Extrapolating survival using flexible parametric models in a relative survival framework with applications in HTA

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Today's talk

- Introduction to the relative survival framework
- Introduction to flexible parametric survival models
- Extrapolating survival using flexible parametric models in a relative survival framework
- Applications in HTA

How might we measure the prognosis of cancer patients?

- We could estimate all-cause mortality (among the patients). In HTA, this is often what we want. It is what we will extrapolate.
- In cancer epidemiology, interest is typically in mortality associated with a diagnosis of cancer so we often prefer cause-specific mortality.
- When estimating cause-specific mortality only those deaths which can be attributed to the cancer in question are considered to be events.

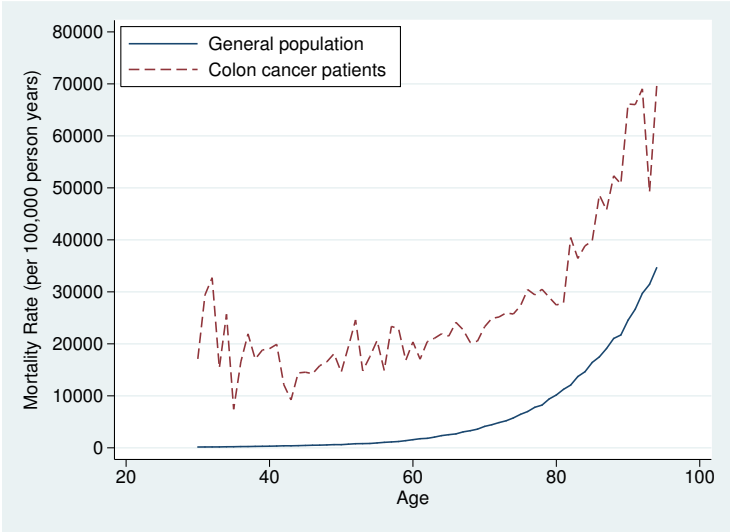
$$\text{cause-specific mortality} = \frac{\text{number of deaths due to cancer}}{\text{person-time at risk}}$$

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

Challenges with the cause-specific framework (with register data)

- 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 male patients and general population



Relative survival / excess mortality

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

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

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

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

Some common survival models

- Commonly used models have the same basic formulation.

$$h_i(t) = h_0(t)\exp(\mathbf{x_i}\beta)$$
$$\ln(h_i(t)) = \ln(h_0(t)) + \mathbf{x_i}\beta$$

- Proportional hazards assumed by default (but can be relaxed).
- Primary difference is in specification of the baseline hazard:
  - Weibull model: $h_0(t) = \lambda\gamma t^{\gamma-1}$
  - Cox model: $h_0(t)$ an arbitrary function of time; not estimated.
  - Flexible parametric model: $h_0(t)$ modelled using splines.

An interview with Sir David Cox (Reid 1994 [1])

Reid "What do you think of the cottage industry that's grown up around [the Cox model]?"

Cox "In the light of further results one knows since, I think I would normally want to tackle the problem parametrically. . . . I'm not keen on non-parametric formulations normally."

Reid "So if you had a set of censored survival data today, you might rather fit a parametric model, even though there was a feeling among the medical statisticians that that wasn't quite right."

Cox "That's right, but since then various people have shown that the answers are very insensitive to the parametric formulation of the underlying distribution. And if you want to do things like predict the outcome for a particular patient, it's much more convenient to do that parametrically."

Flexible Parametric Survival Models [2, 5, 6]

- First introduced by Royston and Parmar (2002) [2].
- Parametric estimate of the baseline hazard without the usual restrictions on the shape of the hazard function (i.e., flexible).
- Applicable for 'standard' and relative survival models.
- Can fit relative survival cure models (Andersson 2011) [3].
- Once we have a parametric expression for the baseline hazard we can easily derive other quantities of interest; e.g., survival function, hazard ratio, hazard differences, expectation of life, marginal (population-averaged) measures.
- Can be fitted in Stata (`stpm2`), R (`rstpm2` or `flexsurv`), and SAS.
- Can also be estimated on the log-hazard scale [4]

Flexible Parametric Models: Basic Idea

- Consider a Weibull survival curve.

$$S(t) = \exp\left(-\lambda t^{\gamma}\right)$$

- If we transform to the log cumulative hazard scale.

