AN APPLICATION IN STATA WHEN INVESTIGATING THE RELATIONSHIP BETWEEN CANCER AND DEMENTIA

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Background

Older people are often affected by several comorbid conditions and by an increasing risk of death that arises with aging.

Studies on the older people with the aim to investigate the association between morbid conditions are often characterized by the presence of competing risks.

Cancer and dementia are two age-related diseases highly prevalent in the elderly population. An inverse association between the two diseases has been observed in the literature. Some have suggested a protective effect of cancer against the onset of dementia.

Methodological problems

Previous studies have usually used standard approaches without taking into account the competing risk of mortality.

Ignoring mortality may not provide valid estimates of risk of dementia, because cancer is strongly associated with the competing risk of death.

Objectives

Aim

To study the association between cancer and the onset of dementia in the older population.

How

The competing risk methodology is used, having death as a competing event.

The intent is to:

- illustrate the appropriate statistical methods for competing risks and their application
- give a correct interpretation of the results

In a competing risk setting:

- The experience of the competing event precludes the subject to experience the outcome of interest.
- The one-to-one correspondence between hazard function and incidence function is no more valid.

Two different hazard functions of interest.

Cause-specific hazard function

$$\lambda_k^{cs}(t) = \lim_{\Delta t \to 0} \frac{P(t \leq T < t + \Delta t, D = k \mid T \geq t)}{\Delta t}$$

- Instantaneous rate of the onset of dementia in subjects who have not yet experienced either event (still alive and dementia free).
- Can be estimated using standard Cox regression and censoring subjects who experience the competing event at the time point of its occurrence.
- In Stata: `. stcox`

Subdistribution hazard function

$$\lambda_k^{sd}(t) = \lim_{\Delta t \to 0} \frac{P(t < T \leq t + \Delta t, D = k \mid T \geq t) \cup (T < t \cap K \neq k))}{\Delta t}$$

- Instantaneous rate of the onset of dementia in subjects who are dementia free (i.e. have not yet expericend neither event) or who have previously died.
- Allows to estimate the effect of the covariates on the cumulative incidence function for the event of interest.
- Can be estimated with the model introduced by Fine and Gray.
- In Stata: `. stcrreg`

