropriate” life-tables for ethnic minorities, risk factors (e.g. smoking), socioeconomic status, geographic areas
- Other-cause mortality may not be well-represented using existing life-table for some cohorts (e.g., patients with screening-detected cancers).
- Although relative survival is the default, SEER uses cause-specific survival to show survival by race/ethnicity.
Cause-specific Survival

- Net survival calculated based on cause of death information
- Uses *cause of death* information:
  - Deaths associated with cancer is the event of interest
  - Deaths due to other causes are treated as censored
- Requires accurate cause of death information

Why improve cause of death information?

- Cause of death (COD) information from death certificate may have misclassification errors
  - Metastatic site of the primary cancer diagnosis may be reported as the underlying COD
  - Difficult to assign CODs to a primary cancer diagnosis for people with multiple primaries
- A new algorithm was recently implemented in SEER*Stat to improve cause of death indicator (Howlader et. al, 2010)
SEER Cause-Specific Death Classification Variable

- The algorithm takes into account COD in conjunction with:
  - Site of original cancer diagnosis
  - Tumor sequence
    - Sequence 00 (only one primary tumor) vs
    - Sequence 01 (first of more than one tumor)
  - Diseases related to the cancer of diagnosis (e.g., HIV/AIDS)
- COD was evaluated using respective International Classification of Disease Codes (ICD)
- Allows SEER data to be used to estimate cause-specific survival
  - For more details: http://seer.cancer.gov/causespecific/index.html

Cases with Non-Hodgkin Lymphoma (Sequence 00)

Five-year NHL cancer survival by age at diagnosis, SEER-13, 1992-2004
100+ Cancer Sites in SEER, Age 65+


<table>
<thead>
<tr>
<th></th>
<th>White</th>
<th>AI/AN</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Relative</td>
<td>C-S</td>
<td>Diff</td>
<td>Relative</td>
<td>C-S</td>
</tr>
<tr>
<td>Breast, In-situ &amp; 65+</td>
<td>107.5</td>
<td>96.6</td>
<td>8.9</td>
<td>95.8</td>
<td>99.0</td>
</tr>
<tr>
<td>Prostate, L/R &amp; 65+</td>
<td>104.5</td>
<td>94.8</td>
<td>9.8</td>
<td>87.4</td>
<td>91.3</td>
</tr>
<tr>
<td>Lung, All Stage &amp; &lt;65</td>
<td>18.7</td>
<td>20.5</td>
<td>-1.8</td>
<td>16.7</td>
<td>19.7</td>
</tr>
<tr>
<td>Oral Cavity, All Stage &amp; &lt; 65</td>
<td>67.2</td>
<td>71.6</td>
<td>-4.4</td>
<td>51.6</td>
<td>58.0</td>
</tr>
</tbody>
</table>

AI/AN = American Indian/Alaska Native
C-S = Cause-specific
L/R=Localized Regional
Relative survival is the preferred method to estimate survival from cancer registry data.
- Does not rely on cause of death
- Adjusts for background mortality
- Assumes expected survival represents other-cause mortality for cancer patients

Cause-specific survival is the best method when it is believed that life tables do not represent the background mortality of the study.

Examples:
- Cancers with common risk factors with other diseases (smoking and lung cancer)
- Healthy screening effect (breast and prostate cancer), geographical differences
- Special populations

EXAMPLES
### All-Cause Survival: Life table for 244,647 women diagnosed with localized breast cancer

