An overview of methods for estimating cancer patient survival

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University *of*
Leicester

Karolinska
Institutet

Overview of today's talk

- About me.
- Measures used in cancer control; why study patient survival?
- Intro to net/relative survival and why it is the measure of choice for estimating patient survival using registry data.
- 'Real-world' alternatives to net survival; crude survival.
- Estimating treatment-related mortality.
- Other measures (very briefly):
  - Proportion cured.
  - Loss in expectation of life.
  - Conditional survival.

About me

- Born in Sydney Australia; studied mathematics and statistics in Newcastle (Australia).
- Worked in health services research;
  dabbled in industrial process control and quality improvement.
- Arrived in Sweden November 1993 for a 10 month visit to cancer epidemiology unit at Radiumhemmet. Stayed in Sweden for most of my PhD.
- Short Postdoc periods at Finnish Cancer Registry and Karolinska Institutet (cancer epidemiology).
- Joined MEB in March 1999, attracted by the strong research environment and possibilities in register-based epidemiology.

I found paradise! [1]

A paradise for epidemiologists?

Hans-Olov Adami

The Lancet 1996;2:588

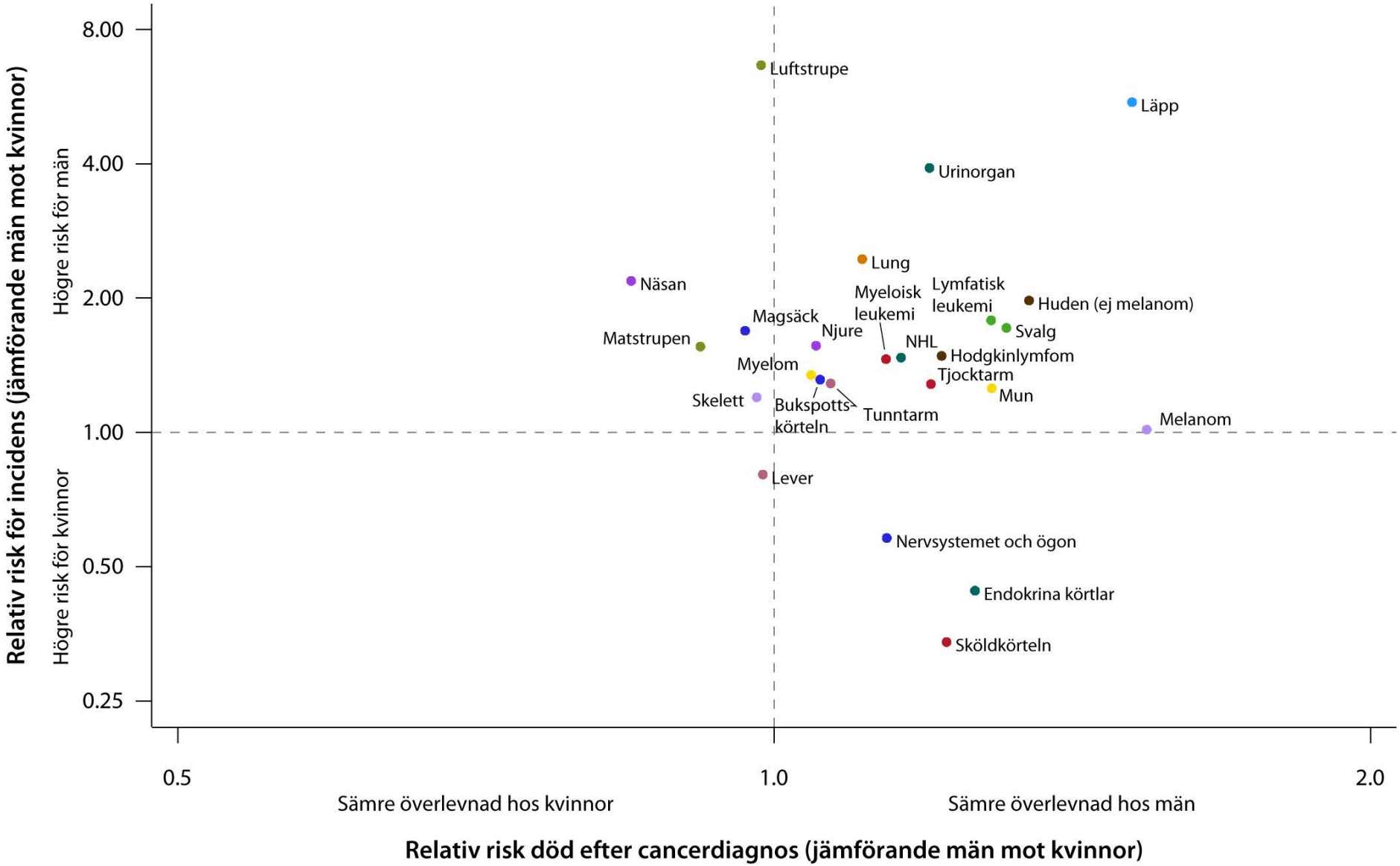
For three reasons—the structure of its health system, the existence of nationwide registers, and the systematic use of national registration numbers—Sweden offers exceptional opportunities for epidemiological research.

- I would add 'willingness of the public to contribute to research'.

My research interests

- Primary research interests are in the development and application of methods for population-based cancer survival analysis, particularly the estimation and modeling of relative survival.
- General interest in statistical aspects of the design, analysis, and reporting of epidemiological studies along with studies of disease aetiology, with particular focus on cancer epidemiology and perinatal/reproductive epidemiology.
- Collaborate closely with Paul Lambert (Biostatistician at University of Leicester) and Magnus Björkholm (Haematologist at KI/KS Solna).

Sex differences (Cecilia Radkiewicz)



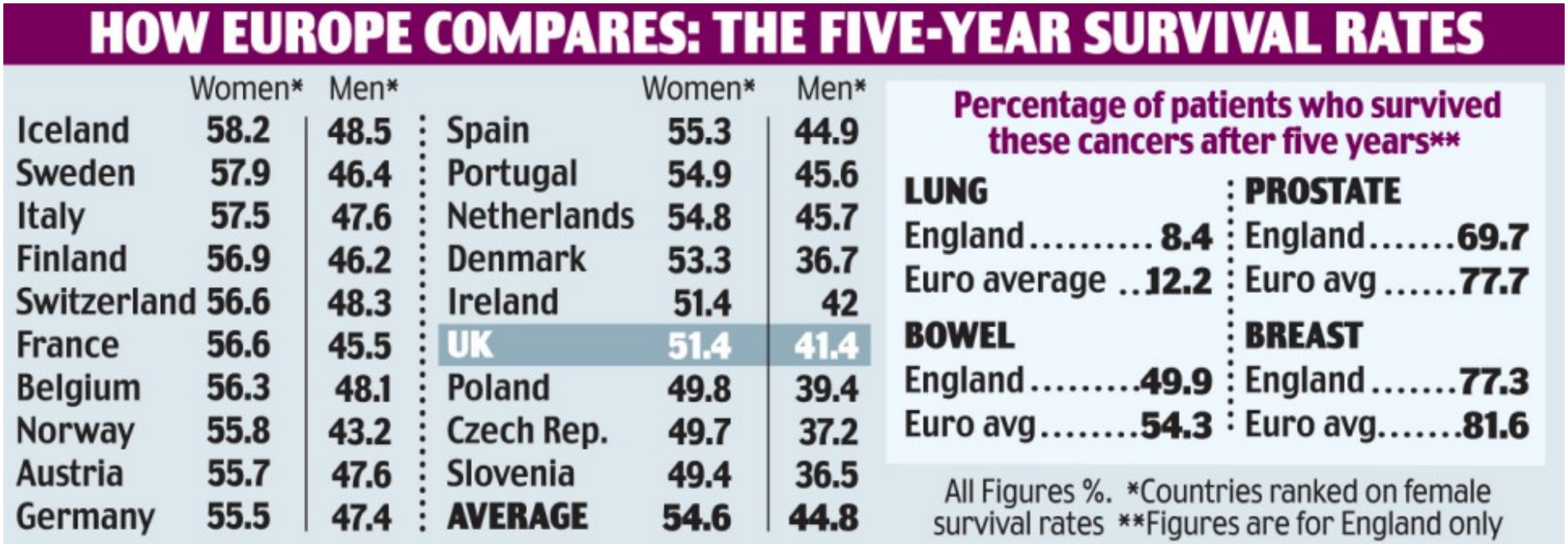
What do we mean by population-based?

- The term 'population-based' refers to the fact that we are estimating survival for all patients in a geographically-defined population (i.e., from a population-based cancer registry) rather than, for example, patients enrolled in a clinical trial.
- Population-based studies of patient survival provide a measure of the effectiveness of the health care system in diagnosing and treating those cancers that arise in the entire population.
- Note that this includes the efforts of the health care system in promoting public awareness of cancer and the importance of recognising symptoms and consulting a doctor when symptoms occur.

Measures used in cancer control

- The key measures are incidence, mortality, and survival.
- By 'mortality' we typically mean mortality in the population, whereas 'survival' is nothing more than mortality among those diagnosed with cancer (transformed to the mortality scale).
- We should not study any one of these three measures in isolation; in particular we should consider incidence trends when interpreting trends in patient survival [2, 3, 4].

International comparisons of survival are hot!



HOW EUROPE COMPARES: THE FIVE-YEAR SURVIVAL RATES

	Women*	Men*		Women*	Men*
Iceland	58.2	48.5	Spain	55.3	44.9
Sweden	57.9	46.4	Portugal	54.9	45.6
Italy	57.5	47.6	Netherlands	54.8	45.7
Finland	56.9	46.2	Denmark	53.3	36.7
Switzerland	56.6	48.3	Ireland	51.4	42
France	56.6	45.5	UK	51.4	41.4
Belgium	56.3	48.1	Poland	49.8	39.4
Norway	55.8	43.2	Czech Rep.	49.7	37.2
Austria	55.7	47.6	Slovenia	49.4	36.5
Germany	55.5	47.4	AVERAGE	54.6	44.8

Percentage of patients who survived these cancers after five years**

LUNG	**PROSTATE**
England 8.4	England 69.7
Euro average .. 12.2	Euro avg 77.7
BOWEL	**BREAST**
England 49.9	England 77.3
Euro avg 54.3	Euro avg 81.6

All Figures %. *Countries ranked on female survival rates **Figures are for England only

From a UK daily newspaper 2009[1].
Based on data from the EUROCARE-4 study.

[1] http://www.dailymail.co.uk/health/article-1164295/Cancer-survival-rates-Britain-wost-Europe.html

The CONCORD-2 Study (2014) [5]

Global surveillance of cancer survival 1995–2009: analysis of individual data for 25 676 887 patients from 279 population-based registries in 67 countries (CONCORD-2)

*Claudia Allemani, Hannah K Weir, Helena Carreira, Rhea Harewood, Devon Spika, Xiao-Si Wang, Finian Bannon, Jane V Ahn, Christopher J Johnson, Audrey Bonaventure, Rafael Marcos-Gragera, Charles Stiller, Gulnar Azevedo e Silva, Wan-Qing Chen, Olufemi J Ogunbiyi, Bernard Rachet, Matthew J Soeberg, Hui You, Tomohiro Matsuda, Magdalena Bielska-Lasota, Hans Storm, Thomas C Tucker, Michel P Coleman, and the CONCORD Working Group**

International Cancer Benchmarking Partnership (2011) [6]

Cancer survival in Australia, Canada, Denmark, Norway, Sweden, and the UK, 1995–2007 (the International Cancer Benchmarking Partnership): an analysis of population-based cancer registry data

*M P Coleman, D Forman, H Bryant, J Butler, B Rachet, C Maringe, U Nur, E Tracey, M Coory, J Hatcher, C E McGahan, D Turner, L Marrett, M L Gjerstorff, T B Johannesen, J Adolfsson, M Lambe, G Lawrence, D Meechan, E J Morris, R Middleton, J Steward, M A Richards, and the ICBP Module 1 Working Group**

Beral & Peto, *BMJ* 2010;341:c4112

UK cancer survival statistics

Are misleading and make survival look worse than it is

RESEARCH, p 335

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Competing interests: Both authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from either

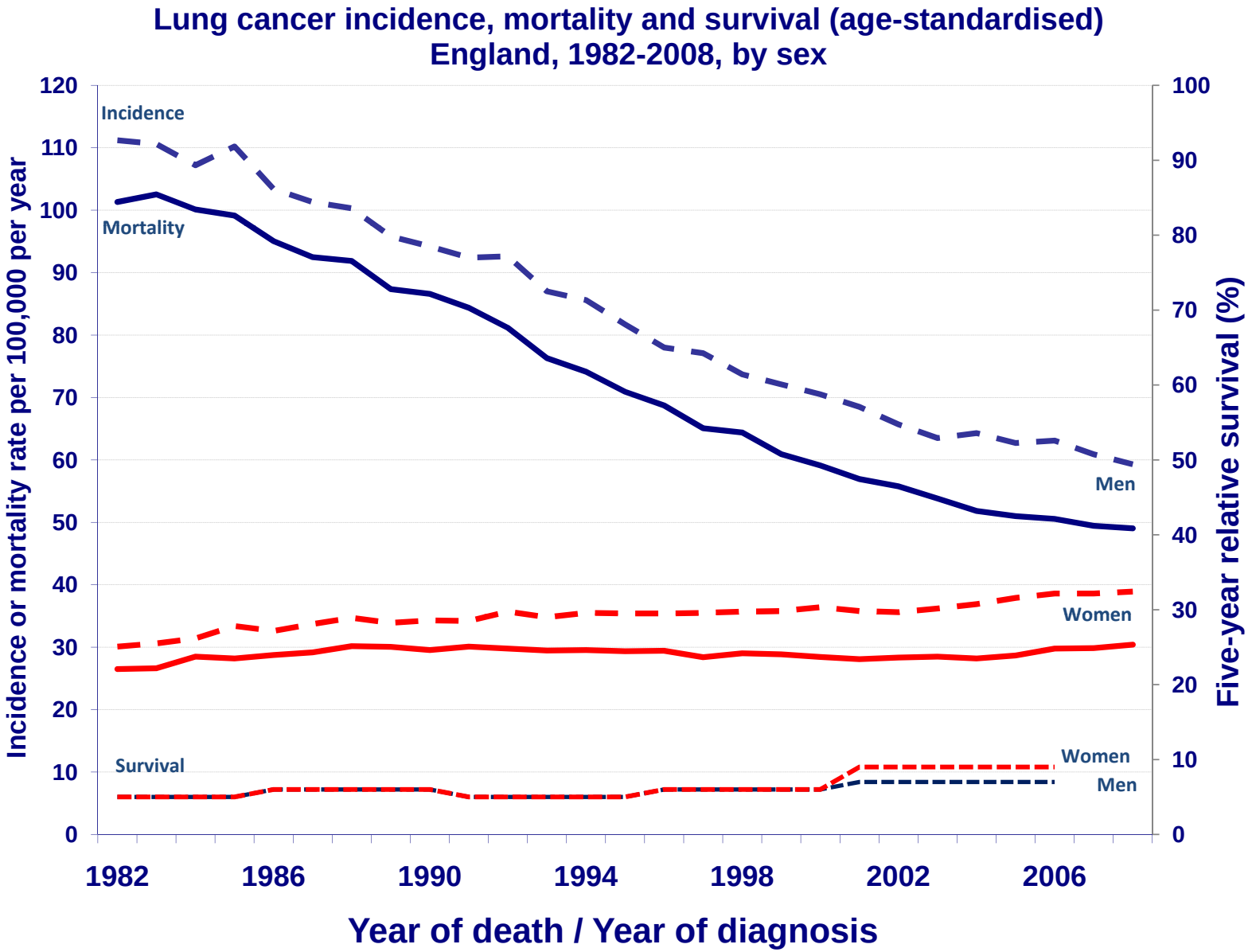
In the linked article, Autier and colleagues report that (population based) breast cancer mortality rates have fallen over the past two decades in many European countries, with a greater decline in the United Kingdom than in any other large country.[1] That the UK is leading Europe in the speed with which national breast cancer mortality rates are falling is in stark contrast to, and at first sight difficult to reconcile with, claims that survival after breast cancer onset is worse in the UK than elsewhere in western Europe.[2]