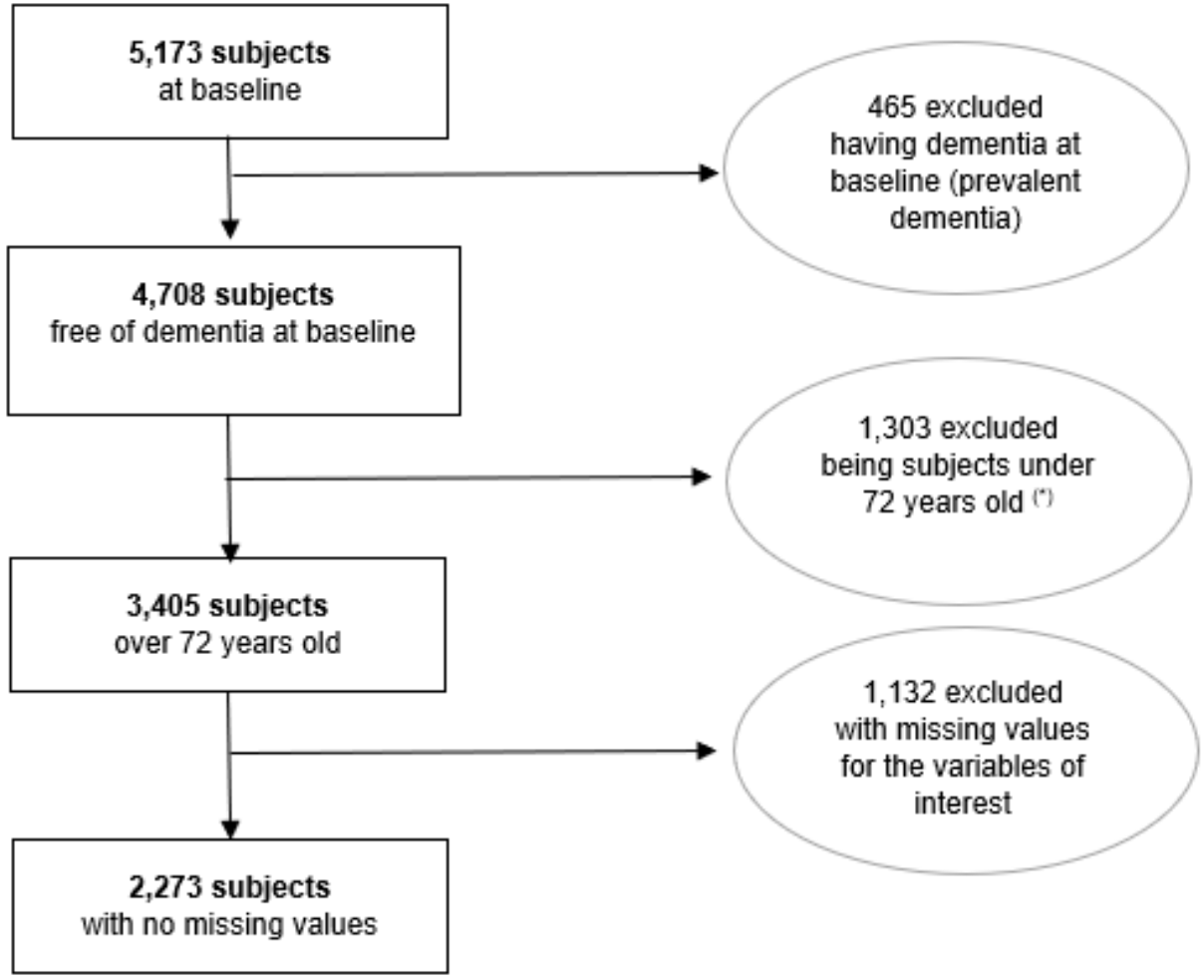
Material & Methods

The study considers people over-72 years old from two Swedish population-based longitudinal studies:

- Kungsholmen Project, KP
- Swedish National Study on Aging and Care – Kungsholmen, SNAC-K

The time period considered covers a maximum of 10 years of follow-up.

The effect of variables related to subjects characteristics were also evaluated.



(*) Only for the SNAC-K cohort.
The KP cohort only considers subjects at least 75 years old.

Exposure
Defined as the presence or absence of cancer.

The following cases identified the presence of the disease:
- Cancer diagnosis prior to the start of the study, documented by the registers (ICD-8 and ICD-9, codes 140-208).
- Cancer diagnosis reported during the follow-up period.

Outcome
The presence of dementia has been investigated at each visit, through clinical and neuropsychological assessments conducted by doctors and psychologists and using a three-step diagnostic procedure.

Three models were built for the analyses:

MODEL 1 - Cause-specific hazard
Cox model with the exposure time-independent, adjusted for the variables of interest.

```
. stcox cancer
```

MODEL 2 - Cause-specific hazard
Cox model with time-dependent exposure, adjusted for the variables of interest.

```
. stcox postcancer
```

MODEL 3 - Subdistribution hazard
Fine and Gray model to take into account the competing risk of death. Time-dependent exposure, adjusted for the variables of interest.

```
.stcrreg postcancer, compete(status==2)
```

