Reference-adjusted cancer survival in population-based cancer studies

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Population-based cancer survival

- Cancer registries attempt to capture all diagnosed cases of cancer.
- Used for monitoring cancer incidence, mortality and survival.
- Ability to link with other data (e.g. treatment, hospital episodes, primary care, social information) makes cancer registry data a crucial research tool.
- Our work is mainly in **survival** of those diagnosed with cancer.
- I will be talking about descriptive measures today, used for comparisions between ....
  - Calendar periods, countries or regions, sex, socio-economic groups etc
- Many ideas for descriptive studies carry over to causal analyses.

Competing causes

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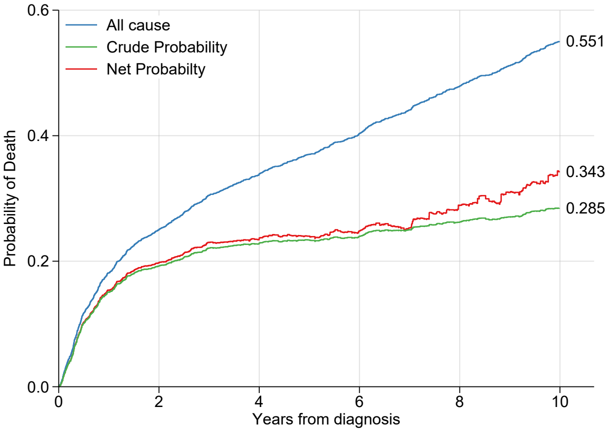
$$h(t|Z_i) = h_o(t|Z_i) + h_c(t|Z_i)$$

- I will explain later how we try to avoid using cause of death information, but first I will consider different probabilities we could measure.

Different probabilities: Bladder Cancer (Women)



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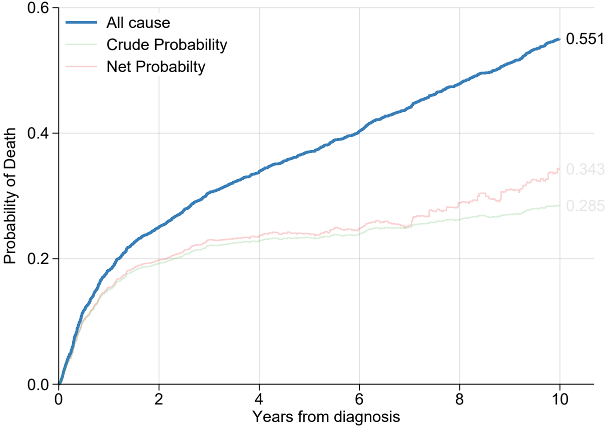

Probability of death from any cause. For every 1000 women diagnosed with bladder cancer, 10 years after diagnosis 551 will have died (from any cause).

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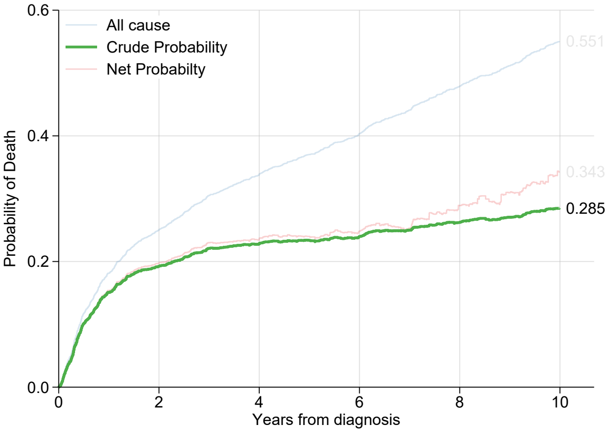

Probability of death due to cancer. For every 1000 women diagnosed with bladder cancer, 10 years after diagnosis 285 will have died due to their cancer (266 will have died from other causes).

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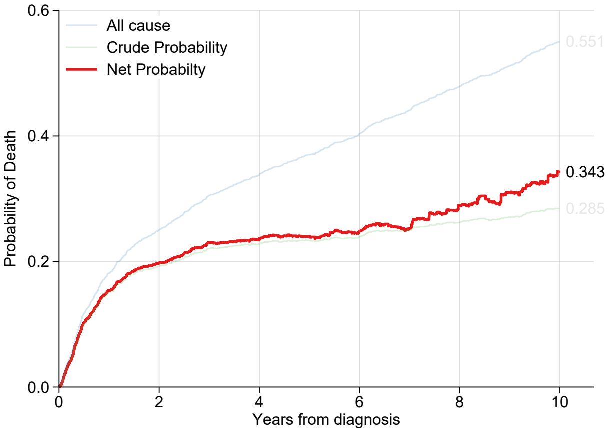

Net probability of death due to cancer. For every 1000 women diagnosed with bladder cancer, 10 years after diagnosis 343 will have died due to their cancer,

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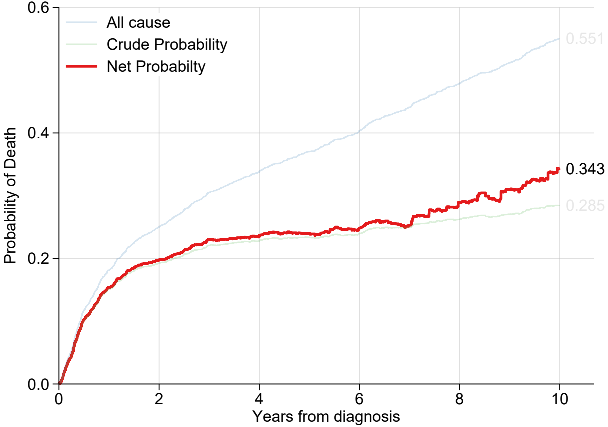

Net probability of death due to cancer. For every 1000 women diagnosed with bladder cancer, 10 years after diagnosis 343 will have died due to their cancer, if it was impossible to die from anything else other than bladder cancer.

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So we estimate $h_c(t|Z_i)$ without using cause of death information.

Excess mortality/Relative survival

Incorporate expected mortality rates

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Relative Survival

$$S(t|Z_i) = S^*(t|Z_i)R(t|Z_i), \qquad R(t|Z_i) = \frac{S(t|Z_i)}{S^*(t|Z_i)}$$

Marginal estimates

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- Estimand of interest is marginal relative survival.

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

- Expectation is over distribution of Z.
- Can do this,
  - Non-parametrically[1].
  - Fit regression model and then use regression standardization[2].
  - Marginal regression model [3].

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Comparability

- When comparing two population groups the distribution of covariates Z will be different.
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- We need to marginalize over the same covariate distribution.
  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.

Warnings of using cause-specific (net) survival?

- Lots of warnings about cause-specific survival in competing risks
  - You should "*Stick this world*" [4]
  - Relies on untestable assumptions.
- However, net survival (estimated in relative survival framework) continues to be used.

Why is net survival used?

