Incidence-based Mortality Method to Partition Tumor-Specific Mortality Trends: Application to Non-Hodgkin Lymphoma Cancer

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Overview
How much do specific NHL subtypes contribute to this trend in mortality?

Source: National Center for Health Statistics (NCHS Mortality, U.S.)
NHL = Non-Hodgkin Lymphoma
Background
Non-Hodgkin Lymphoma (NHL)

• Heterogeneous group of cancer malignancies
  o Arises from lymphoid tissue and has varied clinical and biological features

• NHL has many subtypes
  o Based on cell type

• Main subtypes are derived from either B-cell or T-cell

• Three main B-cell subtypes:
  o Diffuse large B-cell lymphoma (DLBCL)
  o Follicular
    o Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL)

• Common T-cell subtype:
  o Peripheral T-cell lymphoma (PTCL)
Non-Hodgkin Lymphoma (NHL)

- Together these 4 subtypes represent ~70% of NHL cases
  - 29% DLBCL
  - 15% Follicular
  - 22% CLL/SLL
  - 4% PTCL

NHL Incidence and Mortality Trends

• Hypothesized that NHL mortality trends vary by tumor subtypes

  o Incidence and survival trends vary by tumor subtypes
  
  o Treatments improved in some subtypes but not all

  o 1980s HIV epidemic contributed to the NHL incidence trends
Study Aims
Study Aims

• Assess contributions of population-level NHL mortality attributed to each main NHL subtypes over time

• Assess contributions of long term incidence and survival patterns to trends in mortality by tumor subtypes over time
Methods
Methods

• Incidence-based mortality method (IBM)

• Adult (age 20+) NHL cases diagnosed in SEER-9 areas (1975-2011)

• Four main NHL subtypes (based on WHO classification)

• NHL cases of only or first invasive cancer for appropriate mapping of causes of death (COD)

• Excluded death certificate or autopsy
### Mortality versus IBM

<table>
<thead>
<tr>
<th>Mortality</th>
<th>Incidence-based Mortality (IBM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCHS Mortality</td>
<td>SEER Incidence cases linked with NCHS Mortality</td>
</tr>
<tr>
<td>Entire US</td>
<td>SEER (e.g., SEER-9 covers 9% of the US population)</td>
</tr>
<tr>
<td>Deaths from 1950+</td>
<td>Deaths from cases diagnosed 1975+</td>
</tr>
<tr>
<td>By sex, age at death, year at death, geography</td>
<td>By factors related to cancer diagnosis (e.g., histology, stage at diagnosis, biomarkers)</td>
</tr>
<tr>
<td>Complete mortality over any period of time</td>
<td>Complete mortality depends on aggressiveness of the tumor</td>
</tr>
</tbody>
</table>
Example: Mortality versus IBM

[Graph showing trends]

IBM Method: NHL 4 Main Subtypes

- Incidence-based mortality (IBM)

  \[
  \text{IBM rate} = \frac{\text{Death among SEER incident cases}}{\text{SEER Population at risk at the time of death}}
  \]

- COD\(^1\) included in IBM Rate
  - Hodgkin lymphoma, plasma cell, or leukemia in addition to NHL cancer deaths, if they linked to a SEER NHL case

- Require 15 years of data on incident cases prior to each year of mortality data

- Joinpoint to assess IBM trend changes over time

\(^1\) SEER COD recode for detail ICD codes: [http://seer.cancer.gov/codrecode/](http://seer.cancer.gov/codrecode/)
Methods: Incidence and Survival

• Age-adjusted incidence rates by 4 main subtypes over time (1975-2011)
  o Adjusted for reporting delay
  o Due to lack of specific coding, PTCL trends are presented over a shorter period of time

• Joinpoint to assess incidence trend changes over time

• Finally, calculated 5-year cancer-specific survival by 4 main subtypes over time (1975-2006)
Results
Overall NHL Mortality & IBM, SEER-9

A. Overall NHL Death

- Death Certificate Mortality
- Incidence-based Mortality

Age-adjusted rate per 100,000

Calendar Year of NHL Cancer Death


National Cancer Institute
Overall NHL Mortality & IBM Rates By Subtypes, SEER-9

A. Overall NHL Death

- Death Certificate Mortality
- Incidence-based Mortality

B. NHL Death By Tumor Subtypes

- DLBCL
- PTCL
- FL
- CLL/SLL

Calendar Year of NHL Cancer Death

Age-adjusted rate per 100,000

National Cancer Institute
Proportion of NHL Deaths by Subtypes. SEER-9, 2011*

<table>
<thead>
<tr>
<th>Subtypes</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>DLBCL</td>
<td>33</td>
</tr>
<tr>
<td>CLL/SLL</td>
<td>22</td>
</tr>
<tr>
<td>FL</td>
<td>11</td>
</tr>
<tr>
<td>PTCL</td>
<td>7</td>
</tr>
</tbody>
</table>

* Other NHL subtypes contributed 27% of deaths.
DLBCL: Incidence, IBM, & Survival Trends, SEER-9

![Graph showing observed and modeled incidence and survival rates for DLBCL.]