Results – Estimates for the three models

	Model 1		Model 2		Model 3	
	HR	CI 95%	HR	CI 95%	HR	CI 95%
Cancer						
Yes	0.63	0.47-0.85	0.85	0.63-1.14	0.78	0.58-1.05
Age						
80-89	1.76	1.43-2.18	1.78	1.44-2.20	1.51	1.22-1.86
90+	2.88	1.96-4.22	2.90	1.98-4.26	1.34	0.89-2.01
Gender						
Female	0.89	0.69-1.15	0.92	0.71-1.18	1.07	0.84-1.38
BMI						
Underweight	1.31	0.85-2.01	1.31	0.85-2.03	1.02	0.65-1.61
Overweight	0.83	0.66-1.04	0.82	0.65-1.03	0.84	0.67-1.06
Obese	0.81	0.53-1.24	0.80	0.52-1.22	0.82	0.54-1.25
Alcohol						
Yes	0.77	0.62-0.95	0.76	0.61-0.94	0.79	0.64-0.98
Smoking						
Former	0.87	0.67-1.13	0.87	0.67-1.13	0.87	0.67-1.12
Current	0.85	0.60-1.19	0.85	0.60-1.20	0.78	0.55-1.09
Education						
Intermediate	0.82	0.66-1.02	0.82	0.66-1.02	0.85	0.69-1.05
High	0.74	0.51-1.08	0.85	0.51-1.06	0.79	0.54-1.15
Mental activity						
Yes	0.80	0.65-0.98	0.80	0.65-0.98	0.85	0.69-1.04
Social activity						
Yes	0.79	0.62-1.00	0.78	0.62-0.99	0.8	0.63-1.00
Physical activity						
Yes	0.90	0.67-1.19	0.90	0.67-1.20	1.00	0.76-1.32
Cohort						
KP	2.64	1.96-3.56	2.69	1.99-3.63	2.85	2.14-3.81

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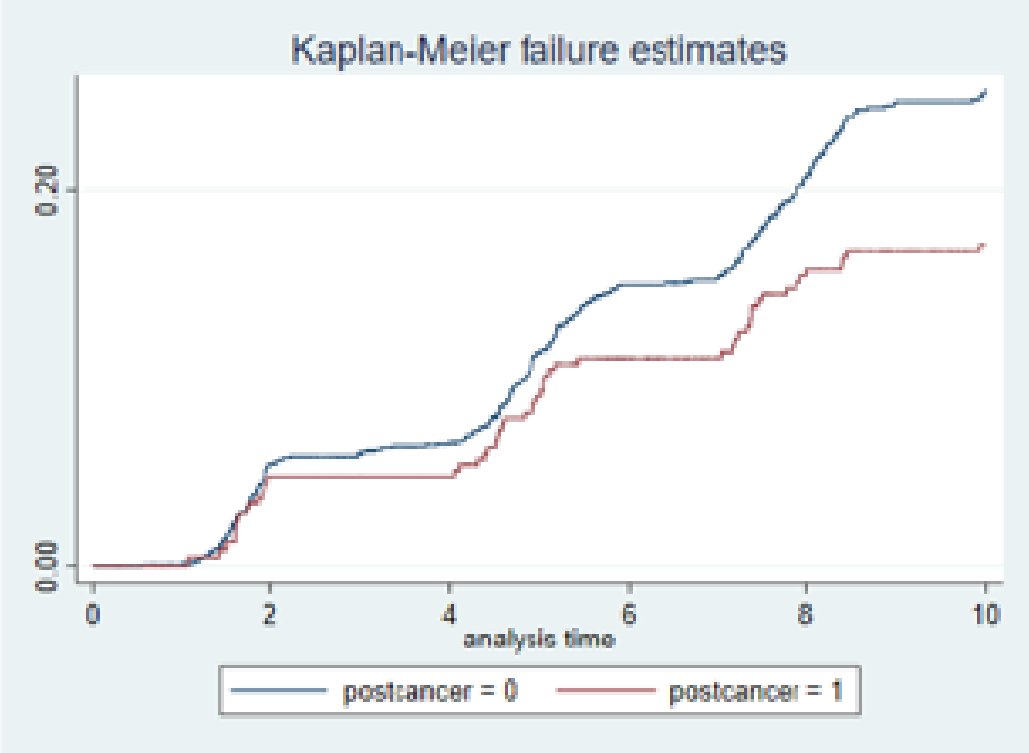
Results – Incidence curves