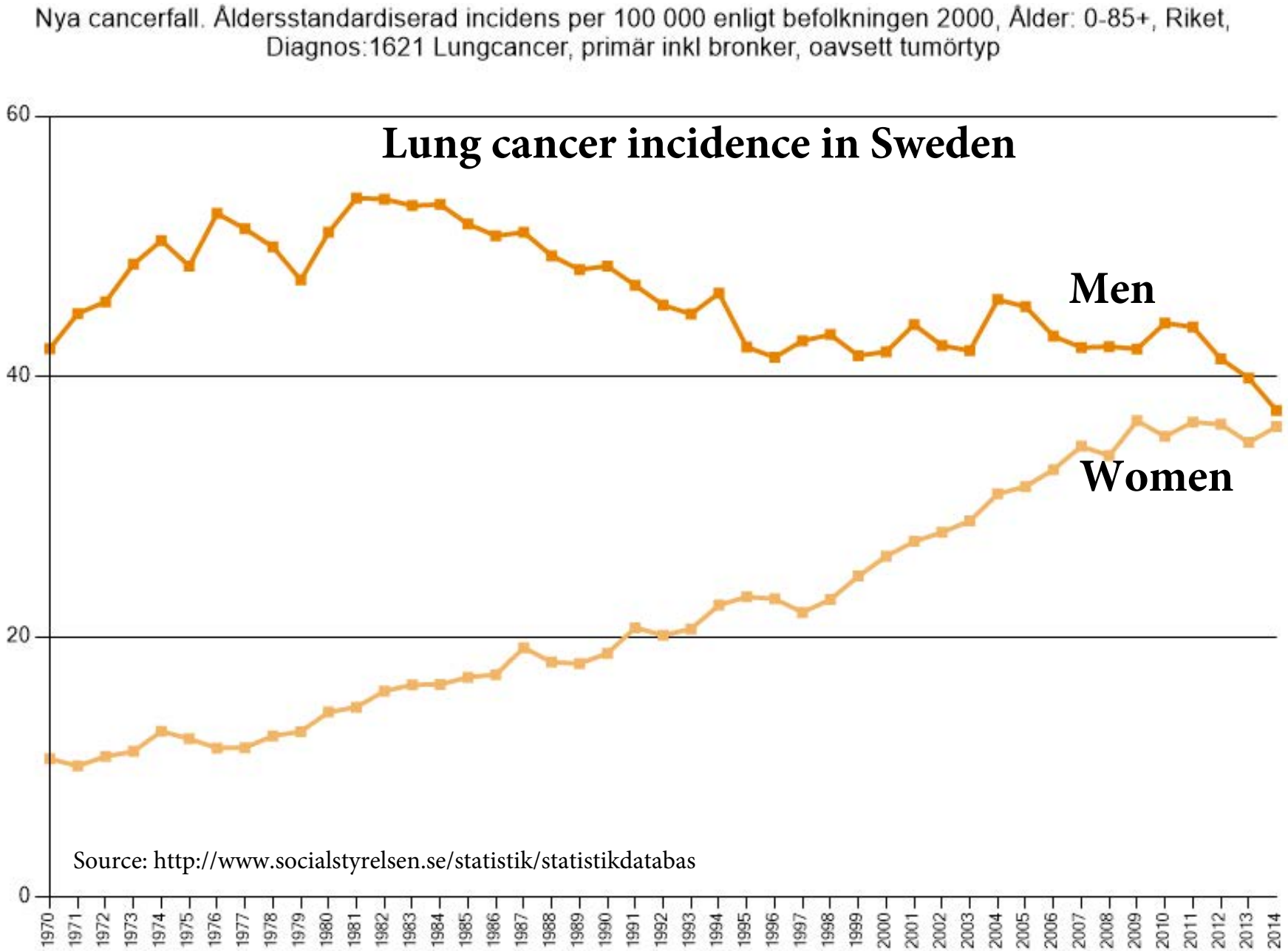
The unpromising UK cancer survival estimates are, however, misleading. In contrast, population based mortality trends are reasonably reliable (at least in middle age, for example, people aged 35-69 years) because a death certificate is legally required before someone can be buried

vival calculations based on registry data make UK cancer survival rates seem significantly worse than they really are.

Information in cancer registries on deaths from cancer is virtually complete because every death certificate that mentions cancer is automatically sent to one of the regional registries that, between them, cover the UK. That cancer is then registered, and further information is sought (not always successfully) from medical records. Death certificates have for decades played an important role in the way UK registries identify people with cancer. Without this source of information, many such cancers could have been missed; even with it, many people who die of cancer may have no record other than the death certificate ever traced by the registry ("death certificate only" cases) or may have had only the later phase

- 'In the absence of internationally comparable data on breast cancer survival rates, it is of interest to compare the reliably known trends in population based mortality rates in middle age.'


Lung cancer incidence, mortality and survival (age-standardised)
England, 1982-2008, by sex
Incidence
Mortality
Men
Women
Survival
Women
Men
Incidence or mortality rate per 100,000 per year
Five-year relative survival (%)
Year of death / Year of diagnosis
120
110
100
90
80
70
60
50
40
30
20
10
0
1982
1986
1990
1994
1998
2002
2006


Nya cancerfall. Åldersstandardiserad incidens per 100 000 enligt befolkningen 2000, Ålder: 0-85+, Riket,
Diagnos:1621 Lungcancer, primär inkl bronker, oavsett tumörtyp
Lung cancer incidence in Sweden
Men
Women
60
40
20
0
1970
1971
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1974
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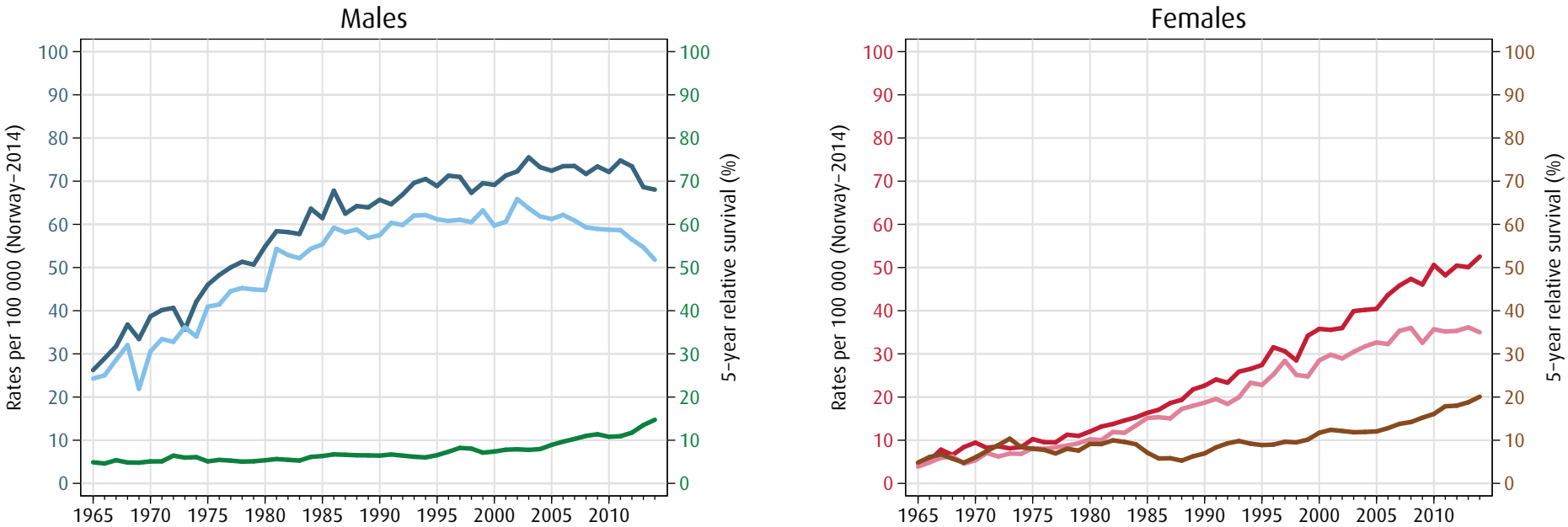
2013
2014
Source: http://www.socialstyrelsen.se/statistik/statistikdatabas

Figure 11. Trends in incidence and mortality rates and 5-year relative survival proportions

Figure 11-J: Lung, trachea (ICD-10 C33–34)



From Dickman & Adami (2006) [2] 'Interpreting trends in cancer patient survival'

- Until primary prevention programmes succeed to the point of eradicating cancer, doctors must effectively diagnose and treat the cancers that arise and require a means of measuring progress in this specific area.
- Patient survival rates provide such a measure whereas population mortality rates may not as they also reflect changes in incidence.
- For example, lung cancer mortality rates are decreasing in many countries, not because we have become better at diagnosing and treating those individuals that develop lung cancer but because successful primary prevention has reduced lung cancer incidence.

How might we measure the prognosis of cancer patients?

- Total mortality (among the patients).
- Our interest is typically in net mortality (mortality associated with a diagnosis of cancer).
- Cause-specific mortality provides an estimate of net mortality (under certain assumptions).
- When estimating cause-specific mortality only those deaths which can be attributed to the cancer in question are considered to be events.

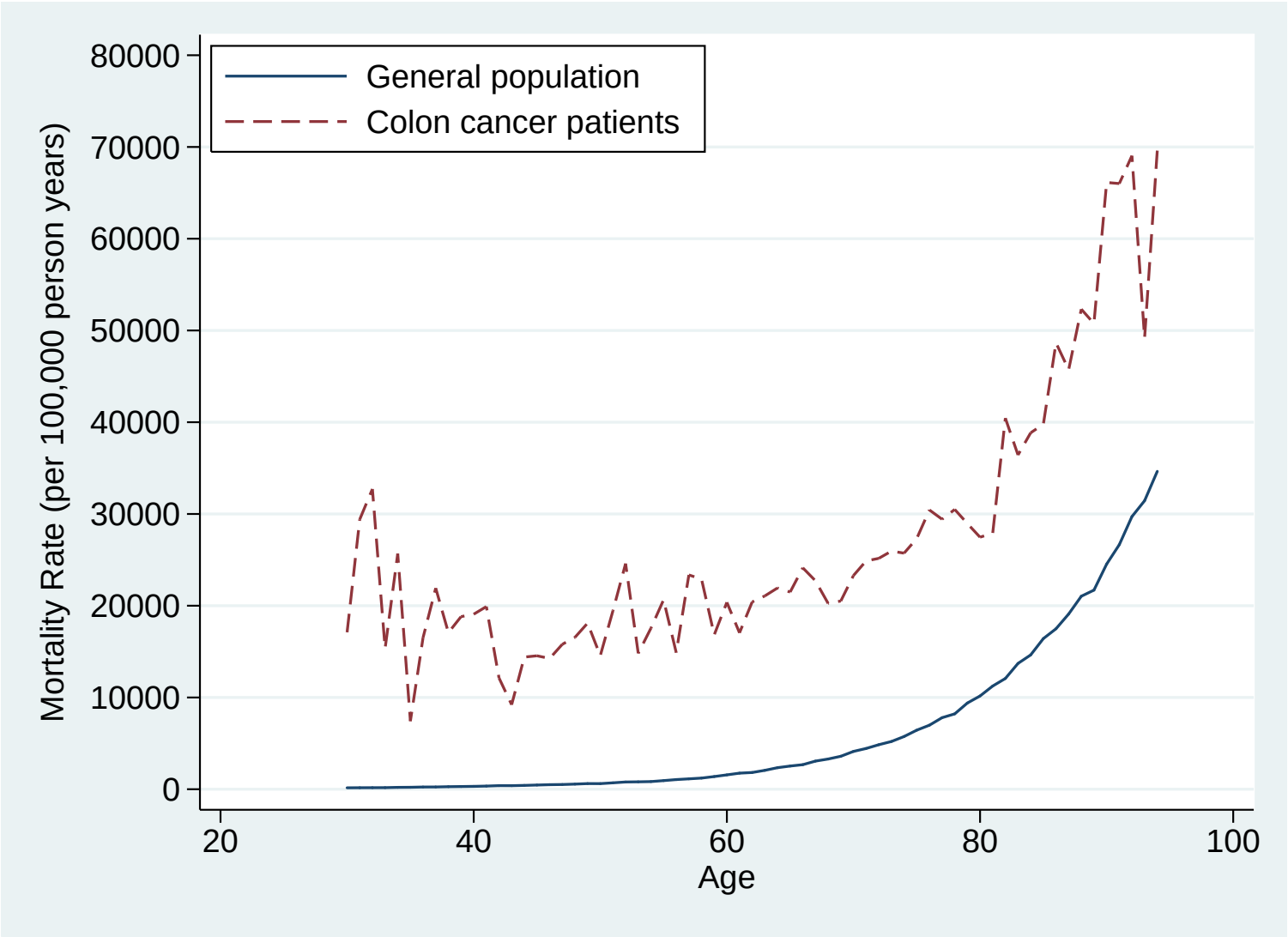
$$\text{cause-specific mortality} = \frac{\text{number of deaths due to cancer}}{\text{person-time at risk}}$$

The survival times of patients who die of causes other than cancer are censored.