- We want to compare population groups.
- These may differ both in cancer mortality rates and other cause mortality rates.
- Attempts to *isolate* the cancer mortality rates by “removing” differences in other cause mortality rates.
- If we compare all cause or crude probabilities of death, then any differences could be due to a combination of differential cancer mortality and other cause mortality rates.
- Desire to present survival rather than hazard rates.

Problems with net survival

Examples from selected National Statistics Offices / National Cancer Charities.

- *“Chance of being alive.”*
- *“Chance of surviving compared to their counterparts in the general population.”*
- *“Probability of surviving your cancer.”*
- *“The probability of surviving cancer adjusted other causes of death.”*

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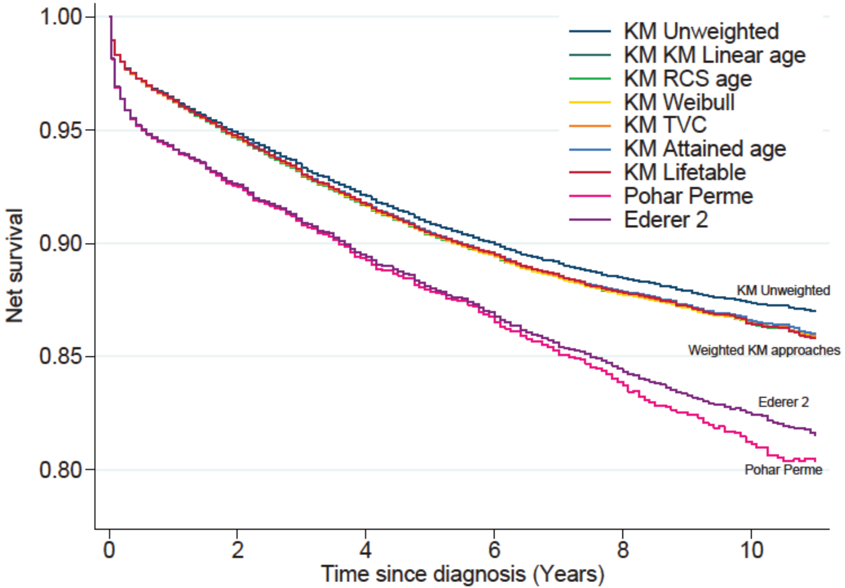
- *"The probability of surviving cancer adjusted other causes of death."* The fact that estimates are often age standardized to an external population complicates interpretation further.

Cause-specific vs relative survival[5]



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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.
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Model

- Flexible parametric relative survival model [6].
- Natural splines with 6 knots for baseline.
- Age modelled continuously using natural splines (4 knots).
- Deprivation binary covariate.
- interactions between age and deprivation.
- Effects of age and deprivation time-dependent (natural splines 4 knots per covariate).

Marginal estimates using regression standardization

- From our regression model we can predict the relative survival function, $\widehat{R}(t|Z_i)$, for an individual with covariate pattern Z_i.
- We take the average of these predictions to get the marginal estimate.

$$\bar{R}_m(t|Z, X = x) = \frac{1}{N}\sum_{i=1}^{N} \widehat{R}(t|Z_i, X = x)$$

- We often want to standardize to an external population (usually just age) and can do this by introducing weights, w_i.

$$\bar{R}_m(t|Z, X = x) = \frac{1}{N}\sum_{i=1}^{N} w_i \widehat{R}(t|Z_i, X = x)$$

Standardization of crude and all cause probabilities

Marginal all-cause survival

$$\bar{S}_m(t|\mathbf{Z}, \mathbf{X} = x) = \frac{1}{N}\sum_{i=1}^{N} w_i S^*(t|\mathbf{Z}_i, \mathbf{X} = x)\widehat{R}(t|\mathbf{Z}_i, \mathbf{X} = x)$$

Marginal crude probability of death

$$\bar{F}_c(t|\mathbf{Z}, \mathbf{X} = x) = \frac{1}{N}\sum_{i=1}^{N} w_i \int_0^t S^*(u|\mathbf{Z}_i, \mathbf{X} = x)\widehat{R}(u|\mathbf{Z}_i, \mathbf{X} = x)\widehat{\lambda}(u|\mathbf{Z}_i, \mathbf{X} = x)du$$

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Age standardization

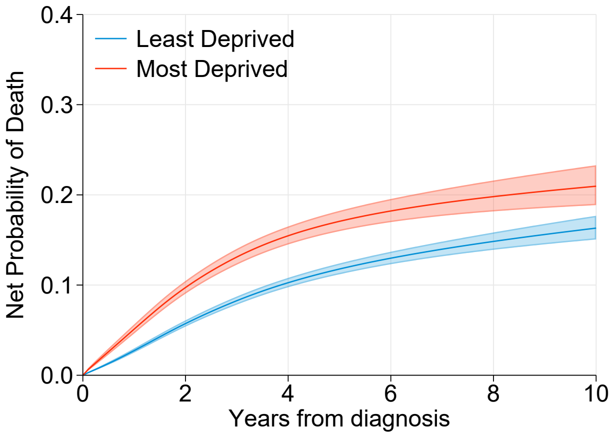
- Below of are the International Cancer Survival Standard (ICSS) age groups[7].

Age	ICSS 1[a]	ICSS 2[b]	ICSS 3[c]
15-44 years	0.07	0.28	0.60
45-54 years	0.12	0.17	0.10
55-64 years	0.23	0.21	0.10
65-74 years	0.29	0.20	0.10
75+ years	0.29	0.14	0.10

[a] 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
[b] Nasopharynx, soft tissues, melanoma, cervix uteri, brain, thyroid gland, bone

[c] Testis, Hodgkin lymphoma, acute lymphatic leukaemia

Net Probability of Death



Age Standardization: Internal (within each group)
Fair Comparison: ✗

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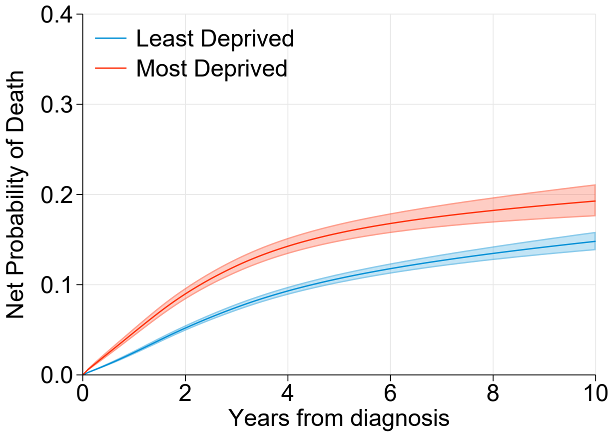