<table>
<thead>
<tr>
<th>Start</th>
<th>Died</th>
<th>Follow-up</th>
<th>Adjusted Start</th>
<th>Adjusted</th>
<th>Observed Start</th>
<th>Observed Interval</th>
<th>SE Obs</th>
<th>SE Obs</th>
<th>SE Obs</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1 yr</td>
<td>244,647</td>
<td>3,842</td>
<td>2,271</td>
<td>243,511.50</td>
<td>98.40%</td>
<td>98.40%</td>
<td>0.00%</td>
<td>0.00%</td>
<td></td>
</tr>
<tr>
<td>1-&lt;2 yr</td>
<td>238,534</td>
<td>5,028</td>
<td>28,183</td>
<td>224,442.50</td>
<td>97.80%</td>
<td>96.20%</td>
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<td>0.00%</td>
<td></td>
</tr>
<tr>
<td>2-&lt;3 yr</td>
<td>205,323</td>
<td>5,124</td>
<td>26,972</td>
<td>191,837.00</td>
<td>97.30%</td>
<td>93.80%</td>
<td>0.00%</td>
<td>0.10%</td>
<td></td>
</tr>
<tr>
<td>3-&lt;4 yr</td>
<td>173,227</td>
<td>4,501</td>
<td>25,172</td>
<td>160,641.00</td>
<td>97.20%</td>
<td>91.00%</td>
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<td>0.10%</td>
<td></td>
</tr>
<tr>
<td>4-&lt;5 yr</td>
<td>143,554</td>
<td>3,854</td>
<td>23,712</td>
<td>131,688.00</td>
<td>97.10%</td>
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<tr>
<td>5-&lt;6 yr</td>
<td>115,988</td>
<td>3,206</td>
<td>23,054</td>
<td>104,461.00</td>
<td>96.90%</td>
<td>85.60%</td>
<td>0.10%</td>
<td>0.10%</td>
<td></td>
</tr>
<tr>
<td>6-&lt;7 yr</td>
<td>89,728</td>
<td>2,489</td>
<td>21,678</td>
<td>78,889.00</td>
<td>96.80%</td>
<td>82.90%</td>
<td>0.10%</td>
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<td></td>
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<tr>
<td>7-&lt;8 yr</td>
<td>65,561</td>
<td>1,801</td>
<td>22,052</td>
<td>54,535.00</td>
<td>96.70%</td>
<td>80.20%</td>
<td>0.10%</td>
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<tr>
<td>8-&lt;9 yr</td>
<td>41,708</td>
<td>1,128</td>
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<td>9-&lt;10 yr</td>
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<td>9,980.50</td>
<td>96.50%</td>
<td>74.60%</td>
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Median survival time (interval = 12 months): Observed is greater than 10 intervals; Relative is greater than 10 intervals.

Confidence interval: Log(-Log()) Transformation. The level is 95%.

Actuarial method.

5-year all-cause survival is 88.4% and 10-year 74.6%.

### Relative Survival for 244,647 women diagnosed with localized breast cancer

<table>
<thead>
<tr>
<th>Died of Lost to</th>
<th>Alive at Breast</th>
<th>Adjusted</th>
<th>Observed</th>
<th>Observed Cumulative</th>
<th>Expected</th>
<th>Expected Cumulative</th>
<th>Relative Cumulative</th>
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<td>9,981</td>
<td>96.5%</td>
<td>74.6%</td>
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Median survival time (interval = 12 months): Observed is greater than 10 intervals; Relative is greater than 10 intervals.

Confidence interval: Log(-Log()) Transformation. The level is 95%.

Actuarial method. Ederer II method used for cumulative expected.
Cancer-Specific Survival: Life table for 243,778 women diagnosed with localized breast cancer

<table>
<thead>
<tr>
<th>Interval</th>
<th>Alive at start</th>
<th>Died of Breast Cancer</th>
<th>Lost to follow-up</th>
<th>Adjusted Alive</th>
<th>Cause-Specific Interval</th>
<th>Cause-Specific Cumulative</th>
<th>SE Cause-Specific Interval</th>
<th>SE Cause-Specific Cumulative</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1 yr</td>
<td>243,778</td>
<td>1,198</td>
<td>4,835</td>
<td>241,360.5</td>
<td>99.5%</td>
<td>99.5%</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>1-&lt;2 yr</td>
<td>237,745</td>
<td>1,921</td>
<td>31,200</td>
<td>222,145.0</td>
<td>99.1%</td>
<td>98.6%</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>2-&lt;3 yr</td>
<td>204,624</td>
<td>1,992</td>
<td>30,007</td>
<td>189,620.5</td>
<td>98.9%</td>
<td>97.6%</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>3-&lt;4 yr</td>
<td>172,625</td>
<td>1,664</td>
<td>27,909</td>
<td>158,670.5</td>
<td>99.0%</td>
<td>96.6%</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>4-&lt;5 yr</td>
<td>143,052</td>
<td>1,275</td>
<td>26,180</td>
<td>129,962.0</td>
<td>99.0%</td>
<td>95.6%</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>5-&lt;6 yr</td>
<td>115,597</td>
<td>931</td>
<td>25,226</td>
<td>102,984.0</td>
<td>99.1%</td>
<td>94.8%</td>
<td>0.0%</td>
<td>0.1%</td>
</tr>
<tr>
<td>6-&lt;7 yr</td>
<td>89,440</td>
<td>636</td>
<td>23,437</td>
<td>77,721.5</td>
<td>99.2%</td>
<td>94.0%</td>
<td>0.0%</td>
<td>0.1%</td>
</tr>
<tr>
<td>7-&lt;8 yr</td>
<td>65,367</td>
<td>440</td>
<td>23,347</td>
<td>53,693.5</td>
<td>99.2%</td>
<td>93.2%</td>
<td>0.0%</td>
<td>0.1%</td>
</tr>
<tr>
<td>8-&lt;9 yr</td>
<td>41,580</td>
<td>247</td>
<td>21,762</td>
<td>30,699.0</td>
<td>99.2%</td>
<td>92.5%</td>
<td>0.1%</td>
<td>0.1%</td>
</tr>
<tr>
<td>9-&lt;10 yr</td>
<td>19,571</td>
<td>72</td>
<td>19,499</td>
<td>9,821.5</td>
<td>99.3%</td>
<td>91.8%</td>
<td>0.1%</td>
<td>0.1%</td>
</tr>
</tbody>
</table>

