Application of `stpm2` to estimate relative survival for cancer patients in the Nordic countries

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The NORDCAN Survival Project

- Comparisons of cancer survival across the Nordic countries
  - Denmark, Finland, Iceland, Norway and Sweden

- Investigate possible differences in survival for nine cancer sites
  - Colon, rectum, lung, skin melanoma, kidney
  - Breast, uterus, ovary, prostate

- Highlight differences using novel measures of survival

Measures of cancer-specific survival

- Crude probability of death due to cancer
  - In the presence of competing risks (other causes of death)
  - Patient prognostic measure

- Net probability of death due to cancer
  - Hypothetical world where you cannot die of other causes
  - Competing risks are assumed to be eliminated
  - Independent of background mortality
  - Comparable across age, calendar time or country

Estimation of cancer survival

- Cause-specific framework: using cause of death information

$$\text{Cause specific mortality} = \frac{\text{number of deaths due to cancer}}{\text{person time at risk}}$$

- Relative survival framework: using expected mortality tables

$$\text{Excess mortality} = \text{all cause mortality} - \text{expected mortality}$$

$$\text{Relative survival ratio} = \frac{\text{all cause survival proportion}}{\text{expected survival proportion}}$$

Material

- Data from the NORDCAN database from five countries
- Individual level data on patients diagnosed 1990-2016
  - Year and month of diagnosis
  - Follow-up time in days
  - Status at end of follow-up (alive, dead, emigrated)
  - Patients' sex, age at diagnosis and country
  - Cancer site
- Population based mortality rates from national statistics offices (expected mortality)
  - By country, age, year and sex

Flexible parametric RS models

- Time since diagnosis as primary time-scale
- Log cumulative baseline excess hazard modelled continuously
  - Restricted cubic splines (rcs) with 5 degrees of freedom
- Age and calendar year included as continuous variables
- Sex included as binary variable where appropriate
- Two-way interactions between age, year and sex
- Two- and three-way interactions with time since diagnosis
  - Relaxing proportional excess hazard assumption
- Separate models for each country and cancer site

Main model – `stpm2`

```
stset followup_days, failure(status==2)                    ///
   exit(time 10*365.24) scale(365.24) id(id)


stpm2 rcs3age* rcs3year* sex                               ///
   rcs2age2year* rcs2agesex* rcs2yearsex* ,                ///
   tvc(rcs3age* rcs3year* sex                              ///
   rcs2age2year* rcs2agesex* rcs2yearsex* )                ///
   scale(hazard) bhazard(rate)                             ///
   df(5) dftvc(2)
```

- Models the log cumulative excess hazard over time since diagnosis

Model stability

- Started with an ’ideal model’
- Defined an algorithm to simplify the model if convergence failed
  - Winsorizing for tails of age (at different percentiles)
  - Fewer degrees of freedom for interaction terms
  - Fewer degrees of freedom for time-varying effects
  - Dropped three-way interactions with time (for age, year and sex)
  - Non-parametric Pohar Perme approach using **`strs`**
- Tested models for all nine sites in each of the five countries

Winsorizing

- 96% of age distribution modelled continuously, individuals outside the 2nd and 98th percentiles of age reassigned to percentile limits
  - Assumed to have the same relative survival

```
_pctile age, per(2)
global age_lo `r(r1)'
gen ageadj = cond(age < $age_lo , $age_lo , age)

_pctile age, per(98)
global age_hi `r(r1)'
replace ageadj = cond(ageadj > $age_hi , $age_hi , ageadj)
```

Outcome measures

- Post-estimation to obtain additional measures using **`standsurv`**
- 1- and 5-year relative survival
  - Age-standardised and age-specific estimates
  - By cancer site, country, sex and calendar year of diagnosis
  - Percentage points change since 1990
- 5-y relative survival conditional on surviving one year
- Period approach for 5-y RS in the most recent period
- Crude probability of death and average number of life-years lost