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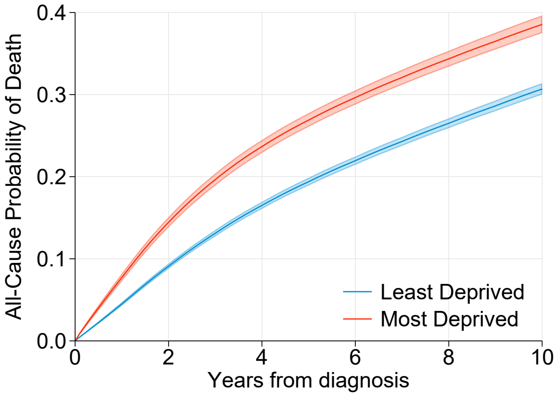
All cause probability of death



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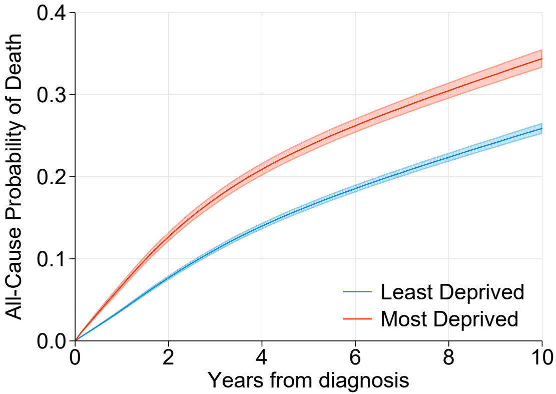

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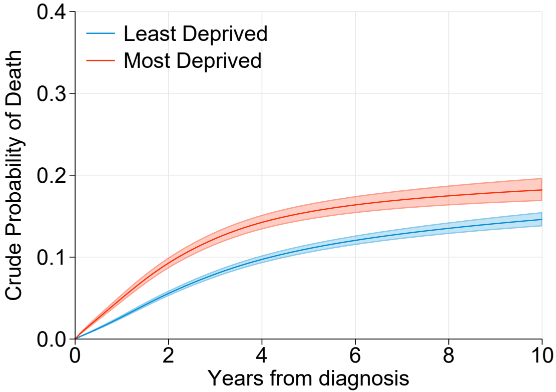
Crude probability of death



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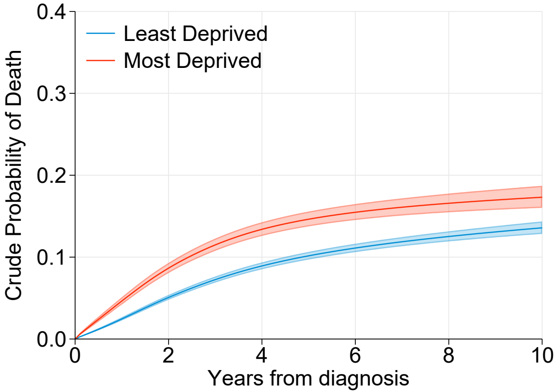

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Making all-cause and crude survival comparable

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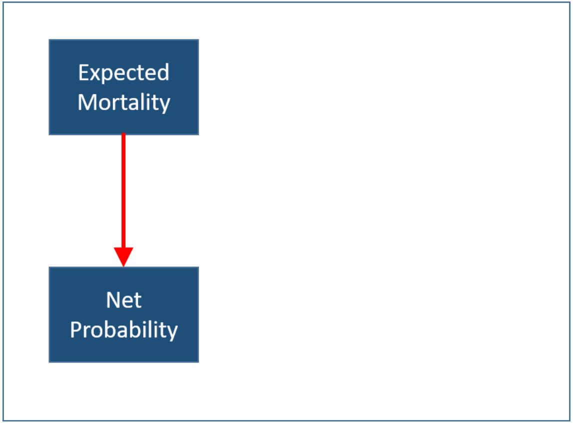

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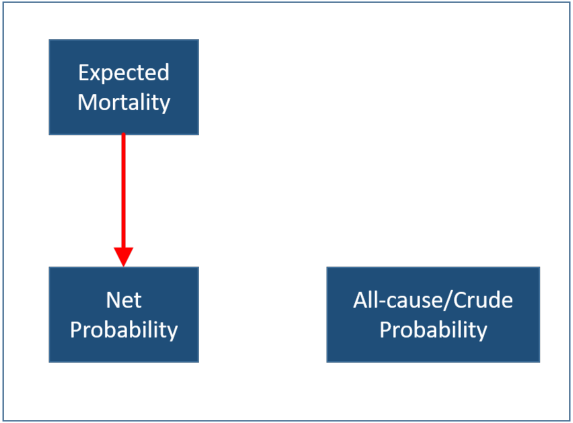

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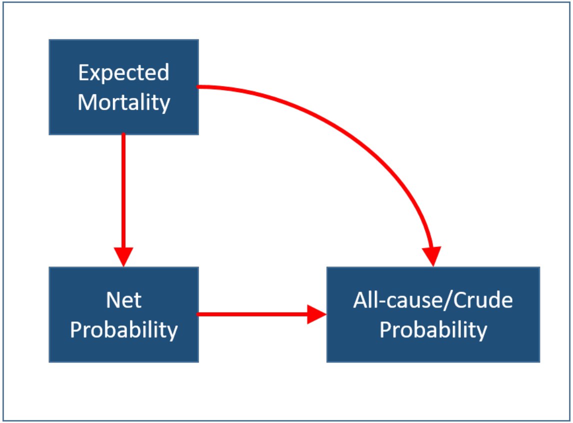

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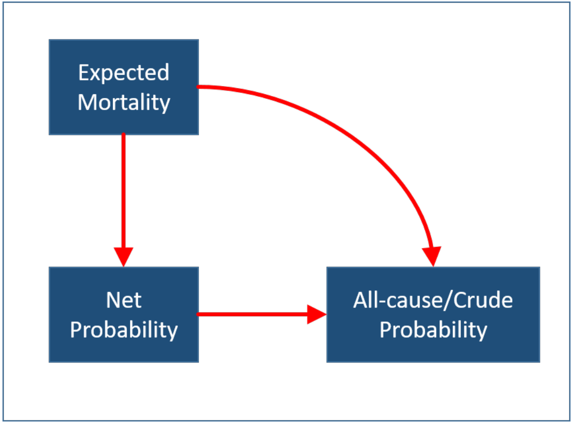

