Overview of today’s talk

- About me.
- Measures used in cancer control; why study patient survival?
- Intro to net/relative survival and why it is the measure of choice for estimating patient survival using registry data.
- 'Real-world' alternatives to net survival; crude survival.
- Communicating survival: to whom?
- Other measures (very briefly):
  - Proportion cured.
  - Loss in expectation of life.
  - Conditional survival.

About me

- Born in Sydney Australia; studied mathematics and statistics in Newcastle (Australia).
- Worked in health services research; dabbled in industrial process control and quality improvement.
- Arrived in Sweden November 1993 for a 10 month visit to cancer epidemiology unit at Radiumhemmet. Stayed in Sweden for most of my PhD.
- Short Postdoc periods at Finnish Cancer Registry and Karolinska Institutet (cancer epidemiology).
- Joined MEB in March 1999, attracted by the strong research environment and possibilities in register-based epidemiology.
A paradise for epidemiologists?

Hans-Olov Adami

For three reasons—the structure of its health system, the existence of nationwide registers, and the systematic use of national registration numbers—Sweden offers exceptional opportunities for epidemiological research.

- I would add ‘willingness of the public to contribute to research’.

My research interests

- Primary research interests are in the development and application of methods for population-based cancer survival analysis, particularly the estimation and modeling of relative survival.
- General interest in statistical aspects of the design, analysis, and reporting of epidemiological studies along with studies of disease aetiology, with particular focus on cancer epidemiology and perinatal/reproductive epidemiology.
- Collaborate closely with Paul Lambert (Biostatistician at University of Leicester) and Magnus Björkholm (Haematologist in Stockholm).

What do we mean by population-based?

- The term ‘population-based’ refers to the fact that we are estimating survival for all patients in a geographically-defined population (i.e., from a population-based cancer registry) rather than, for example, patients enrolled in a clinical trial.
- Population-based studies of patient survival provide a measure of the effectiveness of the health care system in diagnosing and treating those cancers that arise in the entire population.
- Note that this includes the efforts of the health care system in promoting public awareness of cancer and the importance of recognising symptoms and consulting a doctor when symptoms occur.
Measures used in cancer control

- The key measures are incidence, mortality, and survival.
- By 'mortality' we typically mean mortality in the population, whereas 'survival' is nothing more than mortality among those diagnosed with cancer (transformed to the mortality scale).
- We should not study any one of these three measures in isolation; in particular we should consider incidence trends when interpreting trends in patient survival [2, 3, 4].

International comparisons of survival are hot!

From a UK daily newspaper.
Based on data from the EUROCARE study.
Global surveillance of cancer survival 1995–2009: analysis of individual data for 25 676 887 patients from 279 population-based registries in 67 countries (CONCORD-2)


England compares themselves with the best [7]

Quantifying differences in breast cancer survival between England and Norway

**UK cancer survival statistics**

Are misleading and make survival look worse than it is.

- 'In the absence of internationally comparable data on breast cancer survival rates, it is of interest to compare the reliably known trends in population based mortality rates in middle age.'

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**Figure 11. Trends in incidence and mortality rates and 5-year relative survival proportions**

**Figure 11-J: Lung, trachea (ICD-10 C33–34)**

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**Cancer in Norway 2014**

Figure 11. Trends in incidence and mortality rates and 5-year relative survival proportions

Figure 11-J: Lung, trachea (ICD-10 C33–34)
Until primary prevention programmes succeed to the point of eradicating cancer, doctors must effectively diagnose and treat the cancers that arise and require a means of measuring progress in this specific area.

Patient survival rates provide such a measure whereas population mortality rates may not as they also reflect changes in incidence.

For example, lung cancer mortality rates are decreasing in many countries, not because we have become better at diagnosing and treating those individuals that develop lung cancer but because successful primary prevention has reduced lung cancer incidence.

How might we measure the prognosis of cancer patients?

- Total mortality (among the patients).
- Our interest is typically in net mortality (mortality associated with a diagnosis of cancer).
- Cause-specific mortality provides an estimate of net mortality (under certain assumptions).
- When estimating cause-specific mortality only those deaths which can be attributed to the cancer in question are considered to be events.

\[
\text{cause-specific mortality} = \frac{\text{number of deaths due to cancer}}{\text{person-time at risk}}
\]

The survival times of patients who die of causes other than cancer are censored.