Percent surviving DLBCL cancer 5 years after diagnosis:

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</thead>
<tbody>
<tr>
<td>Rate</td>
<td>40%</td>
<td>45%</td>
<td>52%</td>
<td>51%</td>
<td>55%</td>
<td>67%</td>
</tr>
</tbody>
</table>
Follicular: Incidence, IBM, & Survival Trends, SEER-9

Percent surviving FL cancer 5 years after diagnosis

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<tr>
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<tbody>
<tr>
<td>1975</td>
<td>75%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1981</td>
<td></td>
<td>68%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1987</td>
<td></td>
<td></td>
<td>71%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1993</td>
<td></td>
<td></td>
<td></td>
<td>76%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1999</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>78%</td>
<td></td>
</tr>
<tr>
<td>2005</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>86%</td>
</tr>
</tbody>
</table>
CLL/SLL: Incidence, IBM, & Survival Trends, SEER-9

Percent surviving CLL/SLL cancer 5 years after diagnosis

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>%</td>
<td>69%</td>
<td>70%</td>
<td>74%</td>
<td>77%</td>
<td>76%</td>
<td>84%</td>
</tr>
</tbody>
</table>
PTCL: Incidence, IBM, & Survival Trends, SEER-9

Percent surviving PTCL cancer 5 years after diagnosis

<table>
<thead>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>65%</td>
<td>67%</td>
<td>64%</td>
</tr>
</tbody>
</table>
Conclusions
Conclusions

• Mortality trends from B-cell tumor subtypes (DLBCL, FL, CLL/SLL) decreased before incidence decreased

• Survival improvement due to novel therapy
  o Rituximab with CHOP (i.e., R-CHOP) for advanced stage disease among DLBCL and FL cases beginning 1998
  o Fludarabine, cyclophosmade, and rituximab among CLL cases in 1990s

• Mortality trends from PTCL remain unchanged
  o Need better treatment
Conclusions (Cont’d)

• Better diagnostic tool may explain some increase in incidence trends, but not all
  o Known risk factors (e.g., HIV/AIDS for DLBCL) may contribute to the trends

• Novel method to partition mortality by subtypes
  o Strength: address misclassifications in COD by use of broad definition of COD
  o Limitation: IBM rates could be underestimated due to under-ascertainment of hematologic cases (e.g., CLL) in registries

1 Penberthy L et al. Cancer Causes a & Control 2012
Conclusions (Cont’d)

- Survival benefit from these novel treatments were demonstrated in clinical trials
- First study to show large reduction in mortality in particular tumor subtypes at population level
- IBM methods should be valuable for assessing mortality trends for other tumor subtypes
More Information
“Contributions of Subtypes of Non-Hodgkin Lymphoma to Mortality Trends”. Manuscript under preparation

Next step to investigate how HIV epidemic contributed to subtype-specific mortality trends in US general population

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Useful Reference for IBM


• IBM tutorial in surveillance research program website: http://surveillance.cancer.gov/statistics/ibm/
Thank you!
Extra Slides
### IBM: Numerator Definition

<table>
<thead>
<tr>
<th>NCHS COD</th>
<th>NHL</th>
<th>Non-NHL</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHL</td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>Non-NHL</td>
<td>C</td>
<td>D</td>
</tr>
</tbody>
</table>

- **Cell A:** Contributes
- **Cell B: Does not contribute**
  - Breast cancer case die from NHL COD
- **Cell C: Does not contribute**
  - NHL case die from Non-NHL COD (e.g., heart disease)
- **Cell D: Does not contribute**
  - Lung cancer case die from lung cancer

NCHS = National Center for Health Statistics  
COD = Cause of Death
Number of Years Required for IBM to be within 10% Death Certificate Mortality

<table>
<thead>
<tr>
<th>Organ</th>
<th>Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain and central nervous system</td>
<td>3</td>
</tr>
<tr>
<td>Breast (female)</td>
<td>8</td>
</tr>
<tr>
<td>Colon, rectum</td>
<td>5</td>
</tr>
<tr>
<td>Kidney</td>
<td>4</td>
</tr>
<tr>
<td>Lung (males or females)</td>
<td>3</td>
</tr>
<tr>
<td>Mélanoma</td>
<td>10</td>
</tr>
<tr>
<td>Ovary</td>
<td>5</td>
</tr>
<tr>
<td>Prostate</td>
<td>8</td>
</tr>
<tr>
<td>Stomach</td>
<td>2</td>
</tr>
<tr>
<td>Thyroid</td>
<td>11</td>
</tr>
<tr>
<td>Uterus, corpus</td>
<td>6</td>
</tr>
</tbody>
</table>

Chu et al. J Clin Epi, 1994