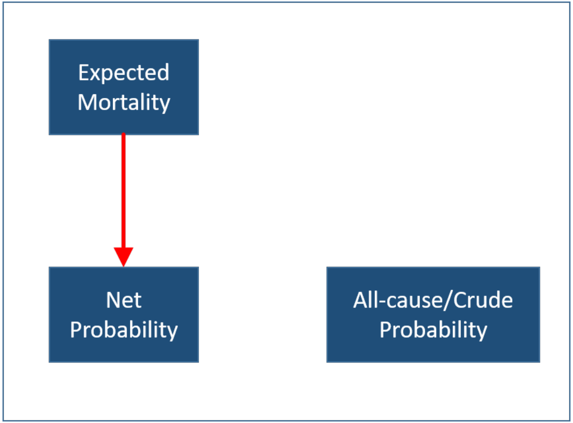

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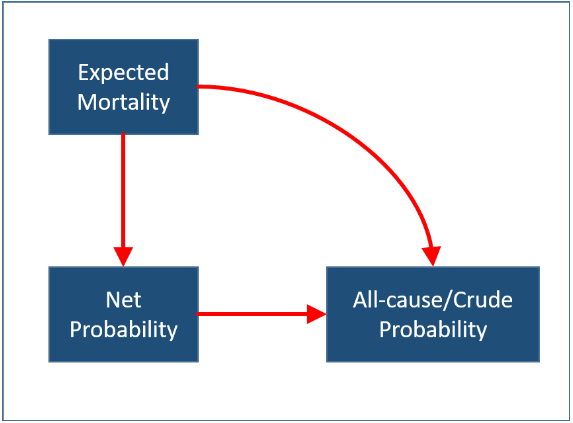

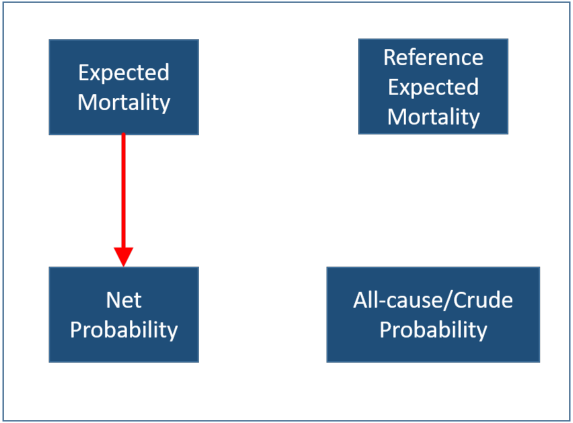

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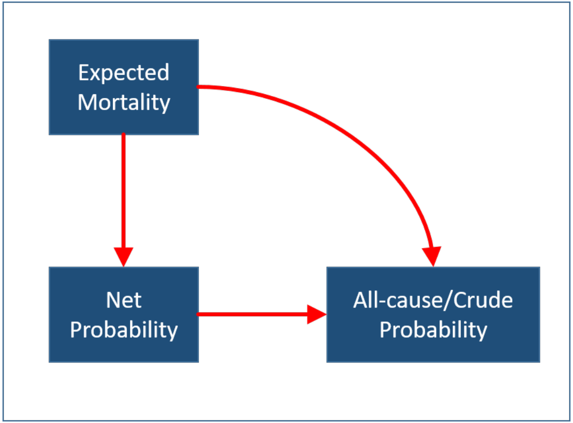

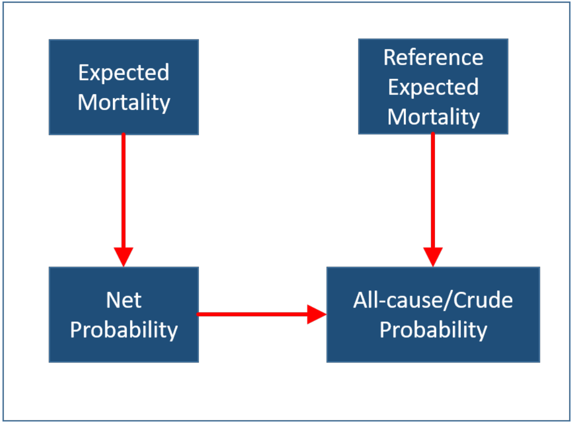

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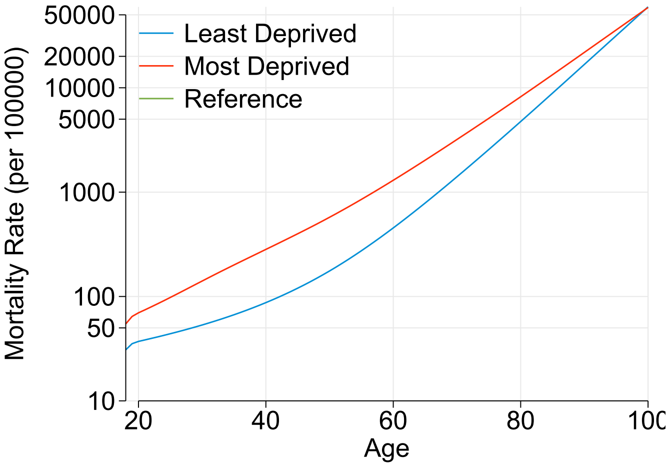
Reference expected mortality rates



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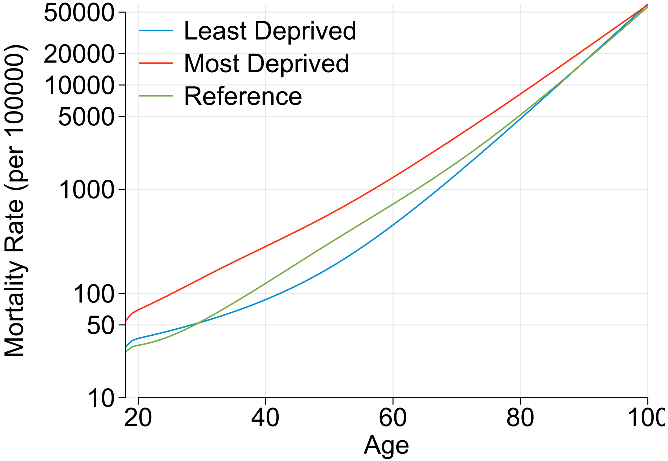

- The reference is the mortality rate for males in England in 2016.

All-cause probability of death

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Crude Probabilities of death due to cancer

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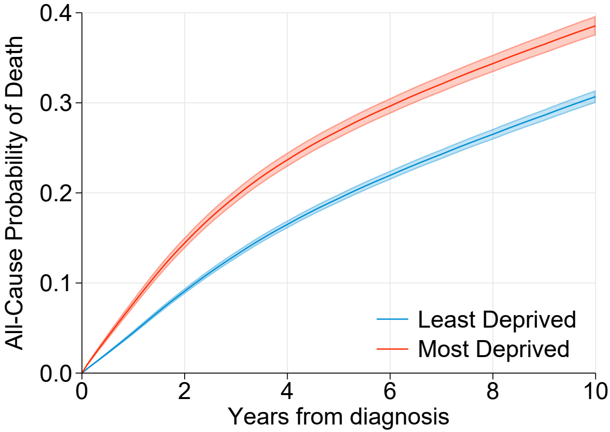
Note if $S^{**}(t|Z_i) = 1$ for all Z_i, this reduces to $1 - \bar{R}_m(t|Z)$.

