Reference adjusted and standardized all-cause and crude probabilities as an alternative to net survival in population-based cancer studies

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Population-based cancer survival

- Cancer registries attempt to capture all diagnosed cases of cancers.
- Our work is mainly in survival of those diagnosed with cancer.
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- Naive comparison of all-cause survival problematic because differences could be due to:
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  1. differences in cancer mortality rates.
  2. differences in other cause mortality rates.
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- We try to ‘isolate’ the mortality associated with the cancer and (age) standardize to ensure comparisons are ‘fair’.
Competing causes

- Individuals diagnosed with a specific cancer are at risk for:
  - dying from their cancer.
  - dying from other causes.
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So we estimate \(h_c(t|Z_i)\) without using cause of death information.
Incorporate expected mortality rates

All-cause mortality = expected mortality + excess mortality

In a perfect world $h_c(t|Z_i) = \lambda(t|Z_i)$.

The world is not perfect.

Transform to survival $S(t|Z_i) = S(t|Z_i)R(t|Z_i)$ hence 'relative survival'
Excess mortality/Relative survival

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Transform to survival

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S(t|Z_i) = S^*(t|Z_i)R(t|Z_i)
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\[
R(t|Z_i) = \frac{S(t|Z_i)}{S^*(t|Z_i)} \quad \text{hence ‘relative survival’}
\]
Marginal estimates

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\text{All-cause} = \text{Expected} \times \text{Relative}
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Marginal estimates

All-cause = Expected × Relative

\[ S(t|Z_i) = S^*(t|Z_i) \times R(t|Z_i) \]

- Estimand of interest is marginal relative survival.

\[ R_m(t|Z) = E_Z [R(t|Z)] \]

- Expectation is over distribution of \( Z \).
- Estimated in a model setting by,

\[ \bar{R}_m(t|Z) = \frac{1}{N} \sum_{i=1}^{N} \hat{R}(t|Z_i) \]

- Predict a survival curve for each of the \( N \) individuals and then average (see Syriopoulou et al. 2020 [1]).
Interpretation of relative/net survival

- We usually present age-standardized marginal relative survival.
- Interpretation as marginal net survival (under assumptions).

Survival in the **hypothetical** situation where...
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Many examples of the media, politicians, clinicians, patients and scientists interpreting incorrectly.

Fair Comparisons?

When comparing population subgroups we are interested in whether there are differences in cancer (excess) mortality rates. For Fair Comparisons differences between population groups should not depend on,

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- Differences in other cause mortality rates.
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2. Differences in other cause mortality rates.

This is the reason we estimate net survival.
Comparability

- When comparing two population groups the distribution of covariates $Z$ will be different.
- Compare $\bar{R}_m(t|X = 1, Z^1)$ and $\bar{R}_m(t|X = 0, Z^0)$

We need to marginalize over the same covariate distribution.

Options
1. Use combined distribution of $X = 1$ and $X = 0$.
2. Use covariate distribution when $X = 1$.
3. Use covariate distribution when $X = 0$.
4. Use external covariate distribution.

(4) is the most common (for age), but I will come back to alternatives.

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Reference adjusted measures

22 September 2020
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External weights

- Define a reference population with covariate distribution $Z^{REF}$.
- We weight individuals relative to this reference population.
- If we do this in both groups (studies) then differences will not be due to differential $Z$.

$$\tilde{R}_m(t|Z^{REF}) = \frac{1}{N} \sum_{i=1}^{N} w_i \hat{R}(t|Z_i)$$
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$$\bar{R}_m(t|Z^{REF}) = \frac{1}{N} \sum_{i=1}^{N} w_i \hat{R}(t|Z_i)$$

- A common example of this is age-standardization.
Age Standardization

Below are the International Cancer Survival Standard (ICSS) age groups.[4]