Age-standardization

- Adapted versions of the International Cancer Survival Standard (ICCS) age-standard weights by 10-year age groups
- Makes estimates comparable across countries with different age distributions among cancer cases
- Regression standardization stratified by calendar year and sex

```
recode age (min/49=1) (50/59=2) (60/69=3) (70/79=4) ///
        (80/max=5), gen(agegrp)

recode agegrp (1=0.11906) (2=0.16735) (3=0.27593)    ///
              (4=0.28897) (5=0.14869) , gen(agewt)
```

5-year relative survival – `standsurv`

```
keep if female == `sex' & yydx == `year'
local totalobs = _N
bysort agegrp: gen standwt = _N/`totalobs'
gen indwt = agewt/standwt

gen tflag = 1 in 1
gen t5 = 5 if tflag == 1

standsurv, at1(.)                                ///
   atvar(surv5_`year'_`sex')                     ///
   timevar(t5) ci indweights(indwt)
```

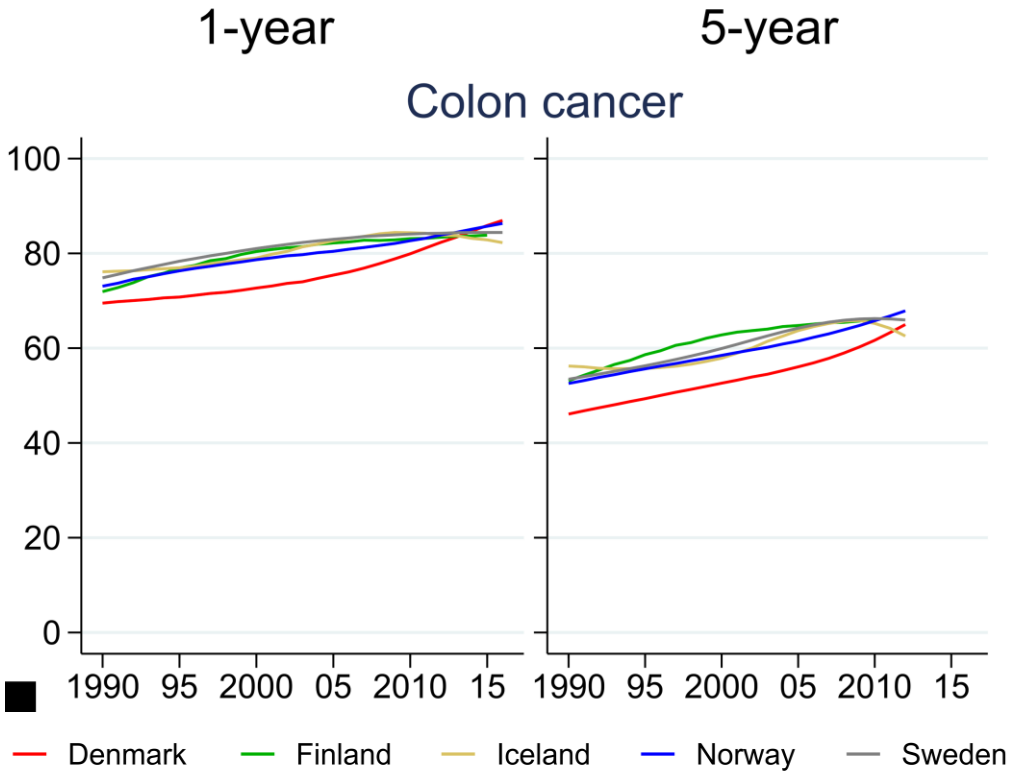
Conditional relative survival – `standsurv`

```
gen t1 = 1 if tflag == 1


standsurv,                                          ///
   at1(., attimevar(t1))                            ///
   at2(., attimevar(t5))                            ///
   atvar(a5_t1_`year'_`sex'                         ///
   b5_t1_`year'_`sex')                              ///
   contrast(ratio)                                  ///
   contrastvar(surv5_c1_`year'_`sex')               ///
   ci indweights(indwt)
```