All-cause Probability of Death



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

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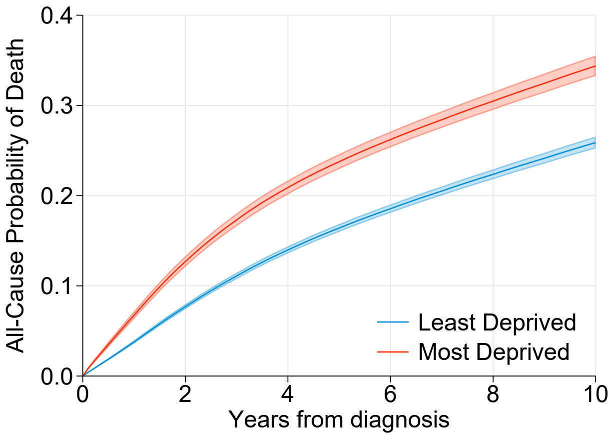

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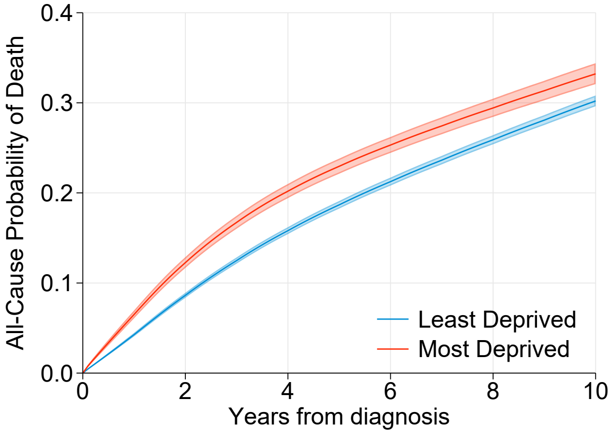

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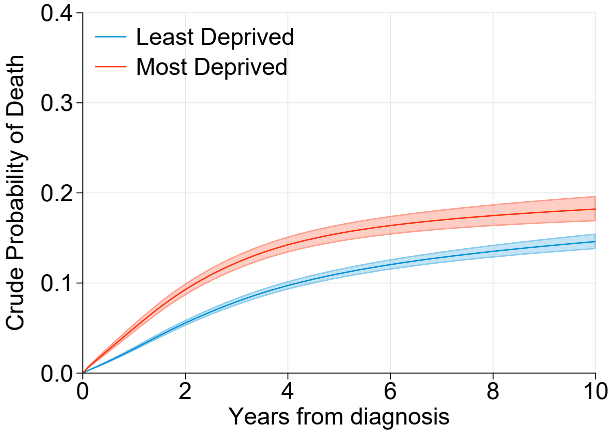

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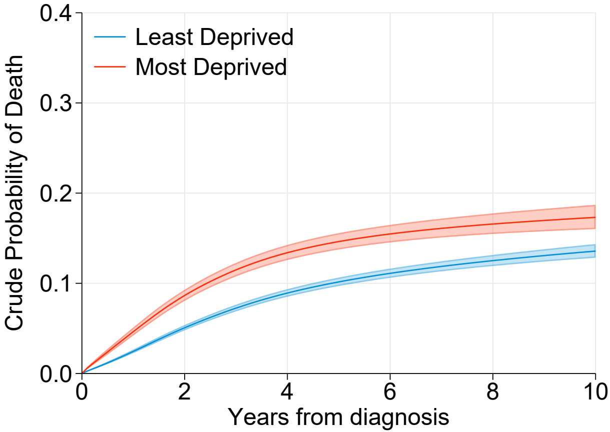

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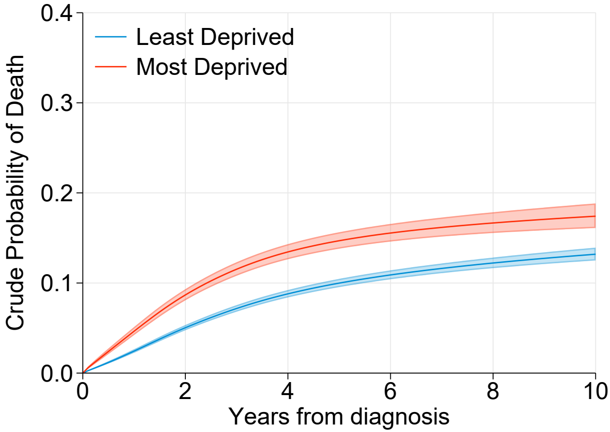
Fair Comparison: ✗

Crude Probability of Death



Age Standardization: ICSS

Expected Rates: Reference

Fair Comparison: ✓

A brief history of non-parametric estimates

- Aim was to calculate net survival.
- Problem boils down to,

$$\frac{\frac{1}{N}\sum_{i=1}^{N} S_i(t)}{\frac{1}{N}\sum_{i=1}^{N} S_i^*(t)} \neq \frac{1}{N}\sum_{i=1}^{N}\frac{S_i(t)}{S_i^*(t)}$$

- For many years the Ederer II methods was used.
- In 2012 Pohar Perme *et al.* showed that Ederer II was a biased estimate of net survival and introduced a new estimator[1].
- Quick transfer of new method into applied research.
- Bias was actually negligible using traditional standardization[9].
- I will shows links between various non-parametric measures[10].

Reference Adjusted

$$\lambda_j = \frac{\overbrace{\sum_{i \in R(t_j)} w_{ij} d_{ij}}^{\text{All Cause}} - \overbrace{\sum_{i \in R(t_j)} w_{ij} h^{*}_{ij} y_j}^{\text{Expected}} + \overbrace{\sum_{i \in R(t_j)} w_{ij} h^{**}_{ij} y_j}^{\text{Reference}}}{\sum_{i \in R(t_j)} w_{ij}}$$

$$w_{ij} = w_i^B \frac{\overbrace{S_i^{**}(t_j)}^{\text{Reference}}}{\underbrace{S_i^{*}(t_j)}_{\text{Expected}}}$$

- This is where we will end up.
- I will build up to this equation to demonstate the relationship with other measures.

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Nelson Aalen

$$\lambda_j = \frac{\overbrace{\sum_{i \in R(t_j)} \cancel{w_{ij}} d_{ij}}^{\text{All Cause}} - \cancel{\overbrace{\sum_{i \in R(t_j)} w_{ij} h^*_{ij} y_j}^{\text{Expected}}} + \cancel{\overbrace{\sum_{i \in R(t_j)} w_{ij} h^{**}_{ij} y_j}^{\text{Reference}}}}{\sum_{i \in R(t_j)} w_{ij}} = \frac{d_j}{n_j}$$

$$w_{ij} = \cancel{w_i^B} \frac{\overbrace{1}^{\text{Reference}}}{\underbrace{1}_{\text{Expected}}}$$

- Numerator is number of deaths at t_j.
- Denominator is number at risk at t_j.