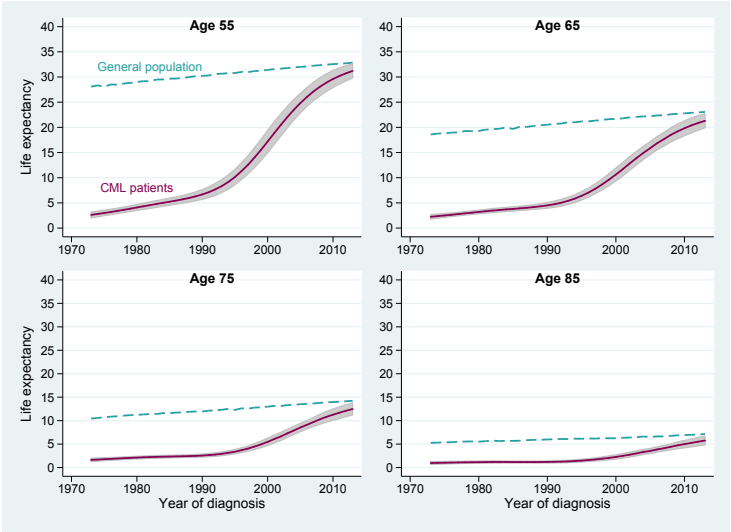
$$\ln\left[H(t)\right] = \ln[-\ln(S(t))] = \ln(\lambda) + \gamma \ln(t)$$

- The log cumulative hazard is a linear function of $\ln(t)$
- Introducing covariates gives

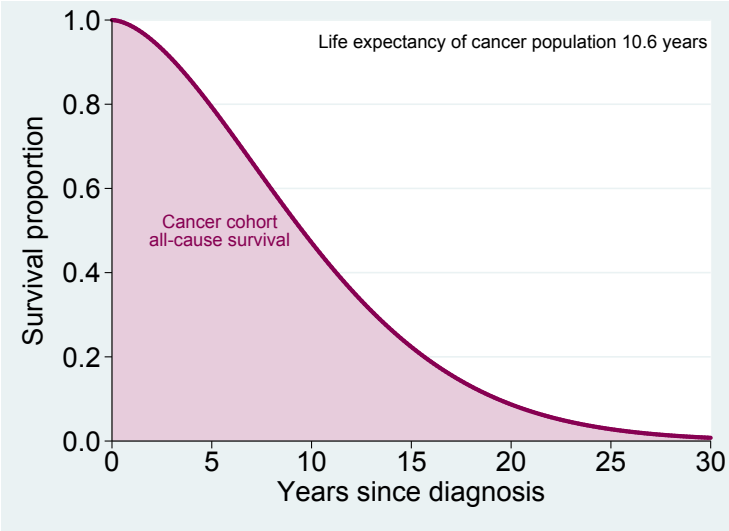
$$\ln\left[H(t|\mathbf{x}_i)\right] = \ln(\lambda) + \gamma \ln(t) + \mathbf{x}_i\boldsymbol{\beta}$$

- Rather than assuming linearity with $\ln(t)$ flexible parametric models, use restricted cubic splines for $\ln(t)$.