Loops and output

```
foreach country in se dk no fi is {
   foreach site in $sitelist {
      //load data, stset, merge with population mortality rates,
      //winsorize, create spline variables and interaction terms
      //run stpm2 model
      forvalues year = 1990/2016 {
         foreach sex in 0 1 {
            foreach endtime in 1 5 {
               foreach starttime in 0 1 {
                  //standsurv
                  //save estimates to dataset
               }
            }
         }
      }
   }
}
//create tables and graphs
```

1- and 5-y RS, women with colon cancer



Supplementary table 4. Trends in 1-year relative survival 1990-intervals, the NORDCAN survival studies

Sex	Country	Site	1990	1995	2000
Women	Denmark	Colon	70 (68-71)	71 (70-72)	73 (72-73)
Women	Finland	Colon	72 (70-74)	77 (76-78)	80 (80-81)
Women	Iceland	Colon	76 (69-84)	77 (73-81)	79 (75-83)
Women	Norway	Colon	73 (72-75)	76 (76-77)	79 (78-79)
Women	Sweden	Colon	75 (74-76)	78 (78-79)	81 (80-82)

Supplementary table 5. Trends in 5-year relative survival 1990-intervals, the NORDCAN survival studies

Sex	Country	Site	1990	1995	2000
Women	Denmark	Colon	46 (44-48)	49 (48-50)	53 (52-54)
Women	Finland	Colon	53 (51-56)	59 (57-60)	63 (61-64)
Women	Iceland	Colon	56 (47-68)	56 (50-62)	58 (53-64)
Women	Norway	Colon	53 (50-55)	56 (55-57)	58 (57-60)
Women	Sweden	Colon	53 (52-55)	56 (55-57)	60 (59-61)

