Reference-adjusted cancer survival measures. What are they, when are they useful, and how are they implemented in Stata?

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(with thanks to other co-authors on various papers)

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Background

- We want to make fair comparisons of prognosis across population groups.
- I'll focus on population-based cancer survival - but the ideas are fairly general.
- I'll focus on survival-based metrics.
- Ideally, we don't want differences in risks of other outcomes impacting on our metrics for our disease of interest.
- Often population groups who are unequal in terms of cancer survival also have different competing risks due to other causes (e.g. deprivation groups).
- Groups could be age, socioeconomic class, regions, countries, calendar periods...

Prognosis across groups

Why might there be differences in all-cause survival between two groups?

1. Differences in disease-specific mortality rates.
2. Differences in other-cause mortality rates.
3. Differences in age (or other covariate) distribution.

Prognosis across groups - How do we typically solve them now?

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This makes pretty hypothetical metrics. Should we do better for some/all purposes? These net, standardised metrics are also often accessible on more patient-focussed material...

Net vs crude measures - Colon cancer, England

Reference-adjusted cancer survival measures

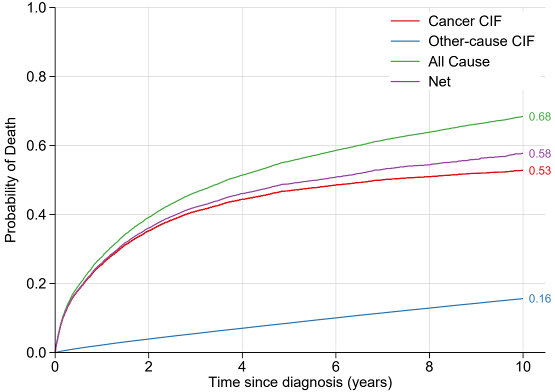
Motivation

Excess Mortality/Relative Survival

Reference Adjustment

Discussion

References



Probability of death from any cause. For every 1000 people diagnosed with colon cancer, 10 years after diagnosis 680 will have died (from any cause). This includes deaths from cancer and other causes.

Net vs crude measures - Colon cancer, England

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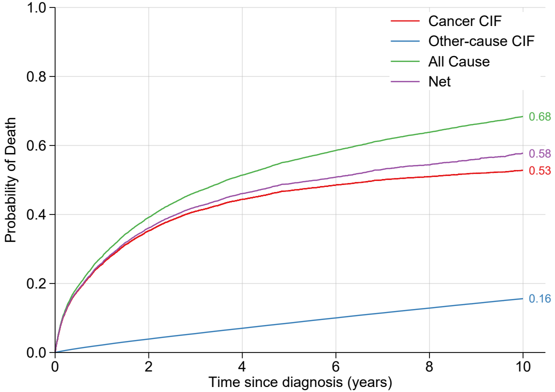
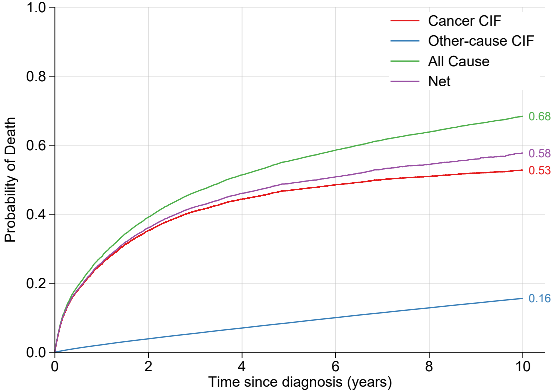


Probability of death due to cancer. For every 1000 people diagnosed with colon cancer, 10 years after diagnosis 530 will have died due to their cancer (160 will have died from other causes).

Net vs crude measures - Colon cancer, England



Net probability of death due to cancer. For every 1000 people diagnosed with colon cancer, 10 years after diagnosis 580 will have died due to their cancer... **if** it was *impossible* to die from anything else other than colon cancer.