Ederer II

$$\lambda_j = \frac{\overbrace{\sum_{i \in R(t_j)} \cancel{w_{ij}} d_{ij}}^{\text{All Cause}} - \overbrace{\sum_{i \in R(t_j)} \cancel{w_{ij}} h^*_{ij} y_j}^{\text{Expected}} + \cancel{\overbrace{\sum_{i \in R(t_j)} w_{ij} h^{**}_{ij} y_j}^{\text{Reference}}}}{\sum_{i \in R(t_j)} w_{ij}} = \frac{d_j - d^*_j}{n_j}$$

$$w_{ij} = \cancel{w_i^B} \frac{\overbrace{1}^{\text{Reference}}}{\underbrace{1}_{\text{Expected}}}$$

- d^*_j is expected number of deaths at t_j.
- If $h^*_i(t) = 0$, we get back to Nelson-Aalen.

Pohar Perme

$$\lambda_j = \frac{\overbrace{\sum_{i \in R(t_j)} w_{ij} d_{ij}}^{\text{All Cause}} - \overbrace{\sum_{i \in R(t_j)} w_{ij} h^{*}_{ij} y_j}^{\text{Expected}} + \overbrace{\cancel{\sum_{i \in R(t_j)} w_{ij} h^{**}_{ij} y_j}}^{\text{Reference}}}{\sum_{i \in R(t_j)} w_{ij}} = \frac{d_j^{w} - d_j^{*w}}{n_j^{w}}$$

$$\cancel{w_i^B} \frac{1}{\underbrace{S_i^*(t_j)}_{\text{Expected}}}$$

- Upweighted by $1/S_i^*(t_j)$
- Accounts for informative dropout.
- Those more likely to die from other causes given higher weights.

(Age) Standardization

- Differences may be due to different covariate distributions.
- Common to age standardize and increasingly over other variables.
- Traditional age standardization estimated separately in age groups and then calculate a weighted average.
- Now commmon to weight at individual level
  - Better in smaller datasets
  - Generalises to more covariates.
- Introduce time-fixed weights, w_i^B

$$w_i(t) = w_i^B \frac{1}{S_i^*(t)} \qquad w_i^B = \frac{w_i^{REF}}{a_i}$$

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Pohar Perme

$$\lambda_j = \frac{\overbrace{\sum_{i \in R(t_j)} w_{ij} d_{ij}}^{\text{All Cause}} - \overbrace{\sum_{i \in R(t_j)} w_{ij} h^{*}_{ij} y_j}^{\text{Expected}} + \overbrace{\cancel{\sum_{i \in R(t_j)} w_{ij} h^{**}_{ij} y_j}}^{\text{Reference}}}{\sum_{i \in R(t_j)} w_{ij}} = \frac{d_j^{w} - d_j^{*w}}{n_j^{w}}$$

$$w_{ij} = w_i^{B} \frac{1}{\underbrace{S_i^{*}(t_j)}_{\text{Expected}}}$$

- Introducing w_i^B allows for (age) standardization.

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Sasieni and Brentnall

- Introduce reference population[11].
- Gives (slightly) biased estimate of net survival.
- Narrower CIs reduces impact of large weights for longer term survival.
- Described as "*a standardized relative survival index designed to accurately and precisely determine the direction and ordering of survival differences between cohorts*"

Sasieni and Brentnall

$$\lambda_j = \frac{\overbrace{\sum_{i \in R(t_j)} w_{ij} d_{ij}}^{\text{All Cause}} - \overbrace{\sum_{i \in R(t_j)} w_{ij} h^*_{ij} y_j}^{\text{Expected}} + \cancel{\overbrace{\sum_{i \in R(t_j)} w_{ij} h^{**}_{ij} y_j}^{\text{Reference}}}}{\sum_{i \in R(t_j)} w_{ij}} = \frac{d_j^w - d_j^{*w}}{n_j^w}$$

$$w_{ij} = w_i^B \frac{\overbrace{S_i^{**}(t_j)}^{\text{Reference}}}{\underbrace{S_i^*(t_j)}_{\text{Expected}}}$$

- Change of weights to Pohar Perme
- "*A standardized relative survival index*"
- If $S_i^{**}(t) = 1$ then back to Pohar Perme.
- If $S_i^{**}(t) = S_i^*(t)$ then back to Ederer II.
- S&B Propose $S_i^{**}(t) \leq S_i^*(t)$ for "*robust estimate*".

Reference Adjusted

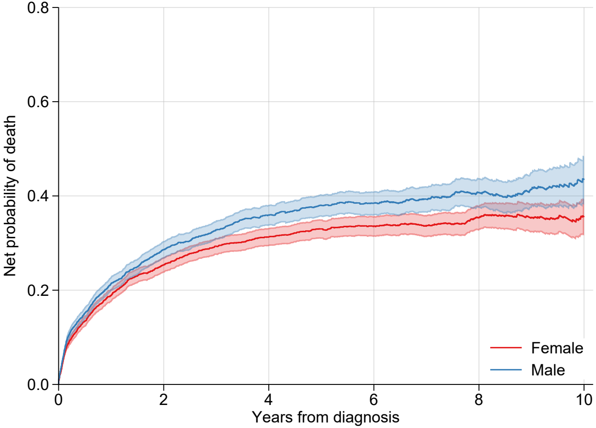
$$\lambda_j = \frac{\overbrace{\sum_{i \in R(t_j)} w_{ij} d_{ij}}^{\text{All Cause}} - \overbrace{\sum_{i \in R(t_j)} w_{ij} h^{*}_{ij} y_j}^{\text{Expected}} + \overbrace{\sum_{i \in R(t_j)} w_{ij} h^{**}_{ij} y_j}^{\text{Reference}}}{\sum_{i \in R(t_j)} w_{ij}}$$

$$w_{ij} = w_i^B \frac{\overbrace{S_i^{**}(t_j)}^{\text{Reference}}}{\underbrace{S_i^{*}(t_j)}_{\text{Expected}}}$$

- All cause survival in a reference population
- If $S_i^{**}(t) = S_i^{*}(t)$ then back to Nelson Aalen
- If $S_i^{**}(t) = 1$ then back to Pohar Perme