Cause-specific survival can estimate net survival (assuming conditional independence)

- Using cause-specific methods requires that reliably coded information on cause of death is available.
- Even when cause of death information is available to the cancer registry via death certificates, it is often vague and difficult to determine whether or not cancer is the primary cause of death.
- How do we classify, for example, deaths due to treatment complications?
- Consider a patient treated with radiation therapy and chemotherapy who dies of cardiovascular disease. Do we classify this death as 'due entirely to cancer' or 'due entirely to other causes'?

All-cause mortality for males with colon cancer and Finnish population



Relative survival aims to estimate net survival (still need conditional independence)

- We estimate excess mortality: the difference between observed (all-cause) and expected mortality.

$$\begin{array}{ccccc} \text{excess} & = & \text{observed} & - & \text{expected} \\ \text{mortality} & & \text{mortality} & & \text{mortality} \end{array}$$

- Relative survival is the survival analog of excess mortality — the relative survival ratio is defined as the observed survival in the patient group divided by the expected survival of a comparable group from the general population.

$$\text{relative survival ratio} = \frac{\text{observed survival proportion}}{\text{expected survival proportion}}$$

Cervical cancer in New Zealand 1994 – 2001
Life table estimates of patient survival

Women diagnosed 1994 - 2001 with follow-up to the end of 2002

I	N	D	W	Effective number at risk	Interval-specific observed survival	Interval-specific relative survival	Cumulative observed survival	Cumulative expected survival	Cumulative relative survival
1	1559	209	0	1559.0	0.86594	0.87472	0.86594	0.98996	0.87472
2	1350	125	177	1261.5	0.90091	0.90829	0.78014	0.98192	0.79450
3	1048	58	172	962.0	0.93971	0.94772	0.73310	0.97362	0.75296
4	818	32	155	740.5	0.95679	0.96459	0.70142	0.96574	0.72630
5	631	23	148	557.0	0.95871	0.96679	0.67246	0.95766	0.70218
6	460	10	130	395.0	0.97468	0.98284	0.65543	0.94972	0.69013
7	320	5	129	255.5	0.98043	0.98848	0.64261	0.94198	0.68219
8	186	3	134	119.0	0.97479	0.98405	0.62641	0.93312	0.67130
9	49	1	48	25.0	0.96000	0.97508	0.60135	0.91869	0.65457

Relative survival example (skin melanoma)

Table 1: Number of cases (N) and 5-year observed (p), expected (p^*), and relative (r) survival for males diagnosed with localised skin melanoma in Finland during 1985–1994.

Age	N	p	p^*	r
15–29	67	0.947	0.993	0.954
30–44	273	0.856	0.982	0.872
45–59	503	0.824	0.943	0.874
60–74	449	0.679	0.815	0.833
75+	200	0.396	0.505	0.784

- Relative survival controls for the fact that expected mortality depends on demographic characteristics (age, sex, etc.).
- In addition, relative survival may, and usually does, depend on such factors.

Examples of Relative Survival Being Problematic (Extract from Table 4 from Howlader *et al.* [7])

Selected cancer cohort	White		
	RS, % (95% CI)	CSS, % (95% CI)	Dif., %
Breast			
In situ and <65 y	100.9†	99.7 (99.6 to 99.8)	1.2
In situ and ≥65 y	107.5†	98.6 (98.4 to 98.8)	8.9
Prostate			
Localized/ regional and <65 y	101.3†	98.3 (98.2 to 98.4)	3.0
Localized/ regional and ≥65 y	104.5†	94.8 (94.6 to 94.9)	9.8

Relative survival not as problematic as one might think for lung cancer [8]

Should relative survival be used with lung cancer data?

SR Hinchliffe*[,1], MJ Rutherford[1], MJ Crowther[1], CP Nelson[1,2] and PC Lambert[1,3]

[1]Department of Health Sciences, Centre for Biostatistics and Genetic Epidemiology, 2nd Floor Adrian Building, University Road, University of Leicester, Leicester LE1 7RH, UK; [2]Department of Cardiovascular Sciences, Clinical Sciences Wing, Glenfield General Hospital, University of Leicester, Leicester LE3 9QP, UK; [3]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, PO Box 281, Stockholm SE-171 77, Sweden

BACKGROUND: Under certain assumptions, relative survival is a measure of net survival based on estimating the excess mortality in a study population when compared with the general population. Background mortality estimates are usually taken from national life tables that are broken down by age, sex and calendar year. A fundamental assumption of relative survival methods is that if a patient did not have the disease of interest then their probability of survival would be comparable to that of the general population. It is argued, as most lung cancer patients are smokers and therefore carry a higher risk of smoking-related mortalities, that they are not comparable to a population where the majority are likely to be non-smokers.

METHODS: We use data from the Finnish Cancer Registry to assess the impact that the non-comparability assumption has on the estimates of relative survival through the use of a sensitivity analysis.

RESULTS: Under realistic estimates of increased all-cause mortality for smokers compared with non-smokers, the bias in the estimates of relative survival caused by the non-comparability assumption is negligible.

CONCLUSION: Although the assumption of comparability underlying the relative survival method may not be reasonable, it does not have a concerning impact on the estimates of relative survival, as most lung cancer patients die within the first 2 years following diagnosis. This should serve to reassure critics of the use of relative survival when applied to lung cancer data.

British Journal of Cancer advance online publication, 3 May 2012; doi:10.1038/bjc.2012.182 www.bjcancer.com

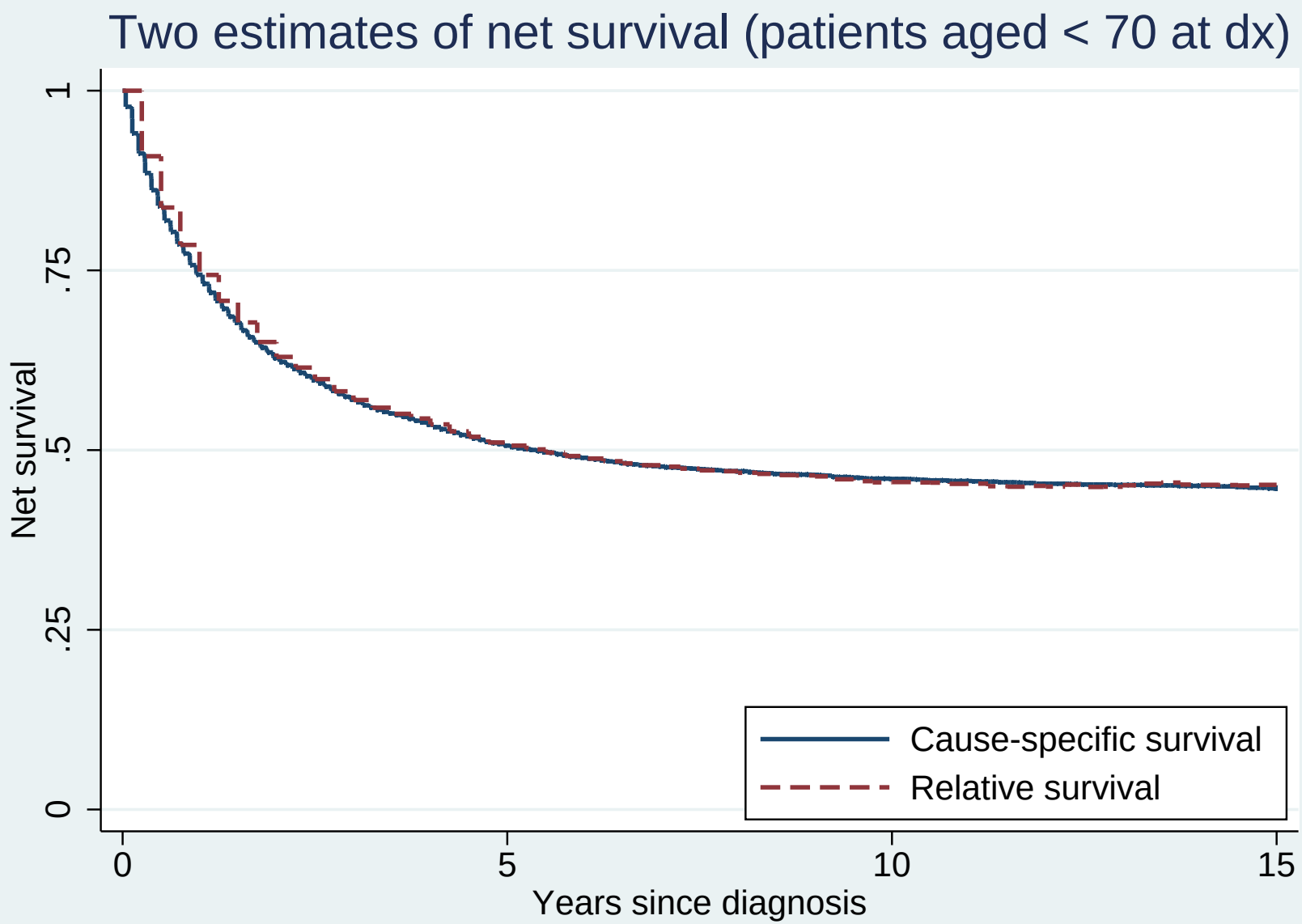
Summary: the choice between relative and cause-specific survival for estimating net survival

- Both aim to estimate the same underlying quantity (net survival).
- Both methods involve assumptions specific to the approach:

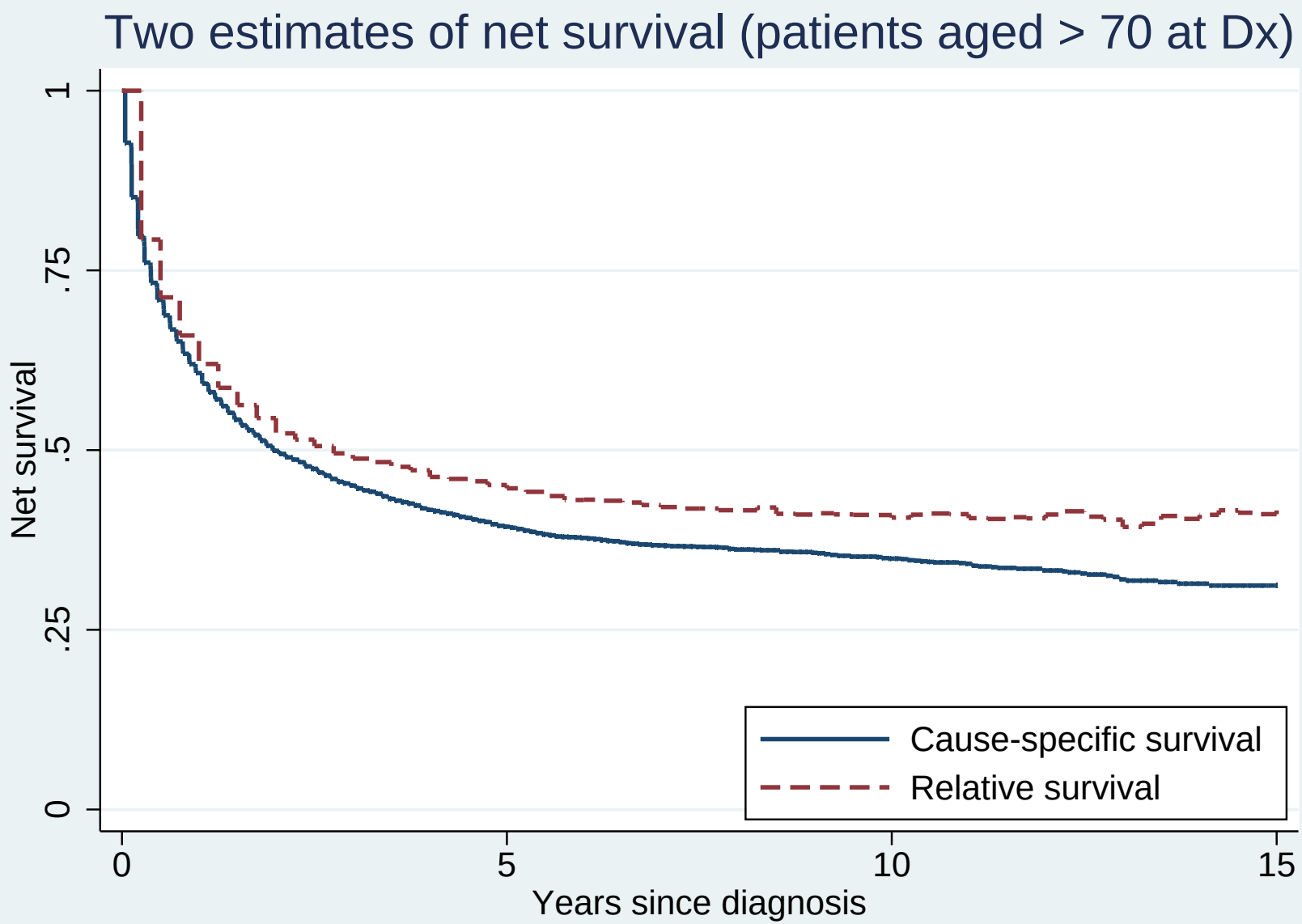
  Cause-specific Accurate classification of cause-of-death

  Relative Appropriate estimation of expected survival
- We choose the approach for which we have the strongest belief in the underlying assumptions.
- For population-based studies this is typically relative survival but every study must be evaluated on its specific merits.

Net survival: colon cancer in Finland



Why the difference for older patients?