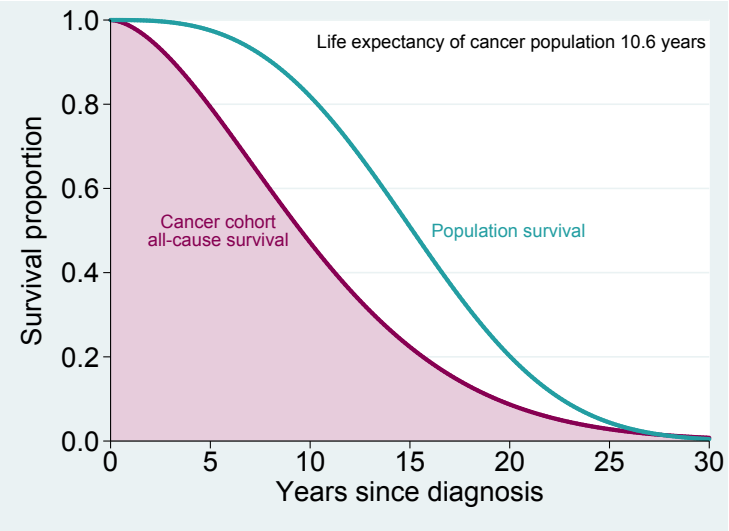
Loss in expectation of life, CML, Sweden [7]