Example of survival statistics on Cancer Research UK website... Bowel Cancer link

Survival for all stages of bowel cancer

Generally for people with bowel cancer in England:

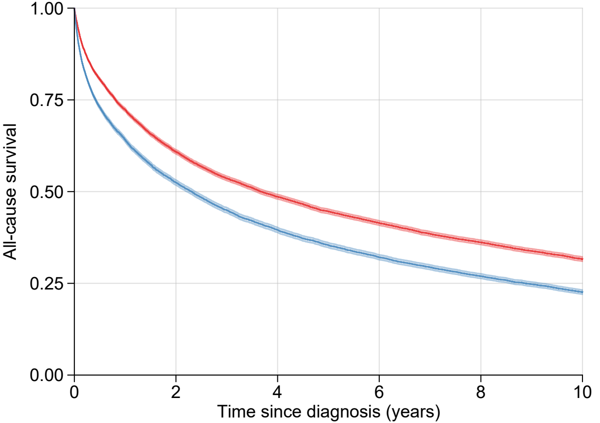
- almost 80 out of 100 people (almost 80%) survive their cancer for 1 year or more
- almost 60 out of 100 people (almost 60%) survive their cancer for 5 years or more
- almost 55 out of 100 people (almost 55%) survive their cancer for 10 years or more

These are net survival metrics.

- But is it clear they are not all-cause survival metrics?
- Is it clear that these are not relating to the probabilities of death due to cancer alone?

Our Example: All-cause survival (Kaplan-Meier) by Deprivation Groups - Colon cancer

We'll focus mostly on the two most extreme groups (labelled Least & Most deprived) defined by an area-based measure (five groups).



N (deaths)											
Least deprived	14094	(5544)	8549	(1680)	6388	(920)	5119	(639)	4258	(522)	3173
Most deprived	10745	(5167)	5743	(1402)	4248	(801)	3423	(552)	2885	(460)	2167

Excess mortality/relative survival

We split the total hazard, $h_i(t)$, into component parts; that due to background mortality, $h_i^*(t)$, and the excess due to the disease, $\lambda_i(t)$.

$$h_i(t) = h_i^*(t) + \lambda_i(t) \tag{1}$$

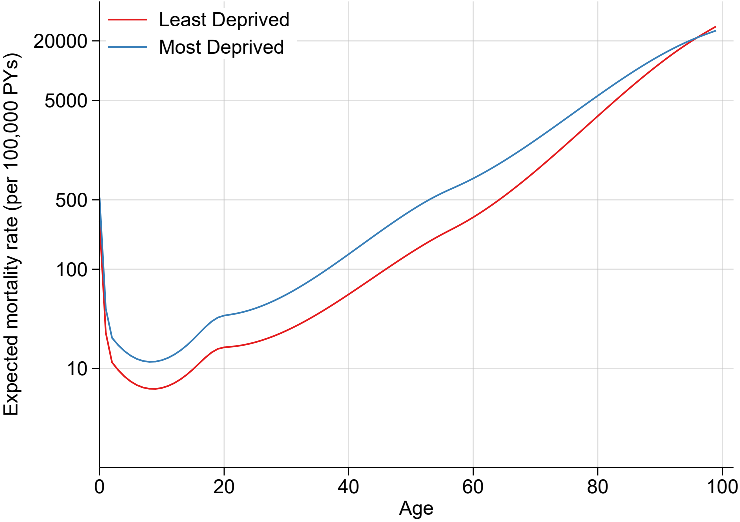
We convert to the survival scale:

$$S_i(t) = S_i^*(t) R_i(t) \tag{2}$$

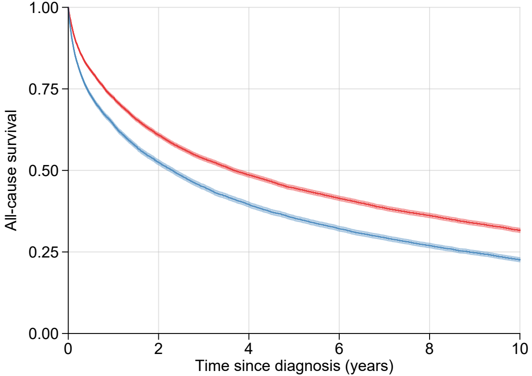
And see why it's called relative survival:

$$R_i(t) = \frac{S_i(t)}{S_i^*(t)} \tag{3}$$

Population mortality (expected rate - h_i^*) by deprivation group



Back to the Example: All-cause survival (Kaplan-Meier) by Deprivation Groups



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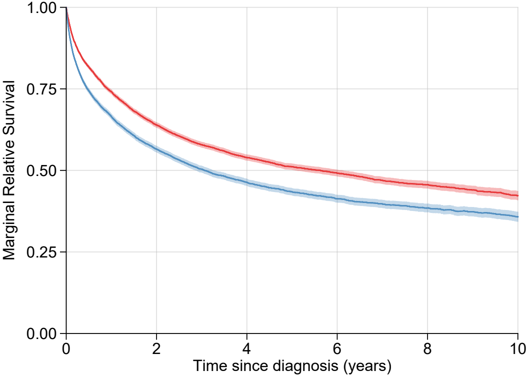
We can see large differences in all-cause survival between the two groups - but some likely driven by non-cancer differences. (`sts graph` in Stata)

Back to the Example: Net survival (Pohar Perme) by Deprivation Groups



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Slightly higher curves when moving to non-parametric net survival estimates. Less of a pronounced difference...
(`stpp` (user-written) in Stata.)

Code for non-parametric net survival estimates.

Code for stpp

```
 . stpp R_pp using popmort,                    ///
>       agediag(agediag) datediag(datediag) ///
>       pmage(age) pmyear(year)             ///
>       pmother(sex dep) by(dep)            ///
>       graphcode(stpp.do,replace) legend(off) allcause(KM)
File stpp.do has been created
```

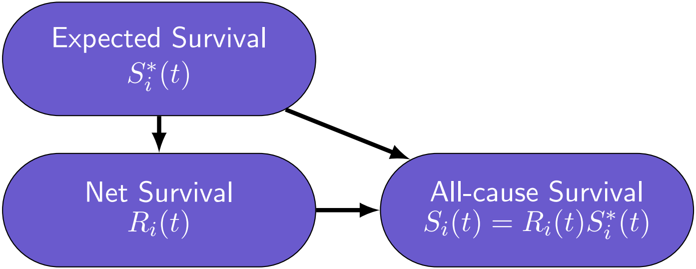
- With the `by` option we estimate the relative survival estimates separately by the deprivation groups.
- We need to give `stpp` the details of the expected mortality estimates - these are contained in the `popmort` file.
- Another key choice is standardising these to the same age distribution. This is possible by further extending the `stpp` code.

Reference Adjustment

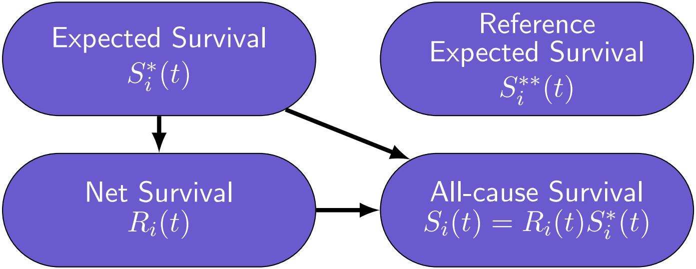
What is reference adjustment?

- The main idea is to estimate excess mortality in a standard way. But...
- ...when converting back to the "real-world" - we use a common, reference rate for general population mortality when comparing across groups.
- i.e. If we compare across Sweden and England - we use each separate population mortality model to estimate excess mortality as usual in each country. But...
- when we come back to the all-cause survival we use the **same** population rates for both countries when converting to the all-cause.
- What should that common population mortality file be?? - **Good question**.