Cause-specific survival: colon cancer

- Coding of vital status

```
Freq.   Numeric  Label
 4642          0  Alive
 8369          1  Dead: colon cancer
 2549          2  Dead: other
```

- The event of interest is death due to colon cancer.
- Other events are known as 'competing events' or 'competing risks'.
- Based on the research question, we choose between one of two quantities to estimate:
  1. *Eliminate* the competing events (estimate net survival)
  2. *Accommodate* the competing events (estimate crude survival)

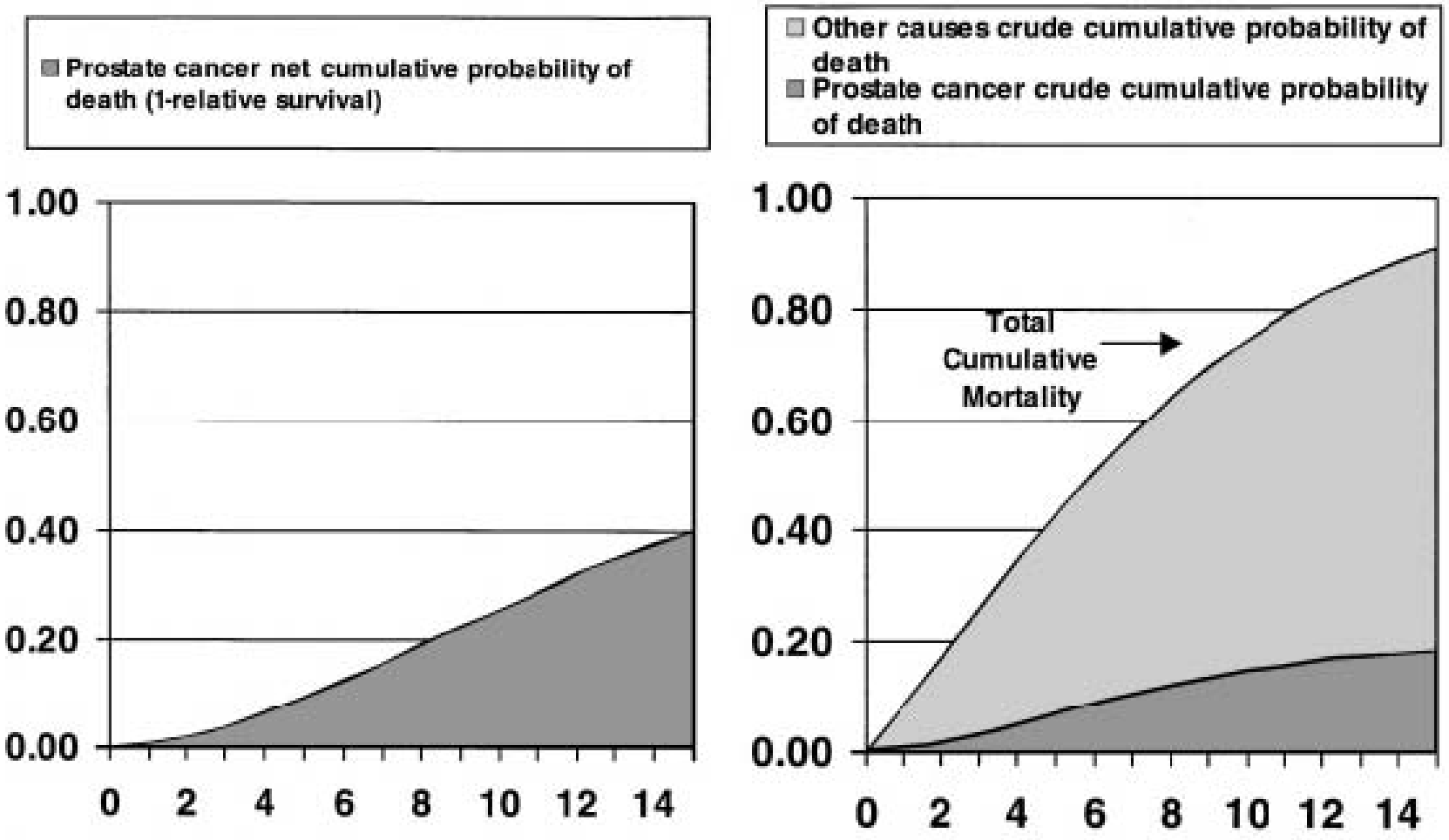
We have a choice of two measures

Net probability of death due to cancer	=	Probability of death in a hypothetical world where the cancer under study is the only possible cause of death

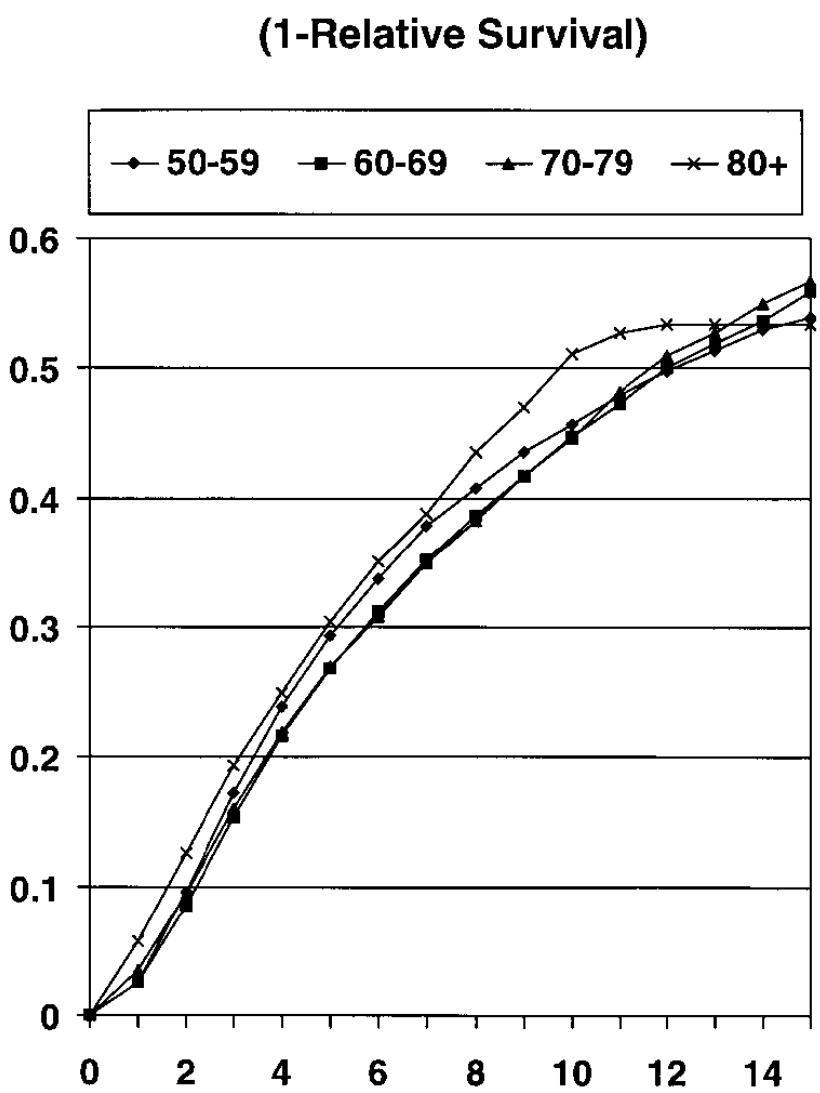
Crude probability of death due to cancer	=	Probability of death in the real world where you may die of other causes before the cancer kills you

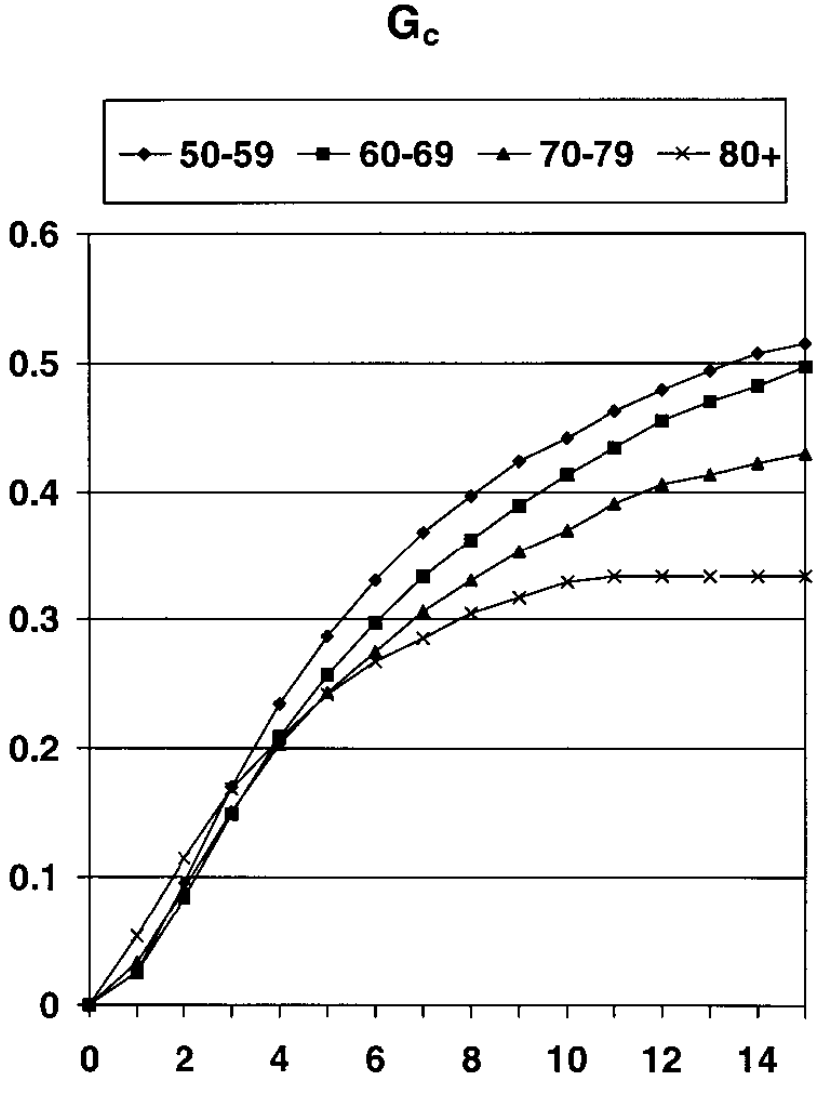
- Net probability also known as the marginal probability.
- Crude probability also known as cumulative incidence function.

Net (left) and crude (right) probabilities of death in men with localized prostate cancer aged 70+ at diagnosis (Cronin and Feuer [9])



Net (left) and crude (right) probabilities of death due to cancer in women with regional breast cancer (Cronin and Feuer [9])





Explaining net/relative survival to non-scientists

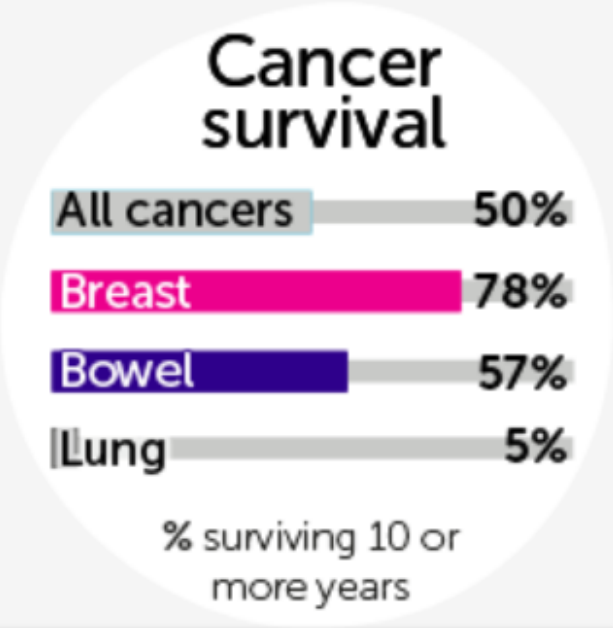
- Organisations that report survival statistics to the general public are often reluctant to describe relative/net survival in a technically correct manner.
- 'Patients will not understand hypothetical world explanations' they argue.
- I argue that, if that's the case, one should report crude (real world) survival rather than estimate net survival and then describe it as something else.

www.cancerresearchuk.org [June 2014]

Net survival was estimated to be 50%.

Cancer survival statistics

- 50% of adult cancer patients diagnosed in 2010-2011 in England and Wales are predicted to survive 10 or more years.
- 46% of men and 54% of women cancer patients diagnosed in 2010-2011 in England and Wales are predicted to survive 10 or more years.
- Cancer survival rates in the UK have doubled in the last 40 years.



www.cancerresearchuk.org/cancer-info/cancerstats/survival/

What does a relative survival of 50% mean? 10-year probabilities of death [10]

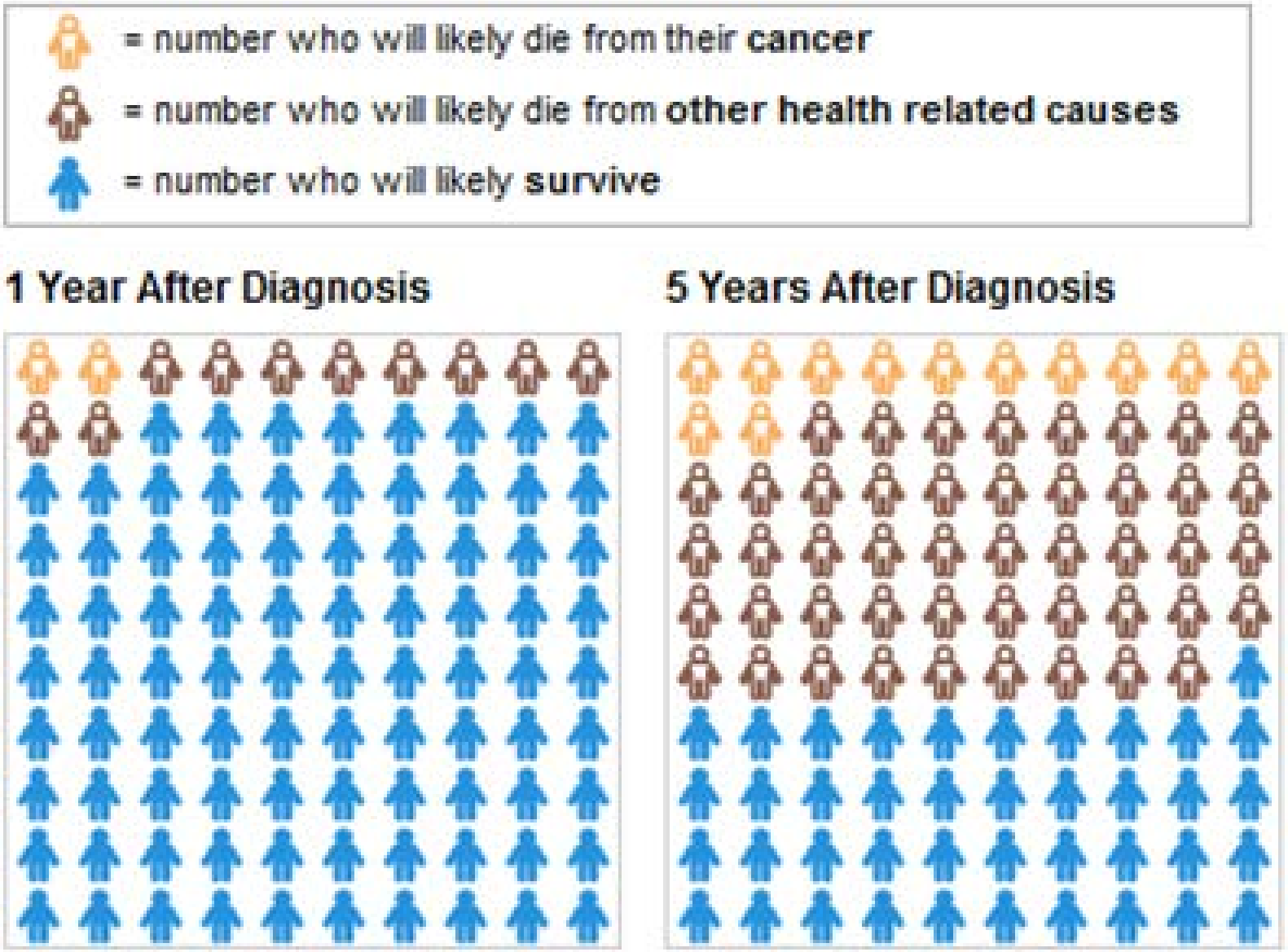
Measure	Age 40	Age 60	Age 80
Net prob. of death (1-rel surv)	0.50	0.50	0.50
Crude (actual): cancer death	0.49	0.48	0.42
Crude (actual): non-cancer death	0.02	0.08	0.42
Crude (actual): any cause death	0.51	0.57	0.84

Page has been updated [June 2015]

- Same data, new interpretation.
- An improvement, but vague.
- How will readers interpret ‘survive cancer’?
- I recognise the need to reduce technical jargon for a general audience.
- Not so for scientific journals.