Colon cancer in Norway: Net probability of death

Males vs Females: age 70-85



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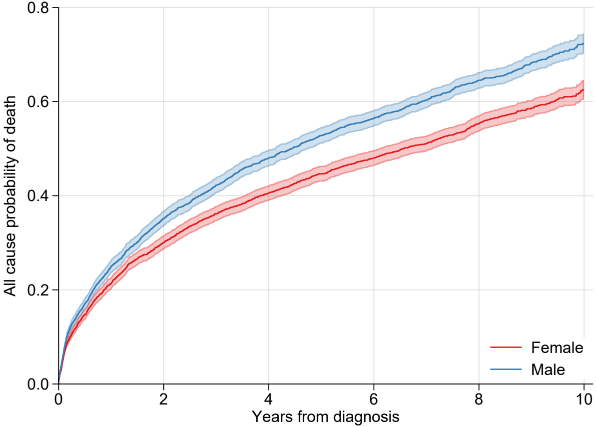
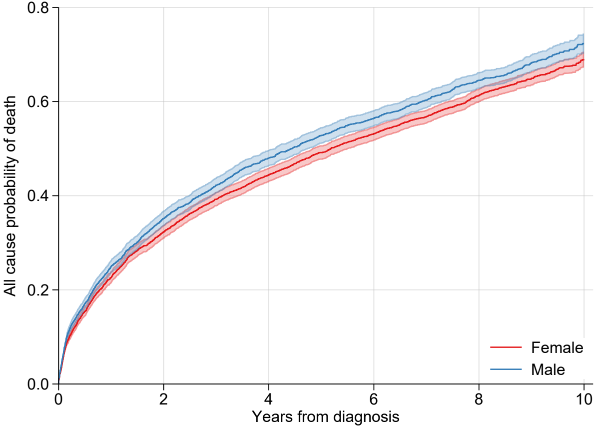
Colon cancer in Norway: All cause

Non reference adjusted



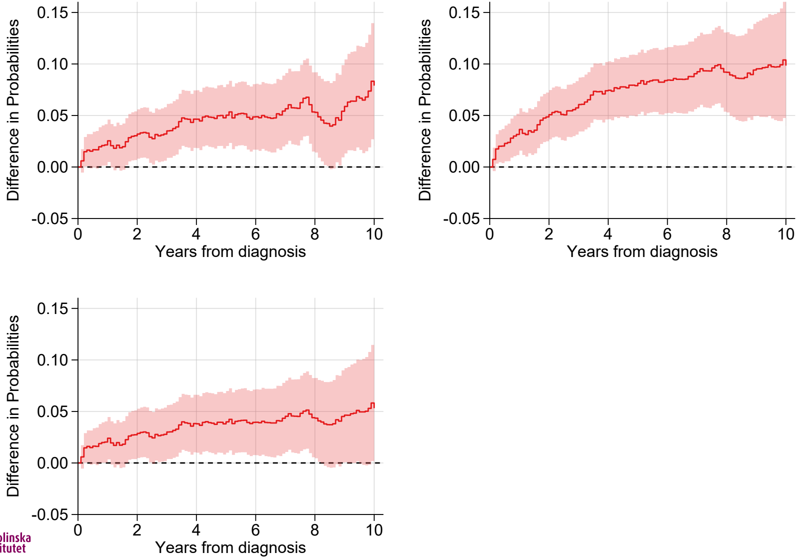
Colon cancer in Norway: All cause

Reference adjusted



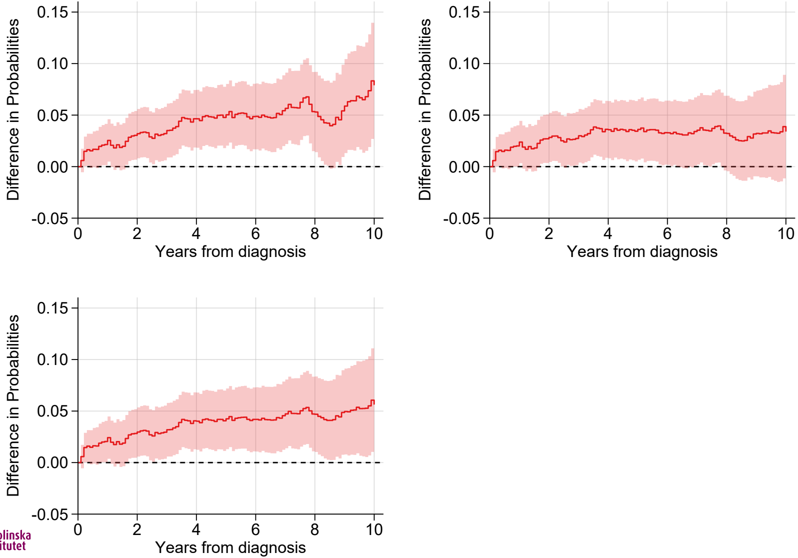
Colon cancer in Norway: Differences

Non reference adjusted



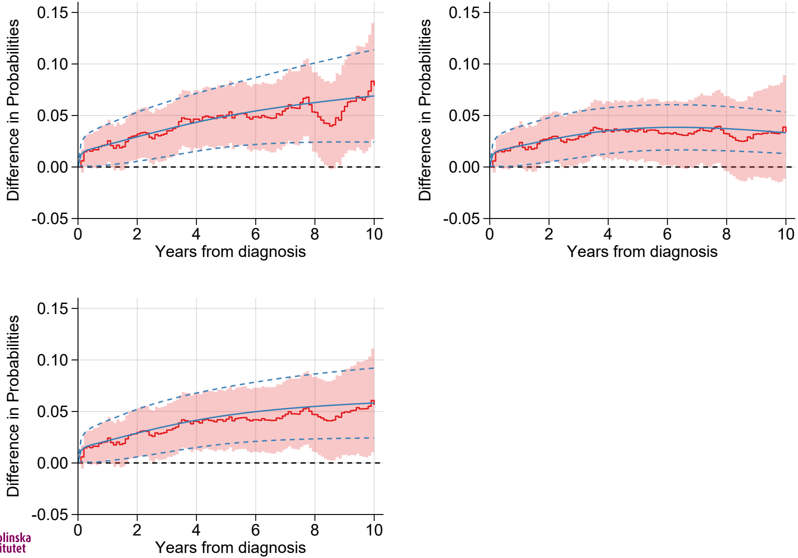
Colon cancer in Norway: Differences

Reference adjusted (using Male expected rates)



Colon cancer in Norway: Differences

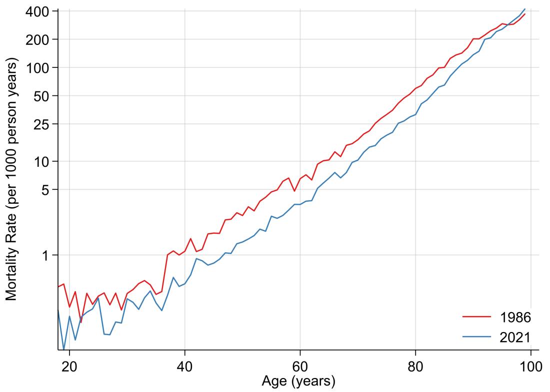
Reference adjusted vs model estimates

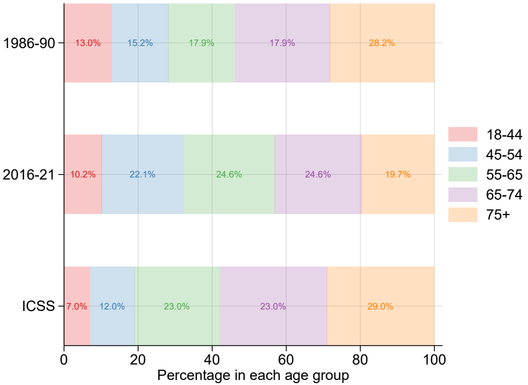


Temporal Trends

- It is common to investigate trends in net survival over calendar time.
- Different countries age standardize in different ways
  - Norway, Finland age standardize to recent calendar period.
  - England age standardize using ICSS age distribution.
- Reference adjusted all cause survival and crude probabilities of death may provide useful alternative to just looking at net survival.
- Example looking at breast cancer 5 year survival in Norway