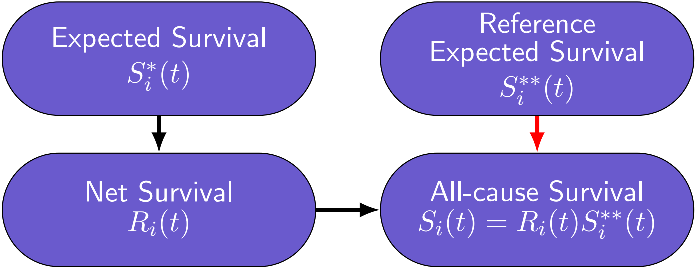
Reference adjustment



Reference adjustment

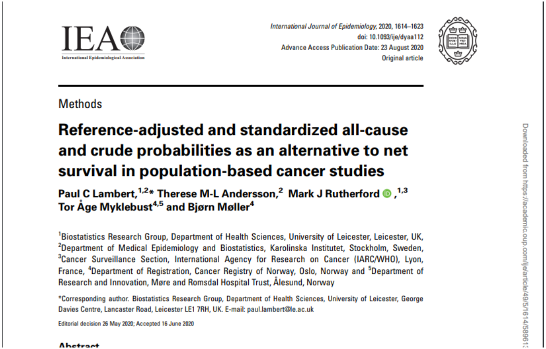


Reference adjustment



Papers on reference adjustment

Original methods paper in modelling framework (user-written `stpm3` in Stata) - discussing the approach as a method to obtaining all-cause survival probabilities (and cause-specific probabilities) that are fair.



IEA International Epidemiological Association

International Journal of Epidemiology, 2020, 1614–1623
doi: 10.1093/ije/dyaa112
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Original article

Methods

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

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Abstract

Papers on reference adjustment

Non-parametric equivalent (user-written `stpp` in Stata) - moving away from modelling alone - requires careful weighting.

Rutherford *et al.*
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BMC Medical Research Methodology

RESEARCH Open Access

Non-parametric estimation of reference adjusted, standardised probabilities of all-cause death and death due to cancer for population group comparisons

Mark J. Rutherford[1*], Therese M.-L. Andersson[2], Tor Åge Myklebust[3,4], Bjørn Møller[3] and Paul C. Lambert[1,2]

Abstract

Background: Ensuring fair comparisons of cancer survival statistics across population groups requires careful consideration of differential competing mortality due to other causes, and adjusting for imbalances over groups in other prognostic covariates (e.g. age). This has typically been achieved using comparisons of age-standardised net survival, with age standardisation addressing covariate imbalance, and the net estimates removing differences in competing mortality from other causes. However, these estimates lack ease of interpretability. In this paper, we motivate an alternative non-parametric approach that uses a common rate of other cause mortality across groups to give reference-adjusted estimates of the all-cause and cause-specific crude probability of death in contrast to solely reporting net survival estimates.

Papers on reference adjustment

Extension to life expectancy comparisons (and an applied comparison) - (again `stpm3` in Stata).

CANCER EPIDEMIOLOGY, BIOMARKERS & PREVENTION | RESEARCH ARTICLE

Reference-Adjusted Loss in Life Expectancy for Population-Based Cancer Patient Survival Comparisons—with an Application to Colon Cancer in Sweden

Therese M.-L. Andersson[1], Mark J. Rutherford[2], Bjørn Møller[3], Paul C. Lambert[1,2], and Tor Åge Myklebust[3]

ABSTRACT

Background: The loss in life expectancy, LLE, is defined as the difference in life expectancy between patients with cancer and that of the general population. It is a useful measure for summarizing the impact of a cancer diagnosis on an individual's life expectancy. However, it is less useful for making comparisons of cancer survival across groups or over time, because the LLE is influenced by both mortality due to cancer and other causes and the life expectancy in the general population.

Methods: We present an approach for making LLE estimates comparable across groups and over time by using reference expected mortality rates with flexible parametric relative survival models. The approach is illustrated by estimating temporal trends in LLE of patients with colon cancer in Sweden.