Cause-specific survival can estimate net survival (assuming conditional independence)

- Using cause-specific methods requires that reliably coded information on cause of death is available.
- Even when cause of death information is available to the cancer registry via death certificates, it is often vague and difficult to determine whether or not cancer is the primary cause of death.
- How do we classify, for example, deaths due to treatment complications?
- Consider a patient treated with radiation therapy and chemotherapy who dies of cardiovascular disease. Do we classify this death as ‘due entirely to cancer’ or ‘due entirely to other causes’?
Relative survival aims to estimate net survival (still need conditional independence)

- We estimate excess mortality: the difference between observed (all-cause) and expected mortality.
  \[
  \text{excess} = \text{observed} - \text{expected} \quad \text{mortality} - \text{mortality} \quad \text{mortality}
  \]

- Relative survival is the survival analog of excess mortality — the relative survival ratio is defined as the observed survival in the patient group divided by the expected survival of a comparable group from the general population.
  \[
  \text{relative survival ratio} = \frac{\text{observed survival proportion}}{\text{expected survival proportion}}
  \]

Life table estimates of patient survival

Women diagnosed 1994 – 2001 with follow-up to the end of 2002

<table>
<thead>
<tr>
<th>I</th>
<th>N</th>
<th>D</th>
<th>W</th>
<th>Effective number at risk</th>
<th>Interval-specific observed survival</th>
<th>Interval-specific relative survival</th>
<th>Cumulative observed survival</th>
<th>Cumulative expected survival</th>
<th>Cumulative relative survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1559</td>
<td>209</td>
<td>0</td>
<td>1559</td>
<td>0.86594</td>
<td>0.86594</td>
<td>0.86594</td>
<td>0.98996</td>
<td>0.87472</td>
</tr>
<tr>
<td>2</td>
<td>1350</td>
<td>126</td>
<td>177</td>
<td>1261.5</td>
<td>0.90991</td>
<td>0.90829</td>
<td>0.78014</td>
<td>0.98192</td>
<td>0.79450</td>
</tr>
<tr>
<td>3</td>
<td>1048</td>
<td>58</td>
<td>172</td>
<td>962.0</td>
<td>0.93971</td>
<td>0.94772</td>
<td>0.73310</td>
<td>0.97362</td>
<td>0.75296</td>
</tr>
<tr>
<td>4</td>
<td>818</td>
<td>32</td>
<td>155</td>
<td>740.5</td>
<td>0.95679</td>
<td>0.96459</td>
<td>0.70412</td>
<td>0.96574</td>
<td>0.72630</td>
</tr>
<tr>
<td>5</td>
<td>631</td>
<td>23</td>
<td>148</td>
<td>577.0</td>
<td>0.95871</td>
<td>0.96679</td>
<td>0.67246</td>
<td>0.95766</td>
<td>0.70218</td>
</tr>
<tr>
<td>6</td>
<td>460</td>
<td>10</td>
<td>130</td>
<td>395.0</td>
<td>0.97468</td>
<td>0.98284</td>
<td>0.65543</td>
<td>0.94972</td>
<td>0.69013</td>
</tr>
<tr>
<td>7</td>
<td>320</td>
<td>5</td>
<td>129</td>
<td>265.5</td>
<td>0.98043</td>
<td>0.98848</td>
<td>0.64261</td>
<td>0.94198</td>
<td>0.68219</td>
</tr>
<tr>
<td>8</td>
<td>186</td>
<td>3</td>
<td>134</td>
<td>119.0</td>
<td>0.97479</td>
<td>0.98405</td>
<td>0.62641</td>
<td>0.93312</td>
<td>0.67130</td>
</tr>
<tr>
<td>9</td>
<td>49</td>
<td>1</td>
<td>48</td>
<td>25.0</td>
<td>0.96000</td>
<td>0.97508</td>
<td>0.60135</td>
<td>0.91869</td>
<td>0.65457</td>
</tr>
</tbody>
</table>
Should relative survival be used with lung cancer data?

Relative survival example (skin melanoma)

Table 1: Number of cases (N) and 5-year observed (p), expected (p*), and relative (r) survival for males diagnosed with localised skin melanoma in Finland during 1985–1994.