Survive cancer for 10 or more years, 2010-11, England and Wales

Natural frequencies presented using infographics

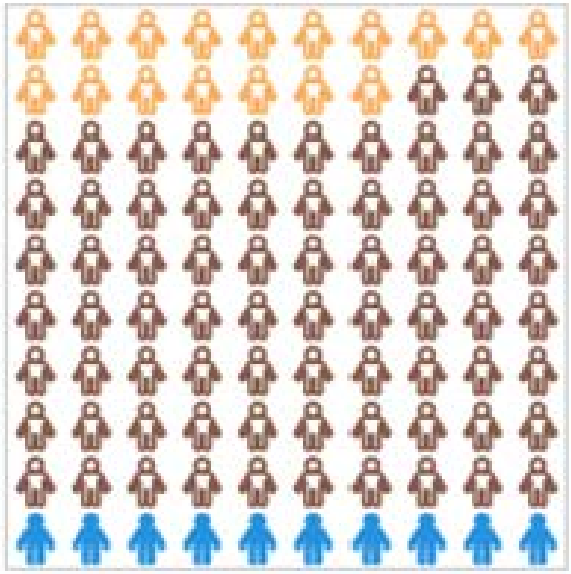


Cancer Survival Query System (Rocky Feuer)

1 Year After Diagnosis

5 Years After Diagnosis

10 Years After Diagnosis



It is estimated that by:

1 year after diagnosis:
Approximately 2 out of 100 will die from their cancer,
Approximately 10 out of 100 will die from other causes,
Approximately 88 out of 100 will survive.

5 years after diagnosis:
Approximately 12 out of 100 will die from their cancer,
Approximately 47 out of 100 will die from other causes,
Approximately 41 out of 100 will survive.

Modify Charts

Type: People Chart

Chart 1: 1 year after diagnosis

Chart 2: 5 years after diagnosis

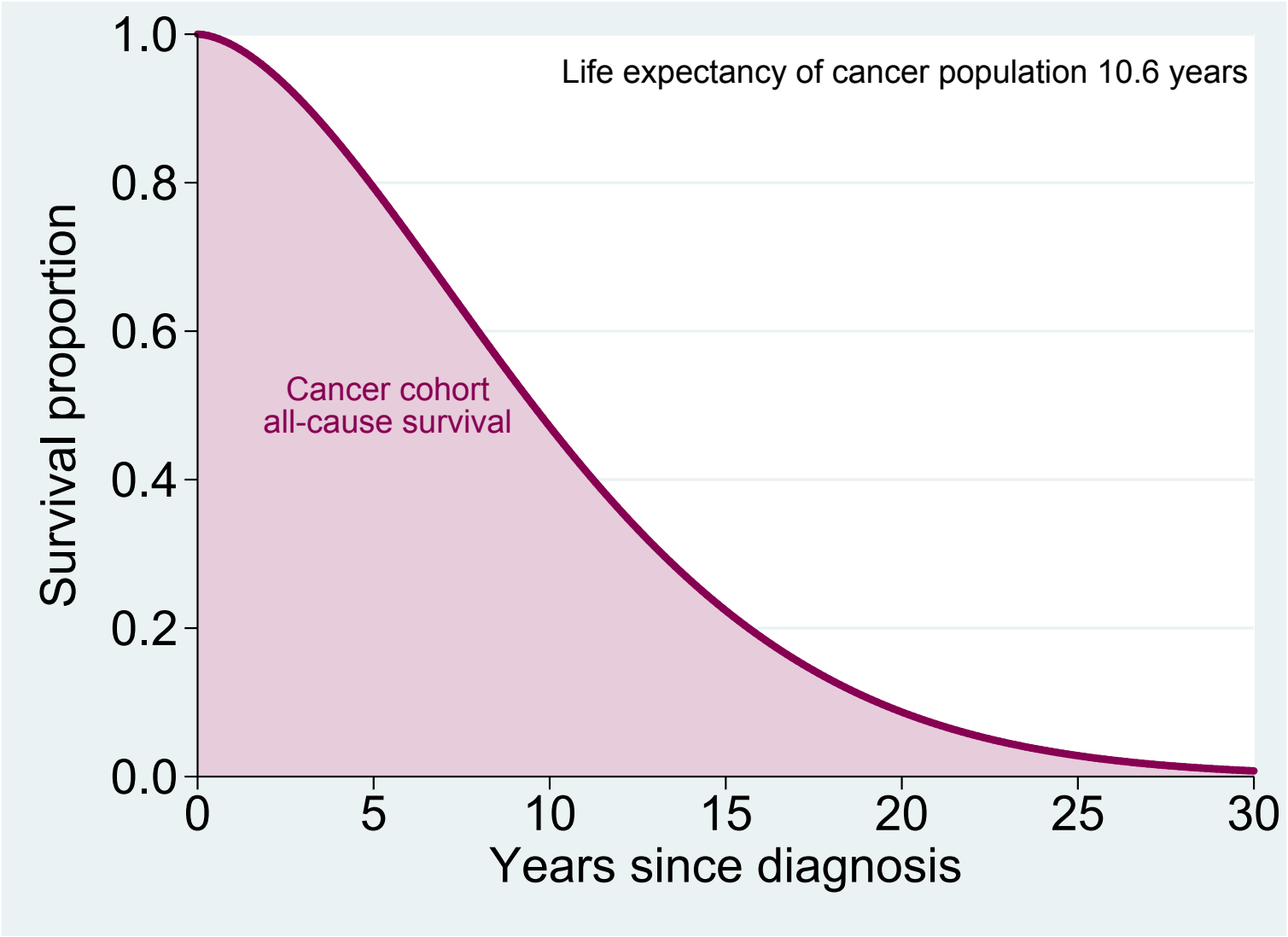
Chart 3: 10 years after diagnosis

Update Charts

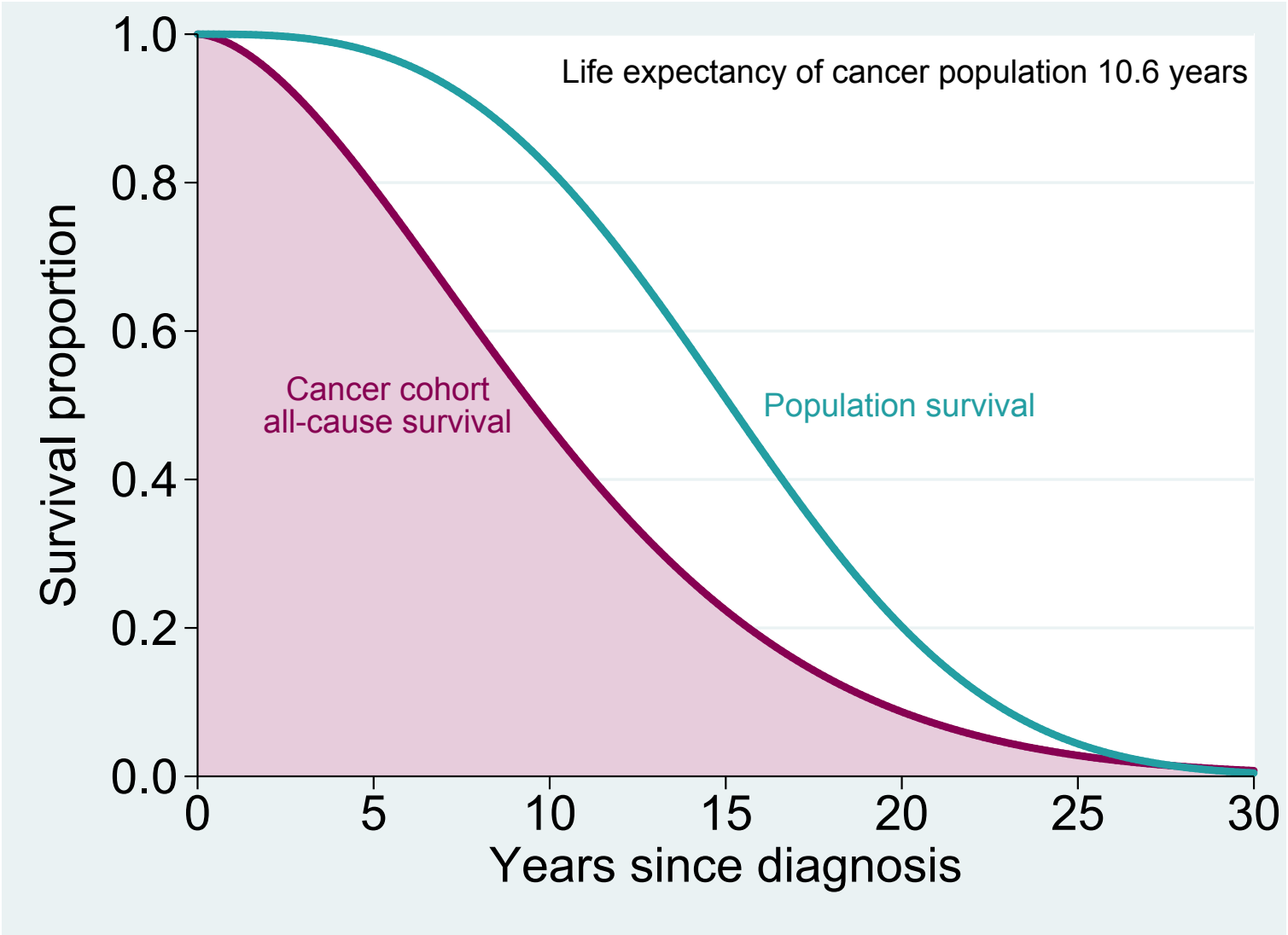
Loss in expectation of life

- A useful summary measure of survival is the mean survival, life expectancy
- The loss in expectation of life is the difference between the mean expected survival (if not diagnosed with cancer) and the mean observed survival (for cancer patients)
- Quantify disease burden in the society "how many life-years are lost due to the disease?"
- Quantify differences between socio-economic groups or countries, "how many life-years are lost in the population due to differences in cancer patient survival between groups?" "how many life-years would be gained if England had the same cancer patient survival as Sweden?"
- Quantify the impact a cancer diagnosis has on a patient's life expectancy