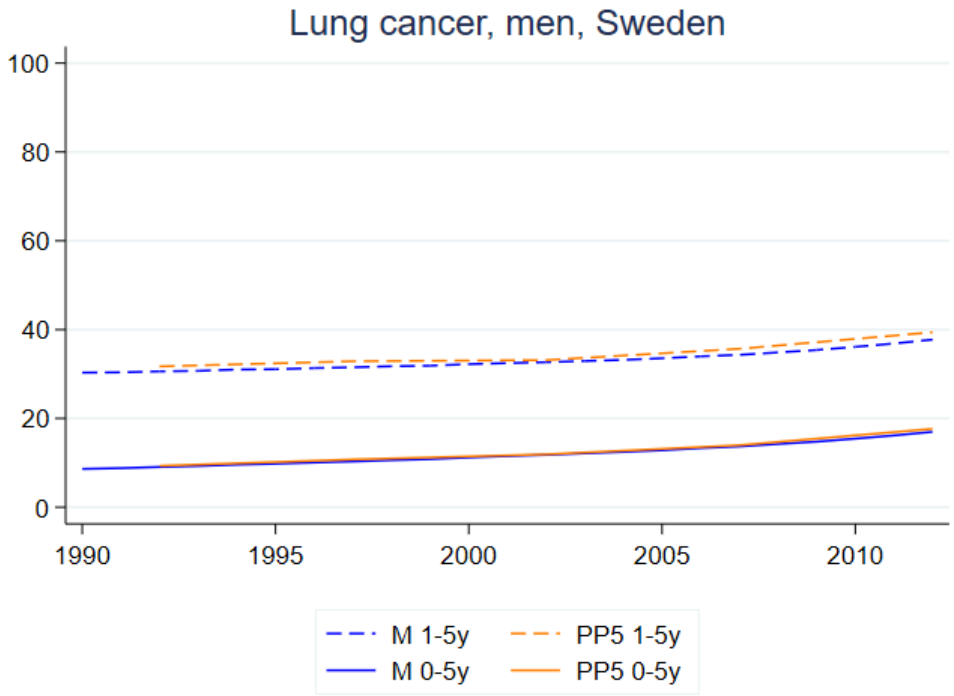
Non-parametric estimates – `strs`

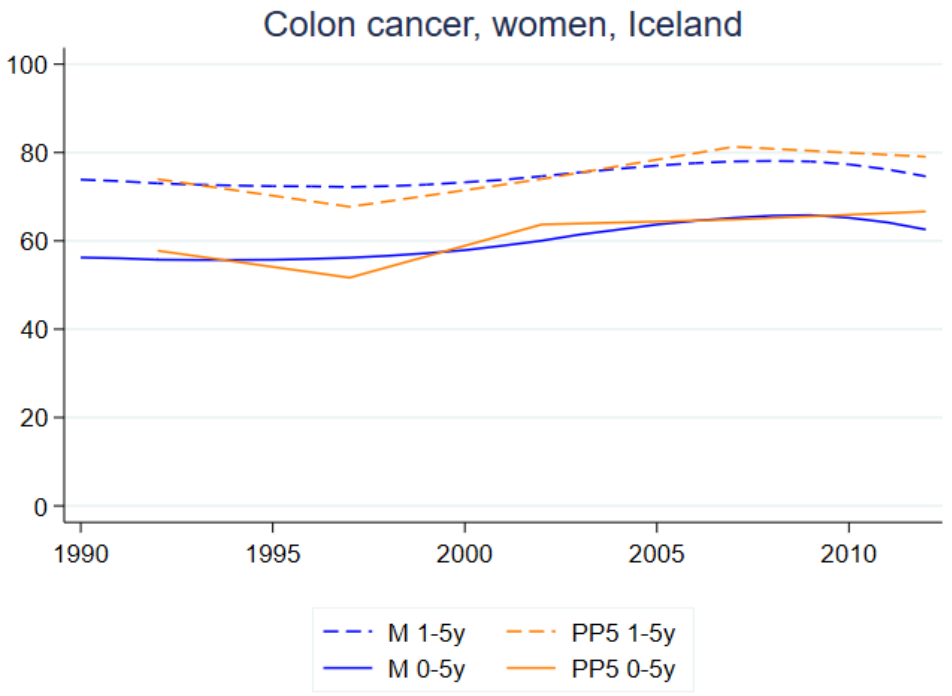
```
bysort yrgrp5 sex: gen totalobs = _N
bysort agegrp yrgrp5 sex: gen totalobs_age = _N
gen standwt = totalobs_age/totalobs
gen indwt = agewt/standwt

stset followup_days, failure(status==2)          ///
   exit(time 10*365.24) scale(365.24) id(id)

strs using popmort_`country'                     ///
 , br(0(0.5)5) mergeby(sex _year _age)           ///
 by(sex yrgrp5) pohar indweight(indwt)
```

Conditional relative survival – `strs`

```
stset followup_days, failure(status==2)          ///
   exit(time 10*365.24) scale(365.24) id(id)     ///
   enter(time 365.24)

strs using popmort_`country'                     ///
 , br(0(0.5)5) mergeby(sex _year _age)           ///
 by(sex yrgrp5) pohar indweight(indwt)
```

Comparisons to non-parametric estimates





Summary

- Advantages of model-based estimation
  - Possible to obtain estimates for specific covariate patterns, e.g. specific ages and years
  - Contrasts for specific covariate patterns
  - Post-estimation of life-years lost and other measures

- Possible limitations
  - Convergence issues especially when data is sparse
  - More work intensive than non-parametric estimation
    - `stpm3` is on the way!

References

- Lundberg FE, et al. Survival trends in patients diagnosed with colon and rectal cancer in the nordic countries 1990–2016: The NORDCAN survival studies. *Eur J Cancer* 2022;172:76–84.
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- Syriopoulou E, et al. Robustness of individual and marginal model-based estimates: A sensitivity analysis of flexible parametric models. *Cancer Epidemiol* 2019;58:17–24.
- Lambert PC, Royston P. Further development of flexible parametric models for survival analysis. *Stata J* 2009;9(2):265–90.

Thank you for your attention!

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