<table>
<thead>
<tr>
<th>Age</th>
<th>N</th>
<th>p</th>
<th>p*</th>
<th>r</th>
</tr>
</thead>
<tbody>
<tr>
<td>15–29</td>
<td>67</td>
<td>0.947</td>
<td>0.993</td>
<td>0.954</td>
</tr>
<tr>
<td>30–44</td>
<td>273</td>
<td>0.856</td>
<td>0.982</td>
<td>0.872</td>
</tr>
<tr>
<td>45–59</td>
<td>503</td>
<td>0.824</td>
<td>0.943</td>
<td>0.874</td>
</tr>
<tr>
<td>60–74</td>
<td>449</td>
<td>0.679</td>
<td>0.815</td>
<td>0.833</td>
</tr>
<tr>
<td>75+</td>
<td>200</td>
<td>0.396</td>
<td>0.505</td>
<td>0.784</td>
</tr>
</tbody>
</table>

- Relative survival controls for the fact that expected mortality depends on demographic characteristics (age, sex, etc.).
- In addition, relative survival may, and usually does, depend on such factors.

Examples of Relative Survival Being Problematic
(Extract from Table 4 from Howlader et al. [8])

<table>
<thead>
<tr>
<th>Selected cancer cohort</th>
<th>White</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RS, % (95% CI)</td>
<td>CSS, % (95% CI)</td>
<td>Dif., %</td>
</tr>
<tr>
<td>Breast</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In situ and &lt;65 y</td>
<td>100.9†</td>
<td>99.7 (99.6 to 99.8)</td>
<td>1.2</td>
</tr>
<tr>
<td>In situ and ≥65 y</td>
<td>107.5†</td>
<td>98.6 (98.4 to 98.8)</td>
<td>8.9</td>
</tr>
<tr>
<td>Prostate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Localized/regional and &lt;65 y</td>
<td>101.3†</td>
<td>98.3 (98.2 to 98.4)</td>
<td>3.0</td>
</tr>
<tr>
<td>Localized/regional and ≥65 y</td>
<td>104.5†</td>
<td>94.8 (94.6 to 94.9)</td>
<td>9.8</td>
</tr>
</tbody>
</table>

Relative survival not as problematic as one might think for lung cancer [9]

Should relative survival be used with lung cancer data?
Summary: the choice between relative and cause-specific survival for estimating net survival

- Both aim to estimate the same underlying quantity (net survival).
- Both methods involve assumptions specific to the approach:
  - **Cause-specific** Accurate classification of cause-of-death
  - **Relative** Appropriate estimation of expected survival
- We choose the approach for which we have the strongest belief in the underlying assumptions.
- For population-based studies this is typically relative survival but every study must be evaluated on its specific merits.

Net survival: colon cancer in Finland

Why the difference for older patients?
Cause-specific survival: colon cancer

- Coding of vital status
  - Freq. | Numeric | Label
  - 4642 | 0 | Alive
  - 8369 | 1 | Dead: colon cancer
  - 2549 | 2 | Dead: other

- The event of interest is death due to colon cancer.
- Other events are known as 'competing events' or 'competing risks'.
- Based on the research question, we choose between one of two quantities to estimate:
  - Eliminate the competing events (estimate net survival)
  - Accommodate the competing events (estimate crude survival)

We have a choice of two measures

Net probability of death due to cancer = Probability of death in a hypothetical world where the cancer under study is the only possible cause of death

Crude probability of death due to cancer = Probability of death in the real world where you may die of other causes before the cancer kills you

- Net probability also known as the marginal probability.
- Crude probability also known as cumulative incidence function.

Net (left) and crude (right) probabilities of death in men with localized prostate cancer aged 70+ at diagnosis (Cronin and Feuer [10])
Explaining net/relative survival to non-scientists

- Organisations that report survival statistics to the general public are often reluctant to describe relative/net survival in a technically correct manner.
- ‘Patients will not understand hypothetical world explanations’ they argue.
- I argue that, if that’s the case, one should report crude (real world) survival rather than estimate net survival and then describe it as something else.

www.cancerresearchuk.org [June 2014]

Net survival was estimated to be 50%.

Cancer survival statistics

- 50% of adult cancer patients diagnosed in 2010-2011 in England and Wales are predicted to survive 10 or more years.
- 46% of men and 54% of women cancer patients diagnosed in 2010-2011 in England and Wales are predicted to survive 10 or more years.
- Cancer survival rates in the UK have doubled in the last 40 years.

www.cancerresearchuk.org/cancer-info/cancerstats/survival/
What does a relative survival of 50% mean?