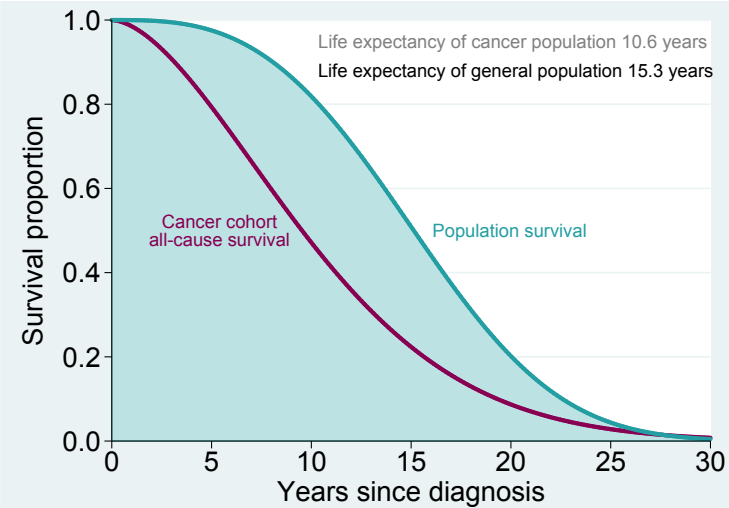
Expectation of life



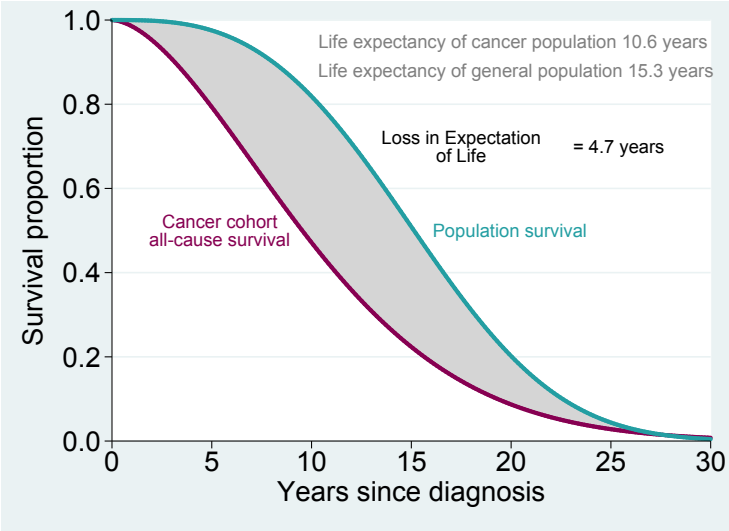
Loss in expectation of life



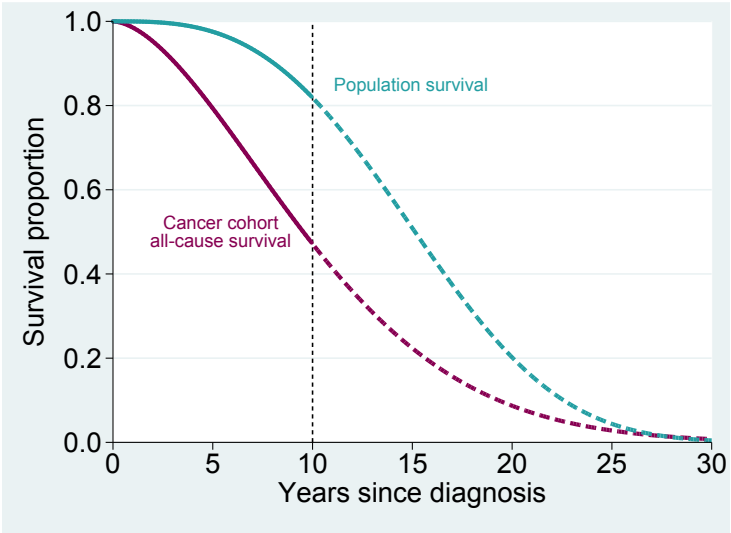
Loss in expectation of life



Loss in expectation of life



Limited follow-up



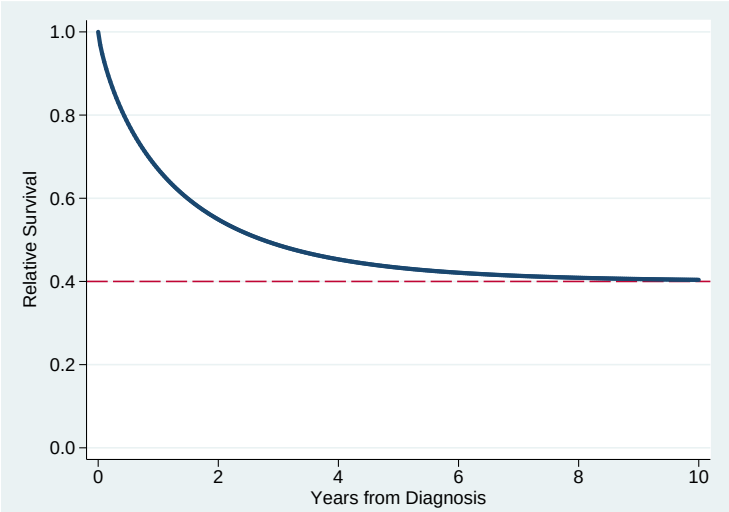
Estimate/extrapolate in a relative survival framework

- 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 relative survival, $R(t)$, than all-cause survival, $S(t)$
- We use flexible parametric models in a relative survival framework [8, 9].

Plateau for relative survival (cure proportion 0.4)



Overview of ongoing research (Enoch Yi-Tung Chen)

		All-cause survival framework		Relative survival framework	
	Outome	SPMs	FPMs	SPMs	FPMs
Andersson2013 [8]	LE			Weibull	X
Gray2021 [10]	10-y RMST	X	X		
In progress	LE and 10-y RMST	X	X	X	X

LE, life expectancy; 10-y RMST, 10-year restricted mean survival time; SPMs, standard parametric models; FPMs, flexible parametric models.

Aim: to assess survival extrapolation for 10-year and lifetime/40-year survival outcomes using SPMs and FPMs within the all-cause and relative survival frameworks and compare with full observed data.

Ongoing research: adding utility functions

- Estimating quality-adjusted life expectancy (QALE) for chronic myeloid leukemia: a multi-state microsimulation approach
- Life-time predictions of costs for chronic myeloid leukaemia patients
- Cost-effectiveness analysis for chronic myeloid leukaemia treatments

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[1] Reid N. A conversation with Sir David Cox. *Statistical Science* 1994;**9**:439–455.

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[8] Andersson TML, Dickman PW, Eloranta S, Lambe M, Lambert PC. Estimating the loss in expectation of life due to cancer using flexible parametric survival models. *Statistics in Medicine* 2013;**32**:5286–5300.

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[10] Gray J, Sullivan T, Latimer NR, Salter A, Sorich MJ, Ward RL, Karnon J. Extrapolation of survival curves using standard parametric models and flexible parametric spline models: Comparisons in large registry cohorts with advanced cancer. *Medical Decision Making* 2020;**41**:179–193.