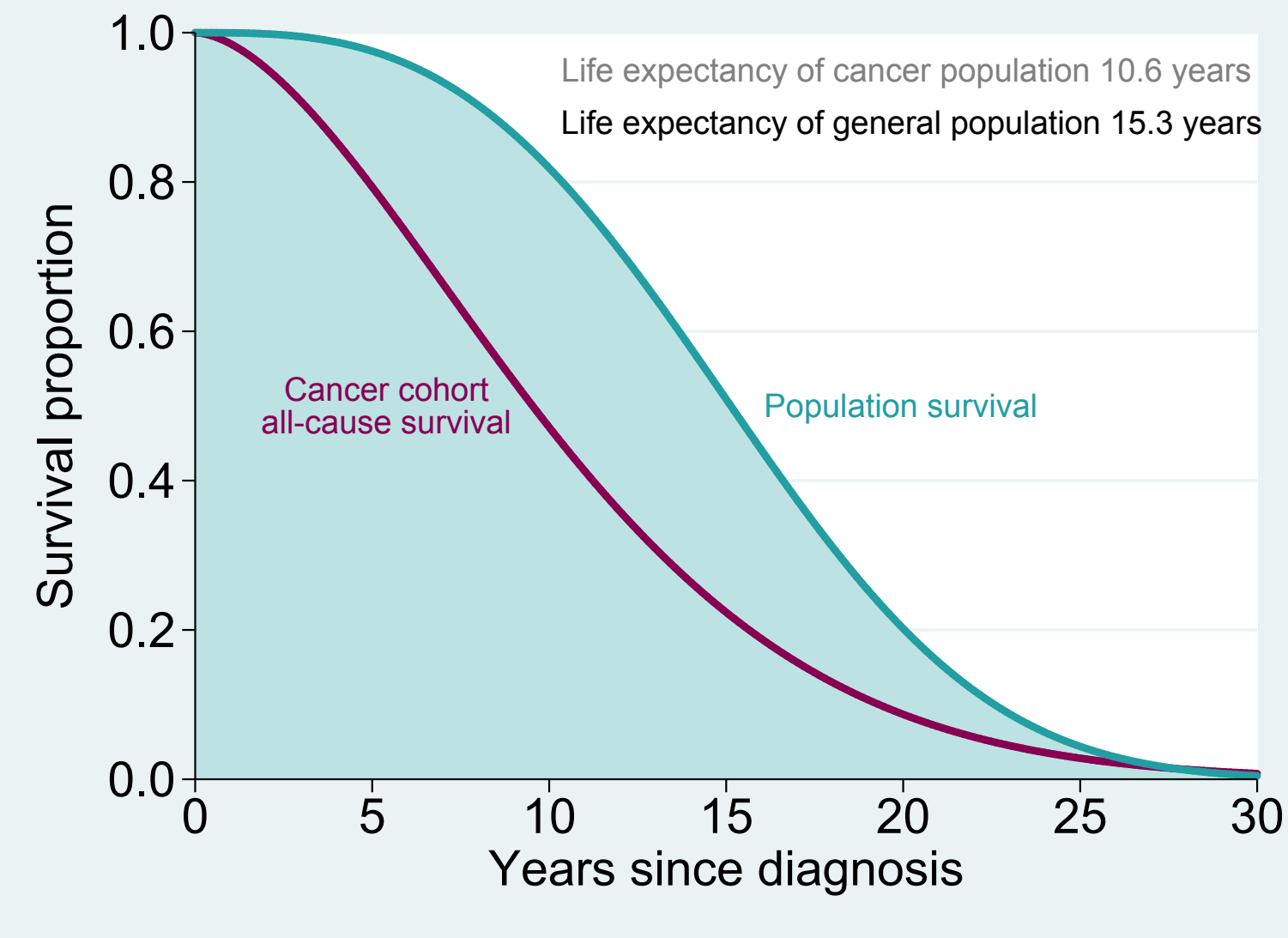
Expectation of life



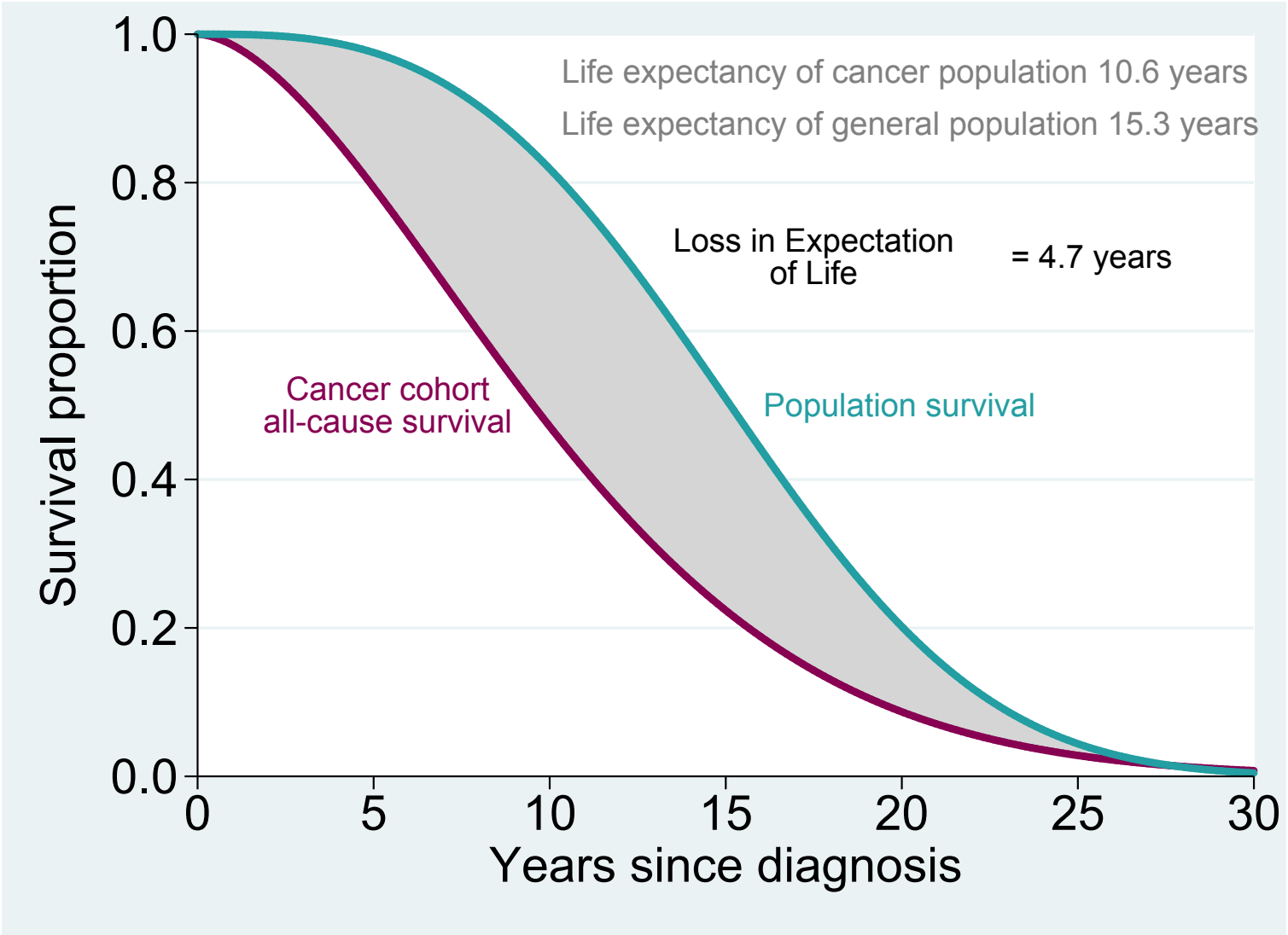
Loss in expectation of life



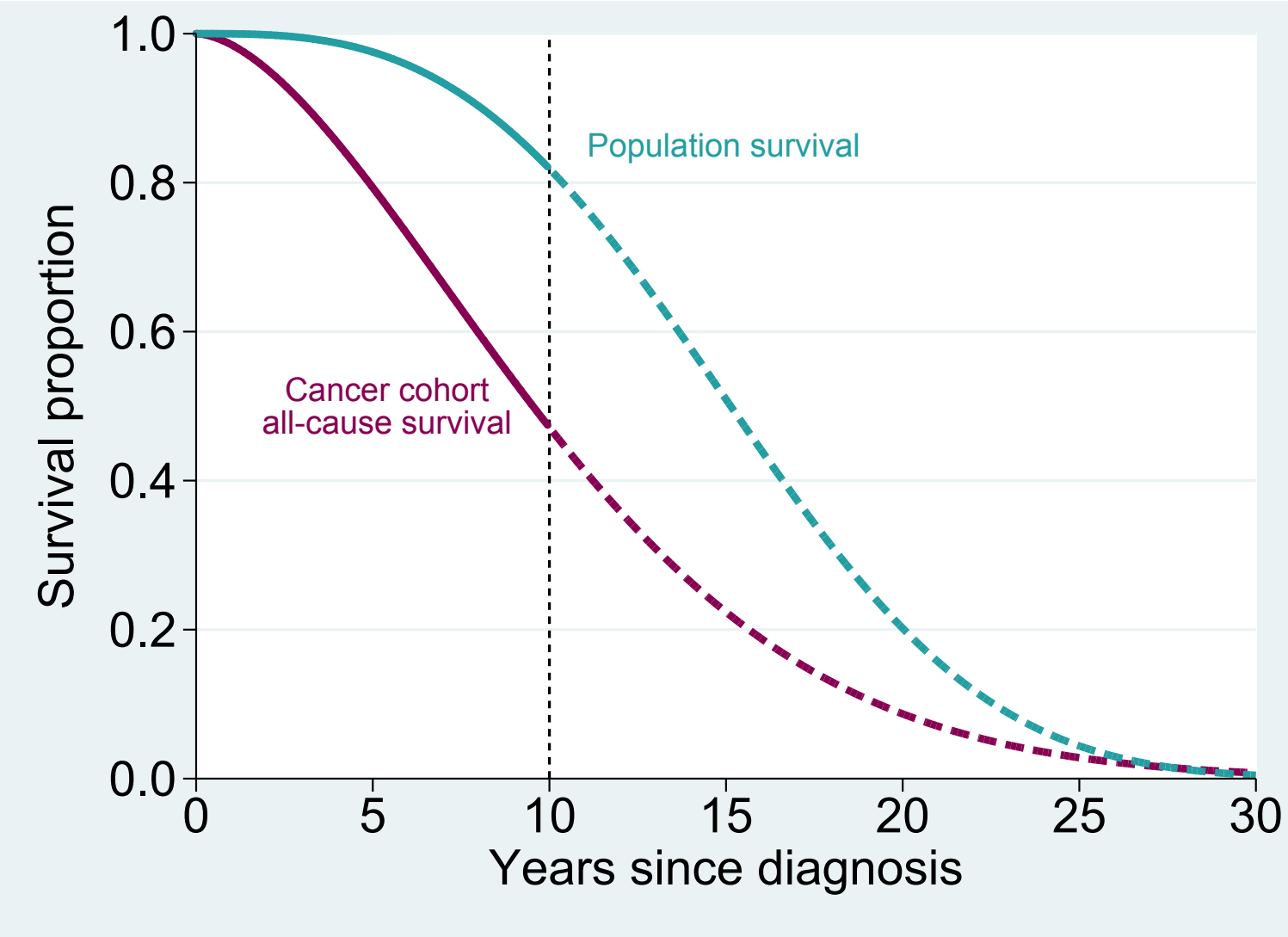
Loss in expectation of life



Loss in expectation of life



Limited follow-up



How do we extrapolate observed survival?

Technical details: recent/current research

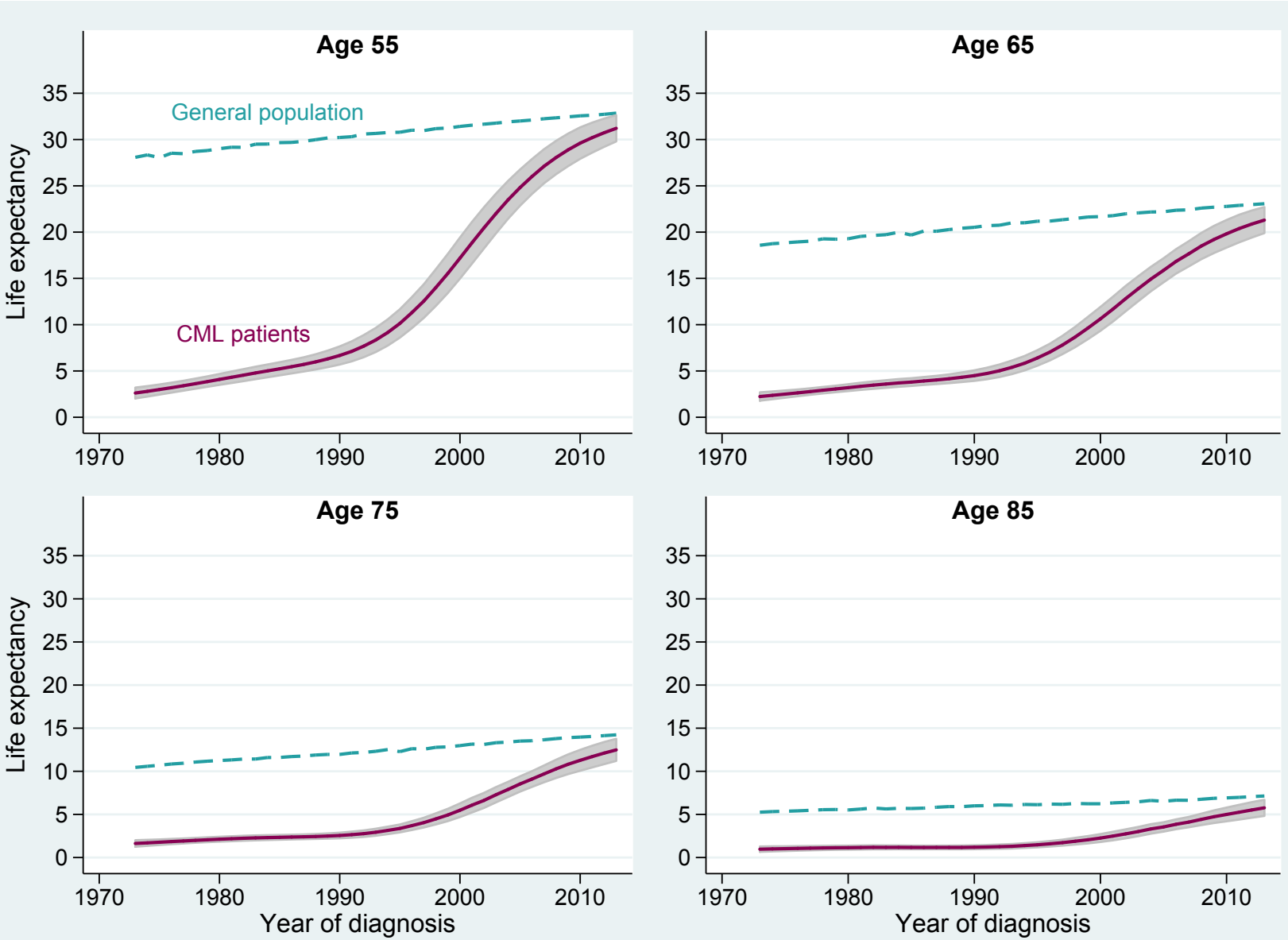
- Even though we are now interested in the all-cause survival we will use a relative survival approach

$$S(t) = S^*(t) \times R(t)$$

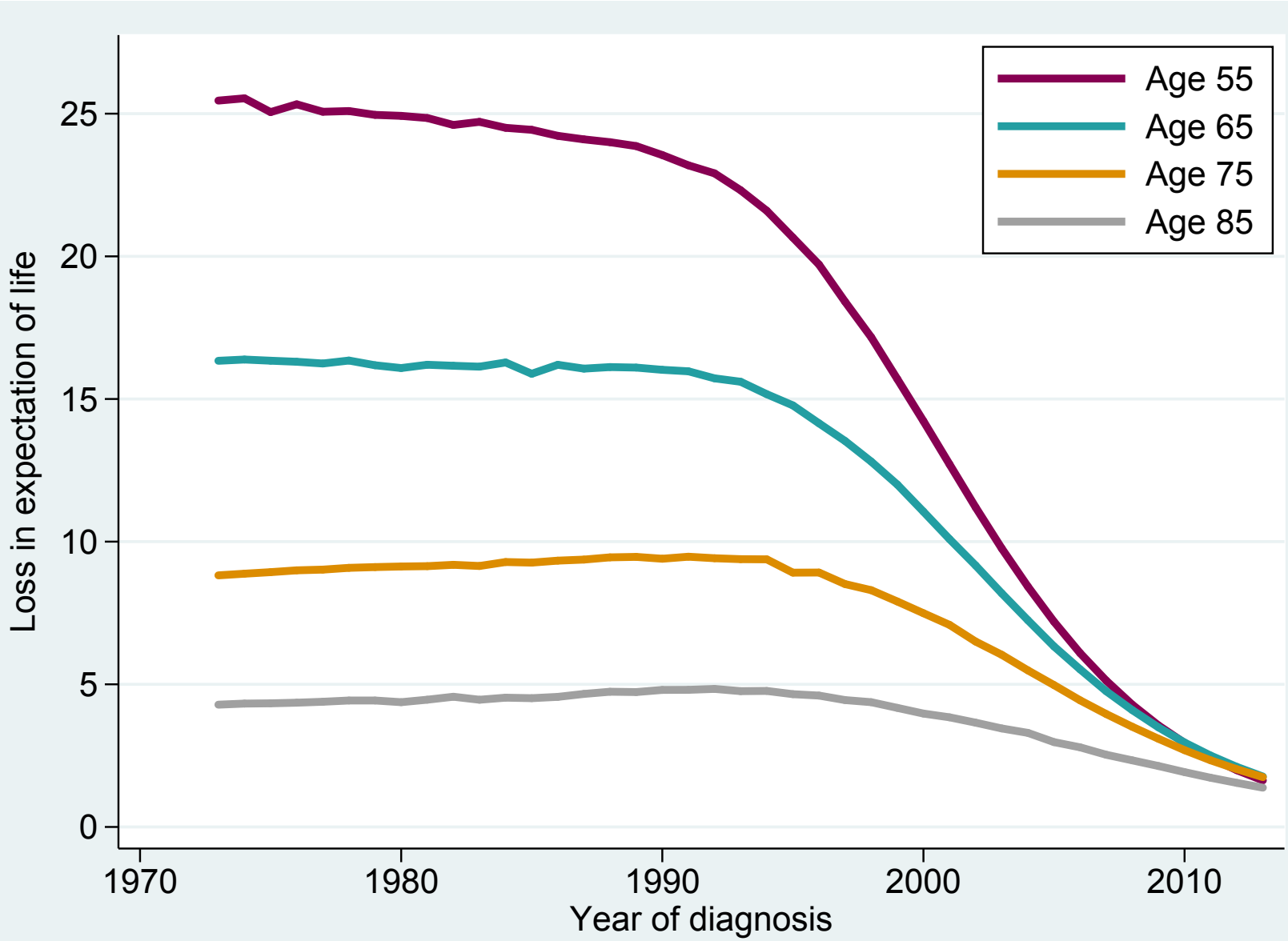
$$h(t) = h^*(t) + \lambda(t)$$

- Easier to extrapolate $R(t)$ than $S(t)$
- Has been done for grouped data (life tables) [13], by assuming $\lambda(t) = 0$ or $\lambda(t) = c$ after some point in time.
- We estimate in the framework of flexible parametric models [14, 15].