<table>
<thead>
<tr>
<th>Age</th>
<th>ICSS 1</th>
<th>ICSS 2</th>
<th>ICSS 3</th>
</tr>
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<tbody>
<tr>
<td>15-44 years</td>
<td>0.07</td>
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<td>0.60</td>
</tr>
<tr>
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- L: Lip, tongue, salivary glands, oral cavity, oropharynx, hypopharynx, head and neck, oesophagus, stomach, small intestine, colon, rectum, liver, biliary tract, pancreas, nasal cavities, larynx, lung, pleura, breast, corpus uteri, ovary, vagina and vulva, penis, bladder, kidney, choroid melanoma, non-Hodgkin lymphoma, multiple myeloma, chronic lymphatic leukaemia, acute myeloid leukaemia, chronic myeloid leukaemia, leukaemia, prostate

- N: Nasopharynx, soft tissues, melanoma, cervix uteri, brain, thyroid gland, bone

- H: Testis, Hodgkin lymphoma, acute lymphatic leukaemia
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Below are the International Cancer Survival Standard (ICSS) age groups[4].

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Obtaining weights

\[ w_i^s \] proportion in age group in reference population to which the \( i^{th} \) individual belongs.

\[ w_i^a \] proportion in the age group in the study population to which the \( i^{th} \) individual belongs.

\[ w_i = \frac{w_i^s}{w_i^a} \]
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<th>ICSSwt</th>
<th>w_a</th>
<th>wt</th>
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<tbody>
<tr>
<td>&lt;45</td>
<td>0.280</td>
<td>0.274</td>
<td>1.020</td>
</tr>
<tr>
<td>45-54</td>
<td>0.170</td>
<td>0.164</td>
<td>1.039</td>
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Example

- Men diagnosed in England with Melanoma.
- Compare 5 deprivation groups derived using national quintiles of the income domain of the area of patients’ residence at diagnosis.
- Simplify here to comparison of most deprived vs least deprived.
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Model

- Flexible parametric relative survival model [5].
- Restricted cubic splines (rcs) with 6 knots for baseline.
- Age modelled continuously using rcs (4 knots).
- Deprivation binary covariate.
- Interactions between age and deprivation.
- Effects of age and deprivation time-dependent (4 knots per covariate).
Marginal Net Probability of Survival

![Graph showing marginal net probability of survival over time for 'Least Deprived' and 'Most Deprived' groups. The x-axis represents years from diagnosis, ranging from 0 to 10, and the y-axis represents net/relative survival, ranging from 0.6 to 1.0. The graph includes two lines: a blue line for 'Least Deprived' and a red line for 'Most Deprived', with shaded areas indicating the range of adjusted measures. The graph also includes a note about age standardization and fair comparison.]
Marginal Net Probability of Death
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Age Standardization: Internal (within each group)
Fair Comparison: X
Marginal Net Probability of Death

Age Standardization: ICSS
Fair Comparison: ✓

Years from diagnosis

Net Probability of Death

Least Deprived
Most Deprived
Comparing Probabilities of death

(1) Net probability of death (1 - net survival)

Probability of death in hypothetical world where not possible to die from causes other than the cancer under study.
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Age standardization for (1), (2) & (3) removes age differences.

However, (2) and (3) depend on other cause mortality.
Crude Probabilities

- Same as a cumulative incidence function in competing risks.
- Partition all-cause probability of death into death to cancer and death due to other causes

**All-cause probability of death**

\[ F(t|Z_i) = 1 - S(t|Z_i) \]

All-cause = prob cancer + prob other cause death

prob of death death
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\[ F(t|Z_i) = F_c(t|Z_i) + F_o(t|Z_i) \]
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**Crude Probability of Death**

\[ F_c(t|Z) = \int_0^t S^*(u|Z) \hat{R}(u|Z) \hat{\lambda}(u|Z_i) du \]
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Can we make them comparable?
Making all-cause and crude survival comparable

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![Diagram showing the relationship between Expected Mortality, Net Probability, All-cause/Crude Probability](image-url)
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![Diagram showing the relationship between expected mortality, net probability, all-cause/crude probability, and reference-adjusted measures.](image)
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## All-cause probability of death

### Reference Population

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Reference Population

\( S^{**}(t|Z_i) \) - expected survival in the reference population.
\( h^{**}(t|Z_i) \) - expected mortality rate in the reference population.