Median survival time (interval = 12 months): Observed is greater than 10 intervals.
Confidence interval: Log( Log()) Transformation. The level is 95%.
Actuarial method.

All-cause survival vs. Cancer-specific survival

➢ The two cohorts were slightly different because women with unknown cause of death were excluded from cancer-specific survival (243,778 vs. 244,647)

➢ 5-year all cause survival, relative and cause-specific survival were respectively, 88.4%, 98.4%, and 95.6%.

➢ Among women diagnosed with breast cancer a higher percent die of other causes of death than breast cancer
OTHER CALCULATIONS AND METHODS

Conditional Survival

Calculate cumulative survival from any pre-defined conditioning points. E.g., probability of surviving 5 additional years, given you have already survived 1, 2, 3, 4, or 5 years from diagnosis.

13-72 (months): Given you have survived into the 13th interval (one complete year of survival), what is the probability you survive through the 72nd (5 additional years)
Kaplan-Meier and Actuarial Method

- Kaplan-Meier method
  - Continuous survival time.

- Actuarial method (Life-table method)
  - Grouped survival time. Data is grouped within interval of fixed length.
  - Ties are more likely.
  - Assumes that lost to follow up (withdrawals) occur randomly throughout the interval, and will occur, on average, halfway between each interval, if the sample size is large.

- Calculations done at 1-month interval with output generally summarized at 12 months.

- Practically negligible differences.

PRODUCING UP-TO-DATE SURVIVAL ESTIMATES
To obtain more up-to-date estimates of recently diagnosed patients.

Grouping survival experience with respect to year of diagnosis and follow-up:

- Cohort: uses the observed survival for a cohort of patients diagnosed in a single calendar year.
- Multiple-year cohort: includes all patients diagnosed in the most recent years spanning the maximum duration to be estimated.
- Period: uses only the most recent interval survival estimate of cases diagnosed in different calendar years (cross-sectional estimate of survival).

**Observed Survival by Year of Follow-up and Year of Diagnosis**

*Stage II Female Breast Cancer, 2005-2009, SEER 18 Registries*

Interval (i.e. conditional) survival probabilities by year of follow-up (t) and year of diagnosis (y)

<table>
<thead>
<tr>
<th>Year of Follow-Up</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-year</td>
<td>97.9%</td>
<td>98.2%</td>
<td>97.9%</td>
<td>98.1%</td>
<td>97.9%</td>
</tr>
<tr>
<td>2-year</td>
<td>96.8%</td>
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<td>96.9%</td>
<td>97.0%</td>
<td></td>
</tr>
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Observed Survival by Year of Follow-up and Year of Diagnosis
Stage II Female Breast Cancer, 2005-2009, SEER 18 Registries

Interval (i.e. conditional) survival probabilities by year of follow-up (t) and year of diagnosis (y)

### Cohort

<table>
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<th>2005</th>
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<th>2007</th>
<th>2008</th>
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### Multiple Year

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84.8% Observed Survival

85.2% Observed Survival
### Observed Survival by Year of Follow-up and Year of Diagnosis

**Stage II Female Breast Cancer, 2005-2009, SEER 18 Registries**

Interval (i.e. conditional) survival probabilities by year of follow-up (t) and year of diagnosis (y)

<table>
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</tbody>
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**Year of Diagnosis**

- **Cohort**
  - Multiple Year
  - Period

**References**

I will now do a live demonstration with the SEER*Stat software