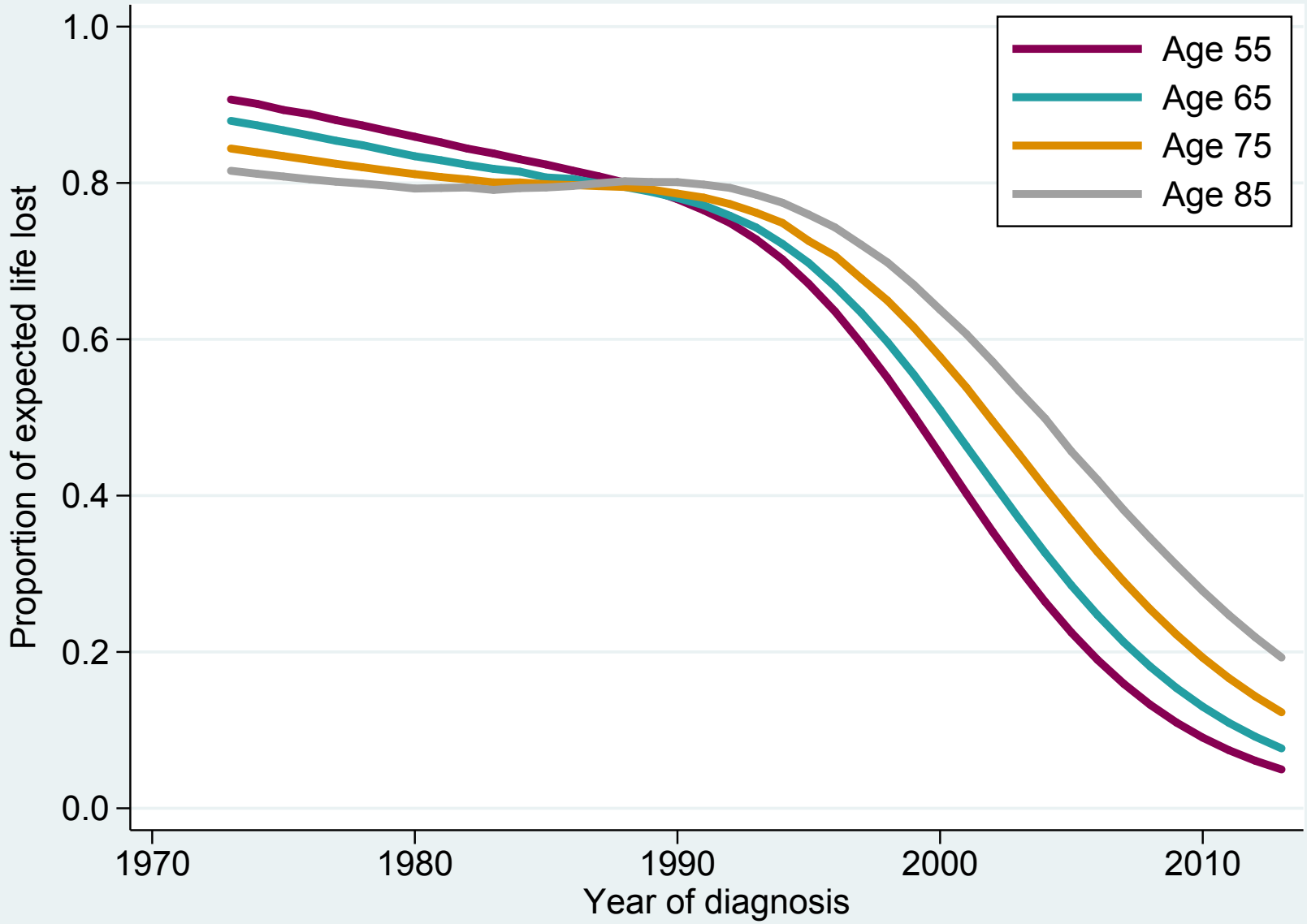
Chronic myeloid leukaemia; Sweden. LE



Chronic myeloid leukaemia; Sweden. LEL



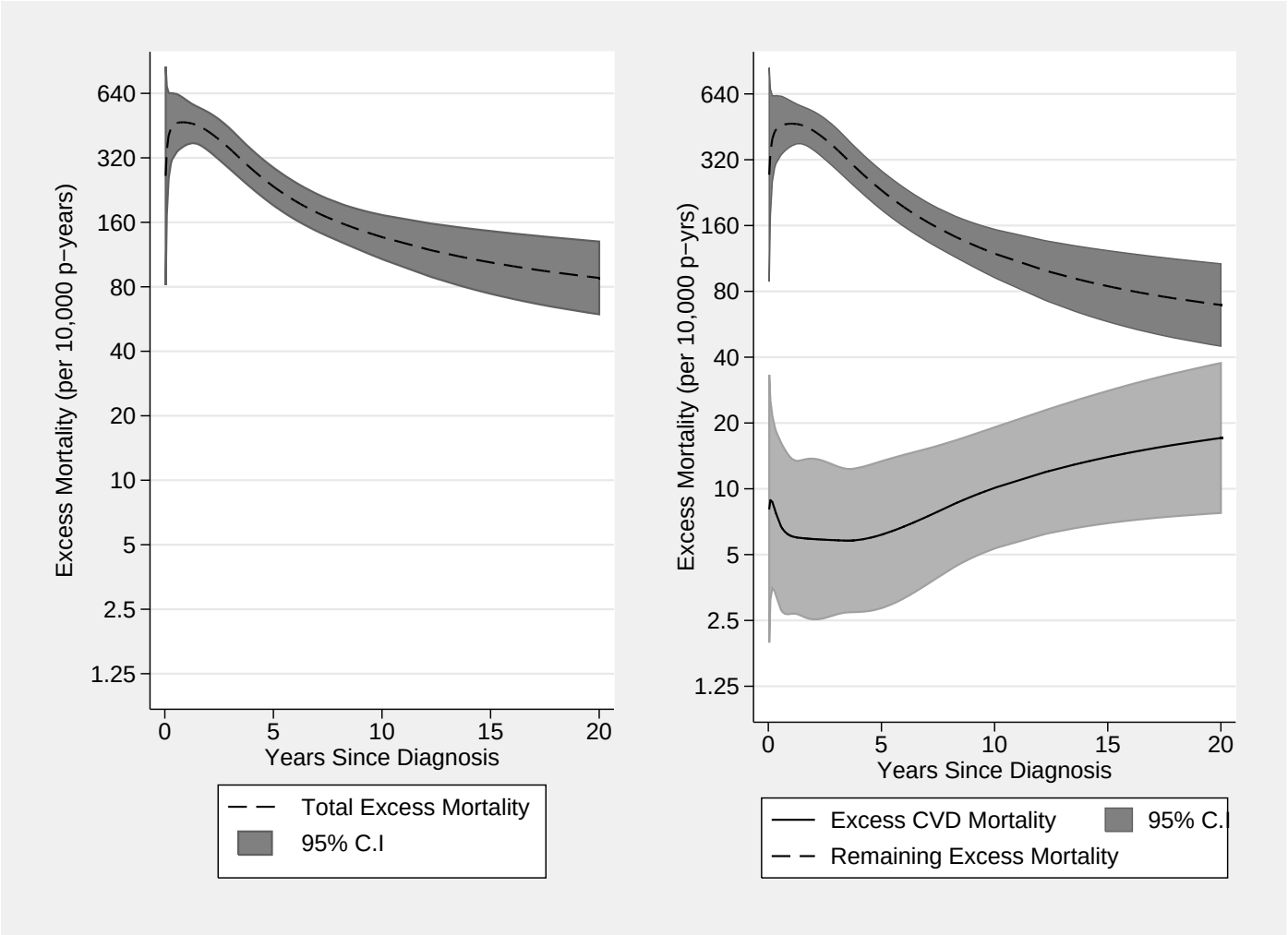
Chronic myeloid leukaemia; Sweden. PELL



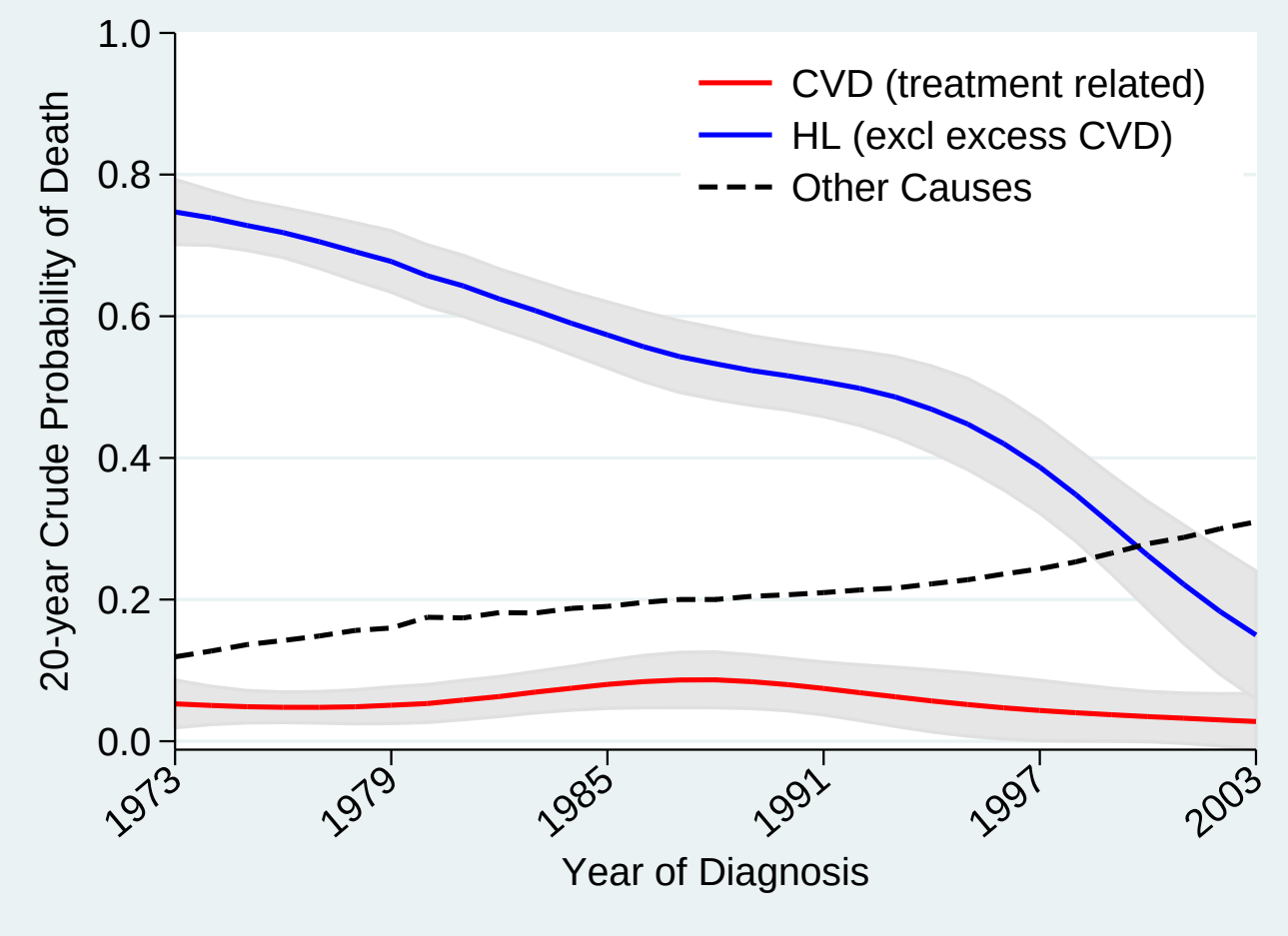
Partitioning excess mortality using flexible parametric survival models

- Relative survival has become the preferred method for studying cancer patient survival as it captures death due to the disease without requiring cause of death information.
- The observed excess mortality might be due to either the underlying disease or treatment-related (CVD, infections, secondary malignancies) but it is not possible to identify these components using a standard relative survival analysis.
- We have developed a method that enables us to partition the total excess mortality into component parts using ideas from classical competing risks theory [16].
- The method was originally developed to study long-term treatment-related excess mortality in patients with Hodgkin lymphoma.