Marginal all-cause survival (study population)

\[
\bar{S}_m(t|Z, X = x) = \frac{1}{N} \sum_{i=1}^{N} S^*(t|Z_i, X = x) \hat{R}(t|Z_i, X = x)
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All-cause probability of death

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**Using reference expected rates.**

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$$
Crude Probabilities of death due to cancer

- Crude probability of death due to cancer (study population).

\[
\bar{F}_{c}(t | Z) = \frac{1}{N} \sum_{i=1}^{N} w_i \int_{0}^{t} S^*(u | Z_i) \hat{R}(u | Z_i) \hat{\lambda}(u | Z_i) du
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Note if \( S^*(t | Z_i) = 1 \) for all \( Z_i \), this reduces to \( 1 - \bar{R}(t | Z_i) \).
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Fair Comparison:

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Net Probability of Death

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Choice of Hypotheticals

### Net Probability of Death

1. Age distribution is that of reference.
2. Mortality rate due to other causes is zero

### All-cause/Crude Probability of Death

1. Age distribution is that of reference.
2. Mortality rate due to other causes is that of reference.

In some situations it is useful to select one group to be non-hypothetical.
- Standardize to age distribution of selected group.
- Use expected mortality rates of selected group.
Age Standardization: Internal (within each group)
Expected Rates: Separate
Fair Comparison: ×
Crude Probability of Death

Age Standardization: Most Deprived
Expected Rates: Most Deprived
Fair Comparison: ✔️
Contrasts

Age Standardization: Internal (within each group)
Expected Rates: Separate
Fair Comparison: ×
Contrasts

Age Standardization: ICSS
Expected Rates: English combined
Fair Comparison: ✓
Contrasts

Age Standardization: Most Deprived
Expected Rates: Most Deprived
Fair Comparison: ✔
We have a choice when making comparisons

- We want to compare probabilities of survival/death
- Need to ‘remove’ differences due to other causes.
- We can do this by

1. Assume rate of death due to other causes is the same in both groups and is equal to zero for all ages (net probability).
2. Assume rate of death due to other causes is the same in both groups and is equal to a reference population (reference adjusted all-cause or crude probability).
We have a choice when making comparisons

- We want to compare probabilities of survival/death
- Need to ‘remove’ differences due to other causes.
- We can do this by

1. Assume rate of death due to other causes is the same in both groups and is equal to zero for all ages (net probability).
2. Assume rate of death due to other causes is the same in both groups and is equal to a reference population (reference adjusted all-cause or crude probability).
   
   1. Using a common external reference population
   2. Using one of the groups as the reference.
Possible to make fair comparisons using all-cause or crude probabilities.
- Need to (age) standardize
- Need to use reference expected mortality rates.

Useful alternative/complement to marginal net survival.

I have explained from a modelling perspective - non-parametric possible. Builds on work by Sasieni and Brentnall 20016 ([7])

Modelling more generalisable.

Ideas also work for competing risks models (‘separable effects’).

Need to think about which covariate distribution to standardize over.

Need to think which reference expected rates to use.
Software

- All analysis in Stata.
- `standsurv` works for many parametric models
  - Exponential, Weibull, Gompertz, LogNormal, LogLogistic
  - Flexible parametric (Splines: log-hazard or log cumulative scales)
- Standard, relative survival and competing risks models
  - Can use different models for different causes.
- Various Standardized related measures.
  - Survival, restricted means, centiles, hazards... and more
- Standard errors calculated using delta-method or M-estimation with all analytical derivatives, so fast

More information on `standsurv` available at
https://pclambert.net/software/standsurv/
Reference-adjusted and standardized all-cause and crude probabilities as an alternative to net survival in population-based cancer studies

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References