Results: The life expectancy of Swedish patients with colon cancer has improved, but the LLE has not decreased to the same extent because the life expectancy in the general population has also increased. When using a fixed population and other-cause mortality, that is, a reference-adjusted approach, the LLE decreases over time. For example, using 2010 mortality rates as the reference, the LLE for females diagnosed at age 65 decreased from 11.3 if diagnosed in 1976 to 7.2 if diagnosed in 2010, and from 3.9 to 1.9 years for women 85 years old at diagnosis.

Conclusions: The reference-adjusted LLE is useful for making comparisons across calendar time, or groups, because differences in other-cause mortality are removed.

Impact: The reference-adjusted approach enhances the use of LLE as a comparative measure.

Back to the example: Our model

- Is a relative survival (excess mortality) model, restricted to females.
- We merge in the other-cause mortality which varies by age, sex, deprivation quintile and calendar year.
- We fit a flexible parametric excess mortality model with sufficient complexity to parametrically capture the baseline hazard using splines.
- We model the effect of age on the excess mortality using splines, and include a categorical variable for deprivation.
- We allow a full interaction effect to allow the age effect to vary by deprivation group.
- We also allow non-proportional excess hazards by further spline functions.

Merging in expected mortality...

- The expected mortality at the time of death is required for the model-based approach.
- Make use of `stset` information to obtain attained age and calendar year.

merging in the population mortality rates

```
. stset dateexit, failure(dead==1) origin(datediag) id(patid)      ///
>       enter(time mdy(1,1,2007)) exit(time datediag+10.01*365.25) ///
>       scale(365.24)
  (output omitted)
.
. gen age = min(int(agediag+_t),99)
. gen year = year(datediag + _t*365.25)
(15,475 missing values generated)
.
. merge m:1 sex  year  age dep using popmort, ///
>       keep(match master) keepusing(rate)
  (output omitted)
    Result                      Number of obs
    -----------------------------------------
    Not matched                        15,475
        from master                    15,475  (_merge==1)
        from using                          0  (_merge==2)
    Matched                            37,379  (_merge==3)
    -----------------------------------------
```

Fitting the excess mortality model...

- `stpm3` fits flexible parametric survival models through using splines to model both the baseline log cumulative hazard and further spline functions to allow departures from the proportional hazards assumption for covariate effects.
- We use the expected mortality rate at the event time in the `bhazard()` option.
- `stpm3` allows us to directly model the effect of age with a natural spline through the extended function syntax - here `ns()`.

Fitting the excess mortality model with stpm3

```
. stpm3 i.dep##@ns(agediag, df(5)), df(5) scale(lncumhazard) ///
>        tvc(i.dep @ns(agediag,df(3))) dftvc(3) bhazard(rate)
```

(*output omitted*)

Predictions...

Let's predict the marginal survival for just those in the most deprived group (N_{D5}) - so we'll standardise to their covariate profile.

For deprivation group 1:

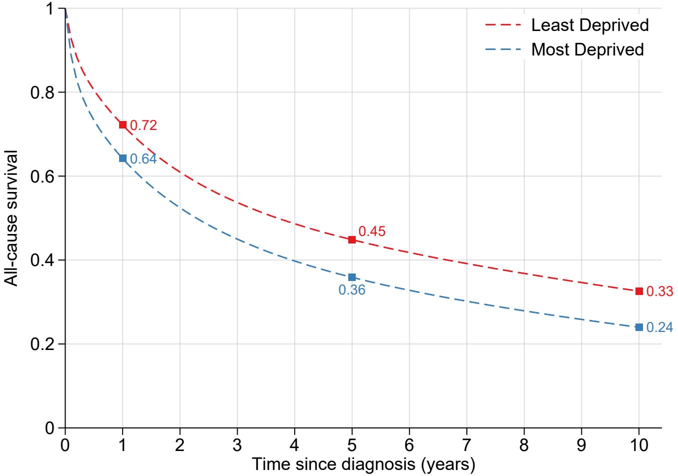
$$\bar{S}_1(t) = \frac{1}{N_{D5}} \sum_{i=1}^{N_{D5}} R_1(t|age) S_1^*(t|age)$$