The general idea of partitioning excess mortality into component parts (Hodgkin lymphoma)



Partitioning the crude probabilities of death into component parts



Additional reading

RESEARCH ARTICLE Open Access

Partitioning of excess mortality in population-based cancer patient survival studies using flexible parametric survival models

Sandra Eloranta[1*], Paul C Lambert[1,2], Therese ML Andersson[1], Kamila Czene[1], Per Hall[1], Magnus Björkholm[3] and Paul W Dickman[1]

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

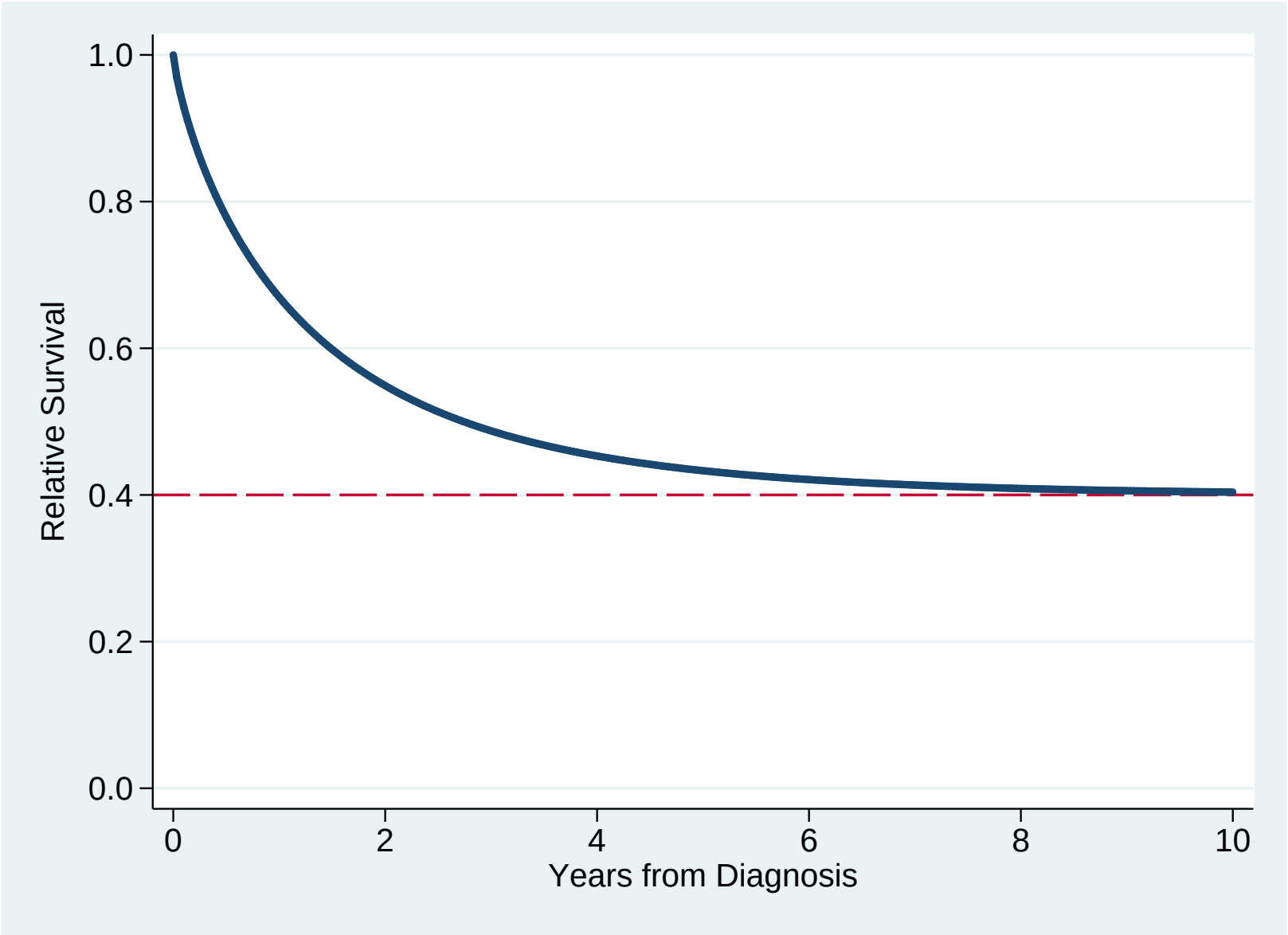
Temporal Trends in Mortality From Diseases of the Circulatory System After Treatment for Hodgkin Lymphoma: A Population-Based Cohort Study in Sweden (1973 to 2006)

Sandra Eloranta, Paul C. Lambert, Jan Sjöberg, Therese M.L. Andersson, Magnus Björkholm, and Paul W. Dickman

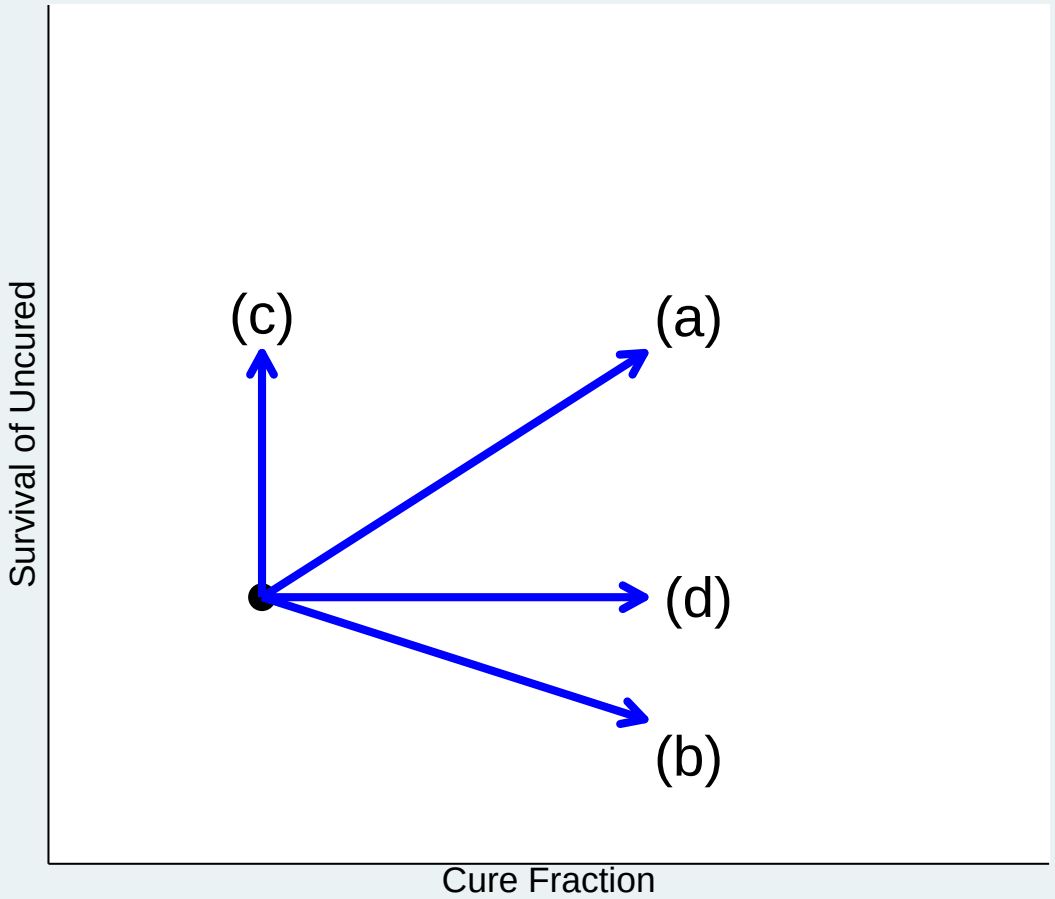
Statistical cure

- Medical cure occurs when all signs of cancer have been removed in a patient; this is an individual-level definition of cure.
- It is difficult to prove that a patient is medically cured.
- Population or statistical cure occurs when mortality among patients with the disease returns to the same level as that expected for the general population.
- Equivalently the *excess* mortality rate approaches zero.
- This is a population-level definition of cure.
- When the excess mortality reaches (and stays) at zero, the relative survival curve is seen to reach a plateau.

Plateau for relative survival



Cure models: Interpreting changes over time



Adapted from Verdeccia (1998)

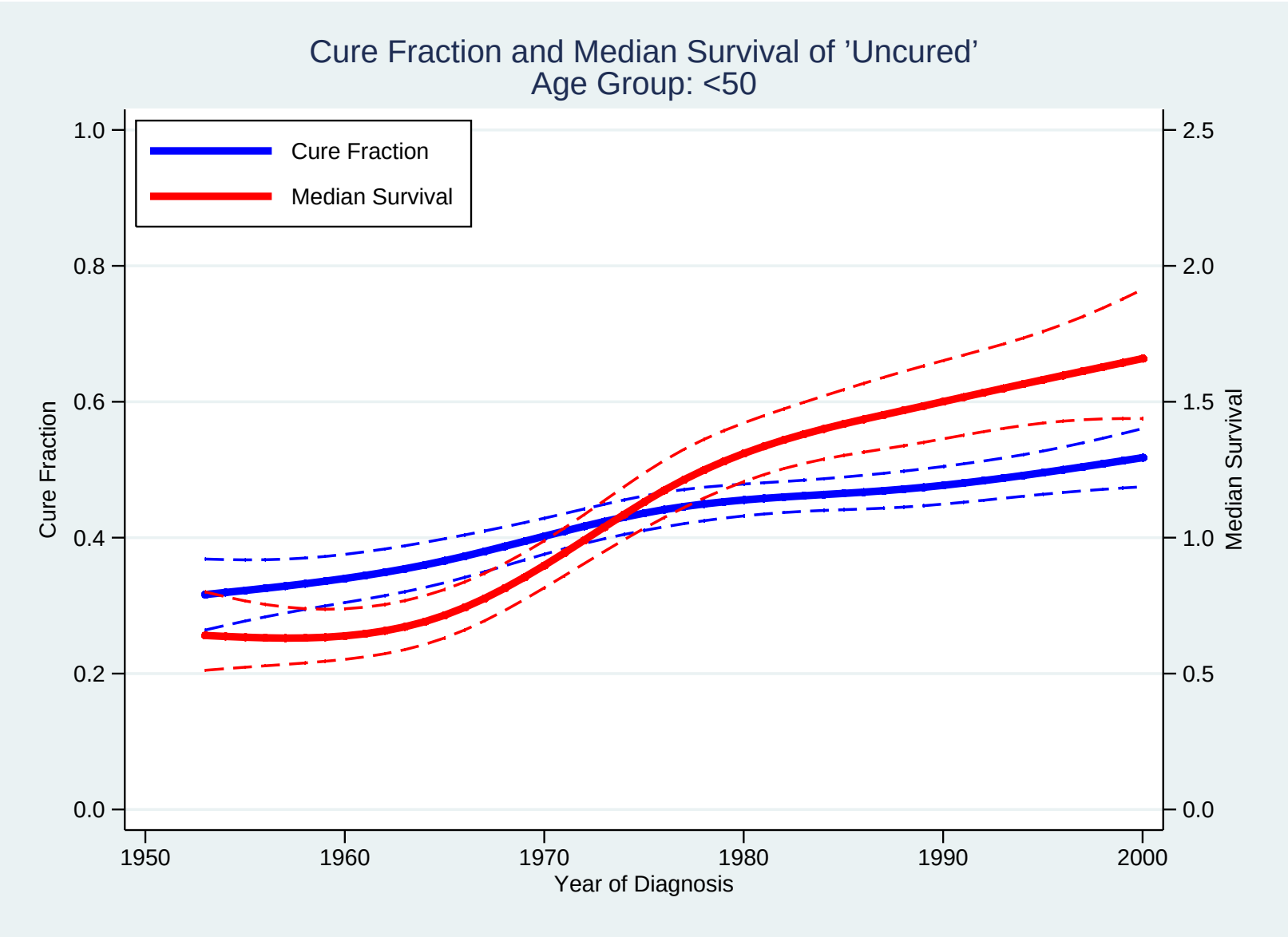
(a) General Improvement

(b) Selective Improvement

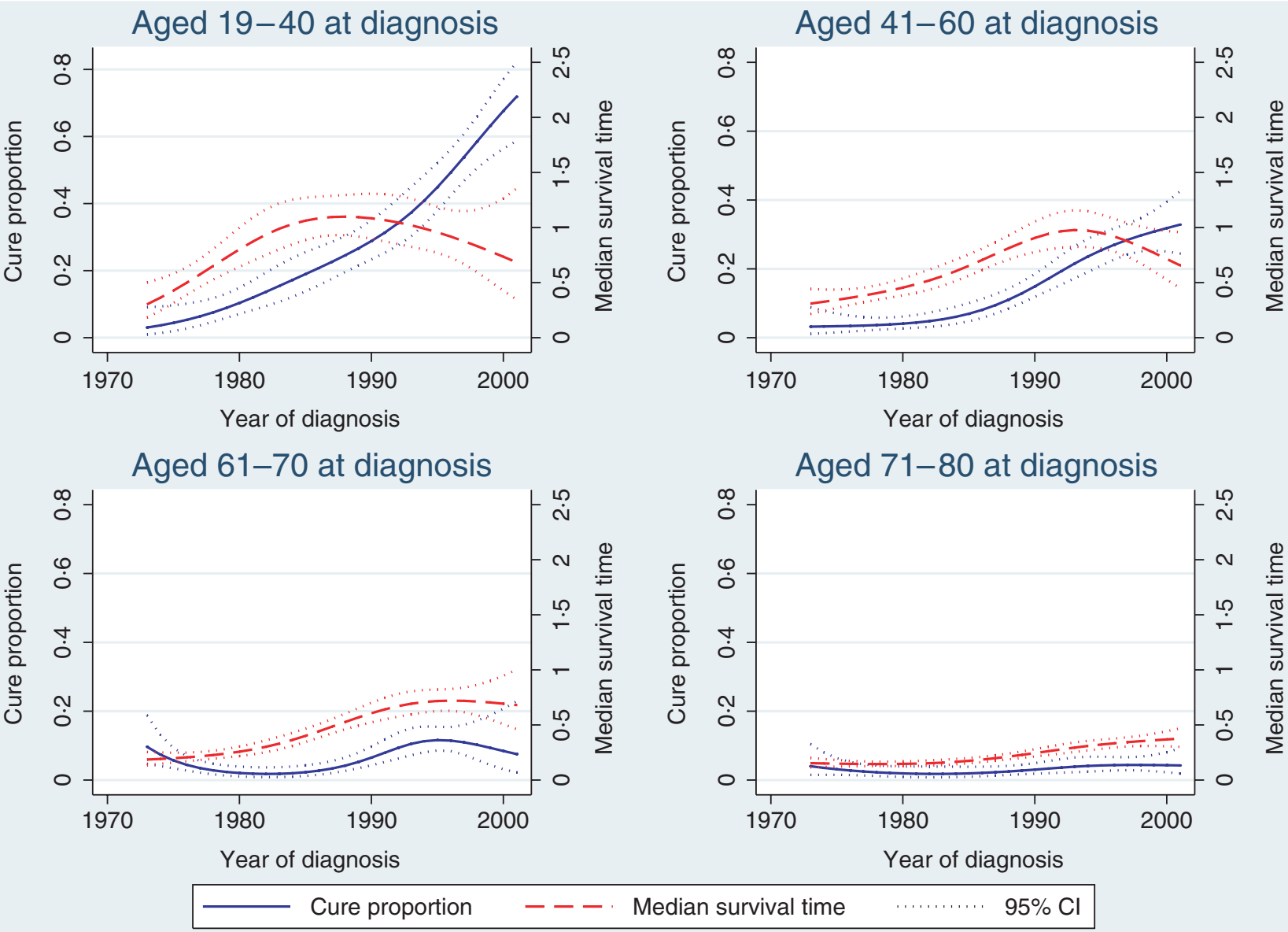
(c) Improved palliative care or lead time

(d) Inclusion of subjects with no excess risk

Time trends for cancer of the colon age <50 [11]



Andersson 2010 [12]: trends for AML



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