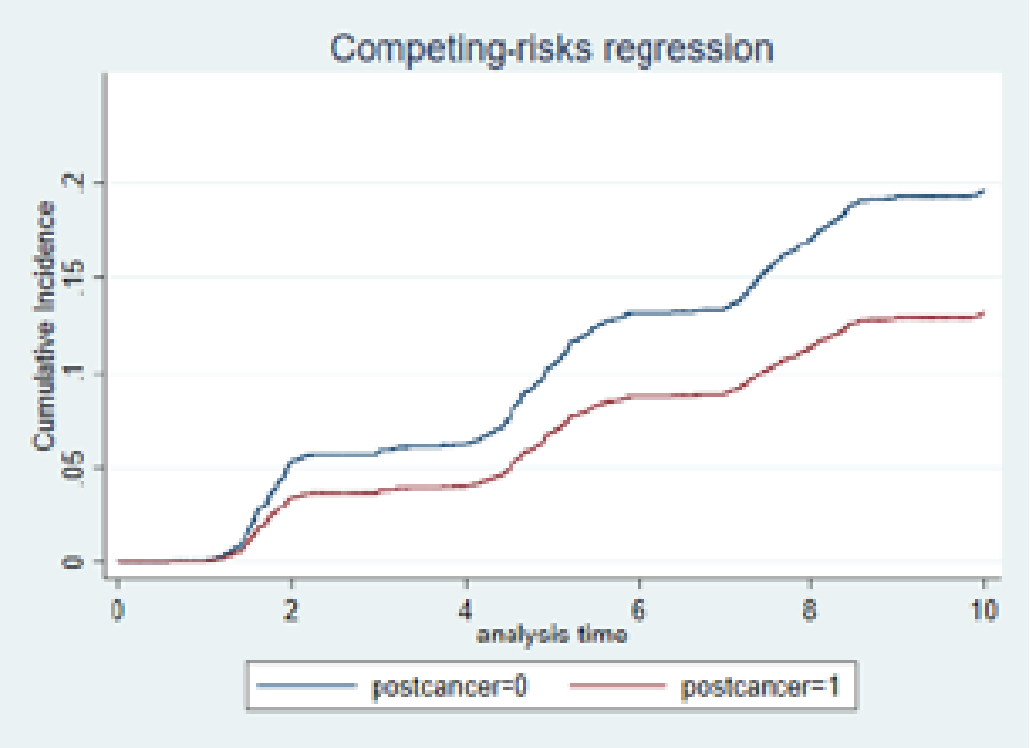
Kaplan-Meier method

```
.sts graph, failure by(postcancer)
```



Fine-Gray method

```
.stcurve, cif at1(postcancer=0) at2(postcancer=1)
```



Conclusions

When using models that are properly constructed and that control for the competing event, having cancer does not appear to be protective on the onset of dementia.

By treating the exposure as a time-independent variable (Model 1) it is possible to observe the wrong inverse association between cancer and dementia.

By treating the exposure as a time-dependent variable (Model 2), it is possible to obtain more reliable estimates and the inverse association between cancer and dementia is not significant.

The incidence curve obtained with the Fine-Gray approach is a more accurate estimate of the incidence of the event in the presence of competing risks.

When studying the association between diseases related to aging, is important to consider the context of high mortality.
Also, be careful to correctly specify the model and correctly interpret the results.

Strenghts of the study:

- The study population includes older people living in institutions or at home
- Prospective study design and long-term follow-up
- High response rates in both original cohorts
- Reliability of information

Limits of the study:

- Information recorded only at the baseline for several variables
- Possible distortion caused by the composition of the sample and by the exclusion of subjects with incomplete data
- Absence of information for other variables that can be associated with the event of interest
- No differentiation for types of cancer

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Thank you