For deprivation group 5:

$$\bar{S}_5(t) = \frac{1}{N_{D5}} \sum_{i=1}^{N_{D5}} R_5(t|age) S_5^*(t|age)$$

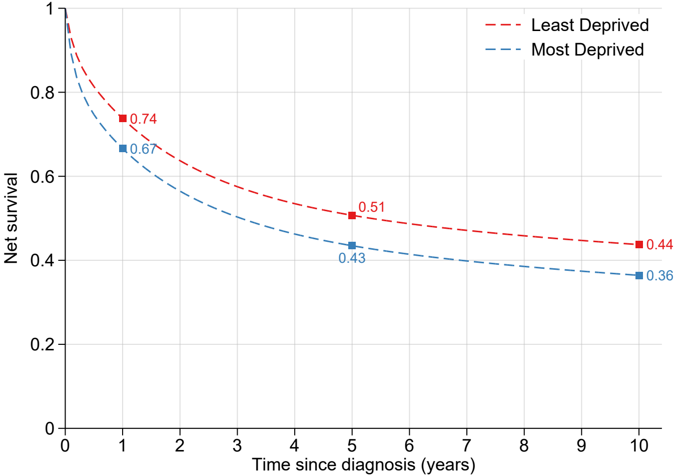
All-cause survival (model-based)

For GROUP 1: $\frac{1}{N_{D5}} \sum_{i=1}^{N_{D5}} R_1(t|age) S_1^*(t|age)$



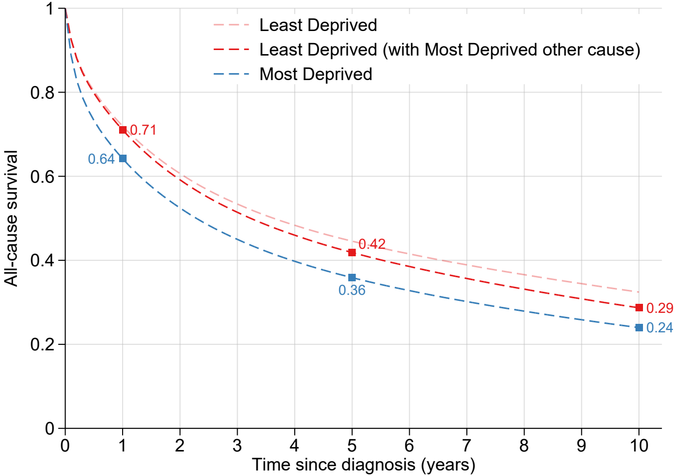
These are the model-based estimates of the all-cause survival and we can now start to intervene in different ways.

Net survival (model-based)
For GROUP 1: $\frac{1}{N_{D5}} \sum_{i=1}^{N_{D5}} R_1(t|age)$



We remove the chance of dying of other-causes to make a fairer comparison of cancer impact. A hypothetical...

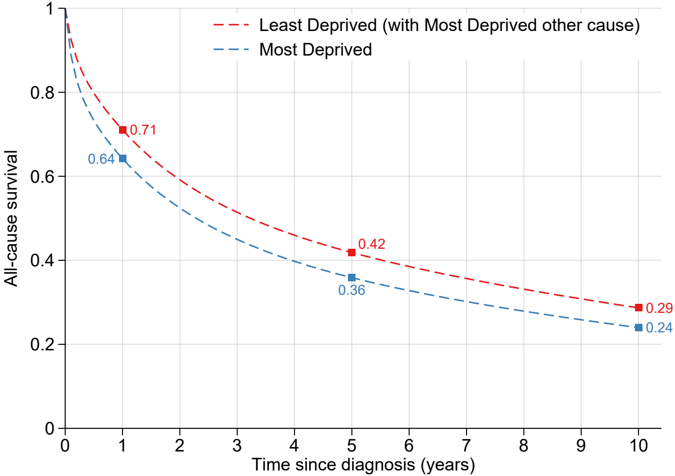
What if only cancer deprivation differences? - all-cause survival. We use reference rates for both



We fix the other-cause mortality from the lifetable to that of the Most Deprived for both groups? A new hypothetical...