<table>
<thead>
<tr>
<th>Measure</th>
<th>Age 40</th>
<th>Age 60</th>
<th>Age 80</th>
</tr>
</thead>
<tbody>
<tr>
<td>Net prob. of death (1-rel surv)</td>
<td>0.50</td>
<td>0.50</td>
<td>0.50</td>
</tr>
<tr>
<td>Crude (actual): cancer death</td>
<td>0.49</td>
<td>0.48</td>
<td>0.42</td>
</tr>
<tr>
<td>Crude (actual): non-cancer death</td>
<td>0.02</td>
<td>0.08</td>
<td>0.42</td>
</tr>
<tr>
<td>Crude (actual): any cause death</td>
<td>0.51</td>
<td>0.57</td>
<td>0.84</td>
</tr>
</tbody>
</table>

Page has been updated [June 2015]

- Same data, new interpretation.
- An improvement, but vague.
- How will readers interpret ‘survive cancer’?
- I recognise the need to reduce technical jargon for a general audience.
- Not so for scientific journals.

Natural frequencies presented using infographics
On Estimation in Relative Survival

Maja Pohar Perme,1,2 Janez Stare,1 and Jacques Estève3

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SUMMARY. Estimation of relative survival has become the first and the most basic step when reporting cancer survival statistics. Standard estimators are in routine use by all cancer registries. However, it has been recently noted that these estimators do not provide information on cancer mortality that is independent of the national general population mortality. Thus they are not suitable for comparison between countries. Furthermore, the commonly used interpretation of the relative survival curve is vague and misleading. The present article attempts to remedy these basic problems. The population quantities of the traditional estimators are carefully described and their interpretation discussed. We then propose a new estimator of net survival probability that enables the desired comparability between countries. The new estimator requires no modeling and is accompanied with a straightforward variance estimate. The methods are described on real as well as simulated data.

KEY WORDS: Age standardization; Cancer registry data; Competing risks; Net survival; Relative survival; Survival analysis.
Statistical cure

- **Medical cure** occurs when all signs of cancer have been removed in a patient; this is an individual-level definition of cure.
- It is difficult to prove that a patient is medically cured.
- **Population or statistical cure** occurs when mortality among patients with the disease returns to the same level as that expected for the general population.
- Equivalently the excess mortality rate approaches zero.
- This is a population-level definition of cure.
- When the excess mortality reaches (and stays) at zero, the relative survival curve is seen to reach a plateau.

Plateau for relative survival

Cure models: Interpreting changes over time

(a) General Improvement
(b) Selective Improvement
(c) Improved palliative care or lead time
(d) Inclusion of subjects with no excess risk
Time trends for cancer of the colon age <50 [18]

Cure Fraction and Median Survival of 'Uncured'
Age Group: <50

Andersson 2010 [19]: trends for AML

Loss in expectation of life

- A useful summary measure of survival is the mean survival, life expectancy
- The loss in expectation of life is the difference between the mean expected survival (if not diagnosed with cancer) and the mean observed survival (for cancer patients)
- Quantify disease burden in the society "how many life-years are lost due to the disease?"
- Quantify differences between socio-economic groups or countries, "how many life-years are lost in the population due to differences in cancer patient survival between groups?"
- "how many life-years would be gained if England had the same cancer patient survival as Sweden?"
- Quantify the impact a cancer diagnosis has on a patient’s life expectancy
Expectation of life

Mean all cause survival 10.6 years

Loss in expectation of life

Mean all cause survival 10.6 years
Mean expected survival 15.3 years
Loss in Expectation of Life = 4.7 years
How do we extrapolate observed survival?

Technical details: recent/current research

- Even though we are now interested in the all-cause survival we will use a relative survival approach
  \[ S(t) = S^*(t) \times R(t) \]
  \[ h(t) = h^*(t) + \lambda(t) \]

- Easier to extrapolate \( R(t) \) than \( S(t) \)
- Has been done for grouped data (life tables) [20], by assuming \( \lambda(t) = 0 \) or \( \lambda(t) = c \) after some point in time.
- We estimate in the framework of flexible parametric models [21, 22].

Chronic myeloid leukaemia; Sweden

- Life expectancy of general population
- Life expectancy of cancer patients
Chronic myeloid leukaemia; Sweden

![Graph showing loss in expectation of life](image)

- **Males**
- **Females**

- **Age 55**
- **Age 65**
- **Age 75**
- **Age 85**

Loss in expectation of life over time for males and females with chronic myeloid leukaemia in Sweden.

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### References

References 2


References 3


References 4