Changing expected mortality rates and age distribution





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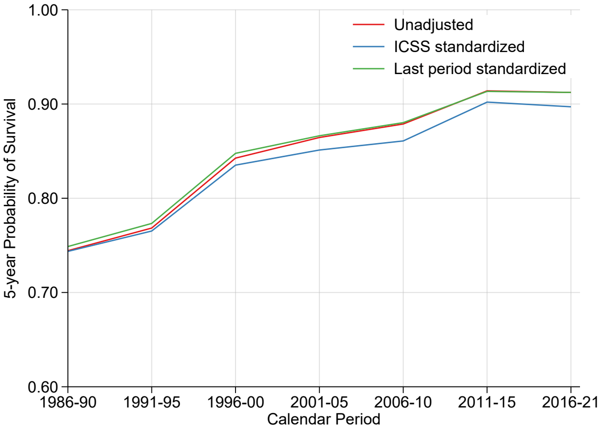
Net survival



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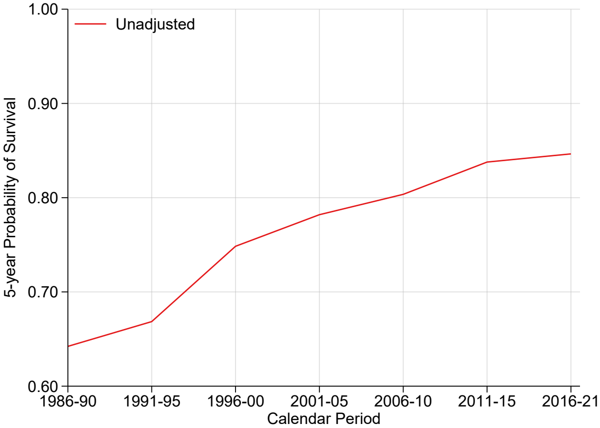
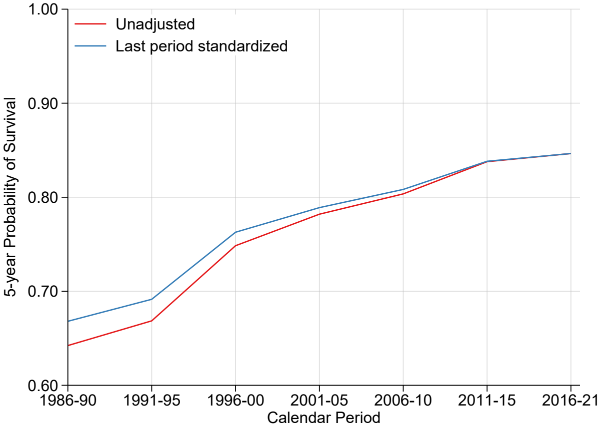
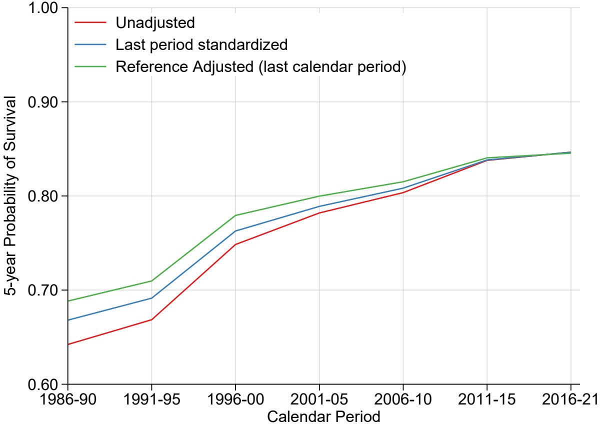
All cause survival



All cause survival



All cause survival



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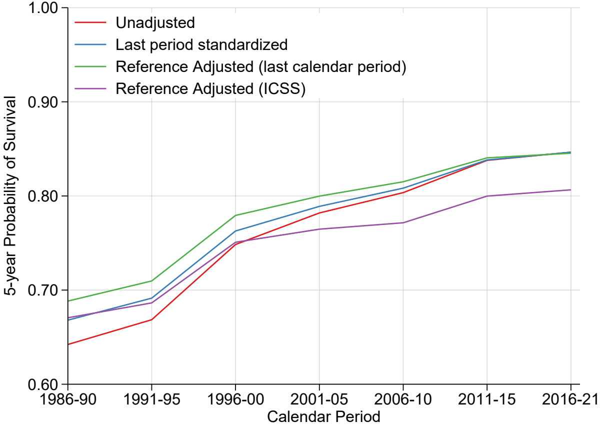
All cause survival



Software (Stata): Parametric model

stpm3

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

standsurv

```
standsurv CPm CPf, crudeprob timevar(tt)  frame(ss_ref, replace) ///
             at1(sex 1) at2(sex 2)                               ///
             expsurv(using("popmort.dta")                        ///
                     agediag(agediag)                            ///
                     datediag(datediag)                          ///
                     pmrate(rate)                                ///
                     pmyear(_year) pmage(_age) pmother(sex)      ///
                     pmmaxyear(2000)                             ///
                     at1(sex 1) at2(sex 1))
```

Software (Stata): Non-parametric

stpp

```
stpp NS                                 /// new variable
     using  "popmort.dta",              /// expected rates
     agediag(agediag)                   /// age at diagnois
     datediag(datediag)                 /// date of diagnosis
     allcause(AC)                       /// calculate allcause
     crudeprob(CPc CP2o)                /// calculate crude prob
     by(sex)                            /// estimate by sex
     list(1 5 10)                       /// list at 1,5,10 years
     pmother(sex)                       /// popmort rates stratified by sex
     using2("popmort_ref.dta",          /// reference rates
            pmother2(.))                /// no other stratification vars
     frame(NS, replace)                 //  store summary result in frame
```

Relationship to separable effects

- I have shown reference adjustment in the relative survival framework.
- Can apply the same ideas to competing risks.
- Force common other cause mortality on groups being compared.
- Motivation and type of data is different, but mechanically this is the same as when calculating seperable effects[12, 13].

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Discussion

- We isolate disparities due to the disease of interest (using the relative survival framework).
- When reporting, real-world metrics beneficial for interpretation.
- We need a common reference expected mortality rate to make sure the estimates only reflect differences in cancer-specific mortality.
- The choice of reference standard is key - will depend on the purpose of the analysis/comparison.
- A further key choice is the age (and other covariate) distribution to standardise to when making comparisons.

References

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