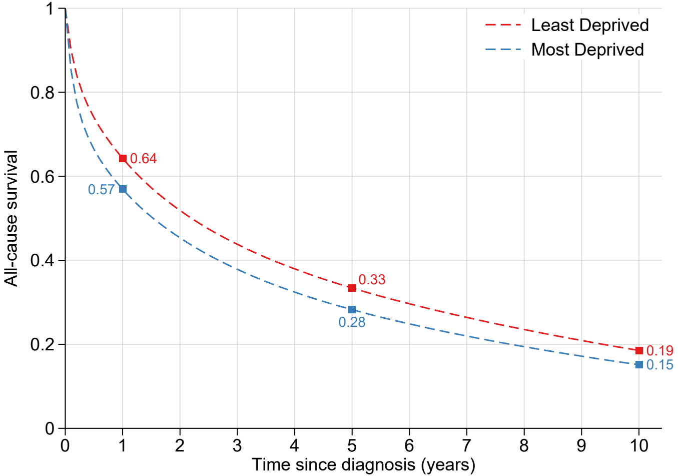
Cancer inequity isolated - all-cause survival

For GROUP 1: $\frac{1}{N_{D5}} \sum_{i=1}^{N_{D5}} R_1(t|age) S_5^*(t|age)$



Use these survival measures to calculate the number of deaths that could be avoided by removing cancer-specific inequities.

Cancer inequity isolated - all-cause survival: Age 70+ only



Can still explore the effect in any subgroups of interest for covariates we have modelled...

Example of code for marginal predictions

Code for standsurv after stpm3

```
. standsurv dep1_marg_exp_d5 if dep==5 & _t0==0, at1(dep 1) ///
>           timevar(timevar)                                ///
>           expsurv(using(popmort) pmage(age) pmrate(rate)  ///
>           pmyear(year) pmother(sex dep)                   ///
>           agediag(agediag) datediag(dx)                   ///
>           at1(dep 5) pmmaxyear(2016))
```

- Here we predict the all-cause survival estimates from the excess mortality model.
- We predict for the least deprived group (`at1(dep 1)`) for the relative survival part.
- But introduce the other cause mortality of the most deprived group (`at1(dep 5)` in the `expsurv` option) .

Discussion

- We isolate the disparities due to the disease of interest (through the relative survival/excess mortality framework).
- However, when reporting, moving back to real-world metrics is perhaps beneficial for interpretation.
- To do so, we need to use a common reference expected mortality rate to make sure the estimates only reflect differences in cancer-specific mortality differences.
- Could extend the ideas to a general competing risks framework when using cause of death information.
- The choice of reference standard is key - and will depend on the purpose of the analysis/comparison.
- Another key choice is the age (and other covariate) distribution to standardise to when making comparisons.

Selected References

P. Royston. and P. C. Lambert.
Flexible Parametric Survival Analysis Using Stata: Beyond the Cox Model
StataCorp LP, 2011.

P.C. Lambert *et al.*
Reference-adjusted and standardized all-cause and crude probabilities as an alternative to net survival in population-based cancer studies.
International Journal of Epidemiology, **49** *(5) 1614–1623, 2020. doi: 10.1093/ije/dyaa112*

M.J Rutherford *et al.*
Non-parametric estimation of reference adjusted, standardised probabilities of all-cause death and death due to cancer for population group comparisons
BMC Medical Research Methodology, **22** *(2), 2022. doi: 10.1186/s12874-021-01465-w*

T. M-L. Andersson *et al.*
Reference-Adjusted Loss in Life Expectancy for Population-Based Cancer Patient Survival Comparisons-with an Application to Colon Cancer in Sweden.
Cancer Epidemiol Biomarkers Prev., **31** *(9) 1720-1726, 2022. doi: 10.1158/1055-9965.EPI-22-0137*

P. Sasieni and A. R. Brentnall.
On Standardised Relative Survival.
Biometrics, 2016. doi: 10.1111/biom.12578

Questions/Thoughts?

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