Estimating and modelling the cure fraction in population-based cancer survival analysis

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Specific aims of the research

1. Develop statistical methods for estimating and modelling the cure fraction in population-based cancer survival analysis.
2. Apply the methods to data from Sweden, Finland, England, and the USA with the joint aim of evaluating the new methodology as well as studying temporal trends in cancer patient survival.

Background: Relative Survival

$$\text{Relative Survival} = \frac{\text{Observed Survival}}{\text{Expected Survival}} \qquad R(t) = S(t)/S^*(t)$$

- Expected survival obtained from national population life tables stratified by age, sex, year of diagnosis, other covariates.
- Estimate of mortality associated with a disease without requiring information on cause of death(1; 2; 3).
- On hazard scale

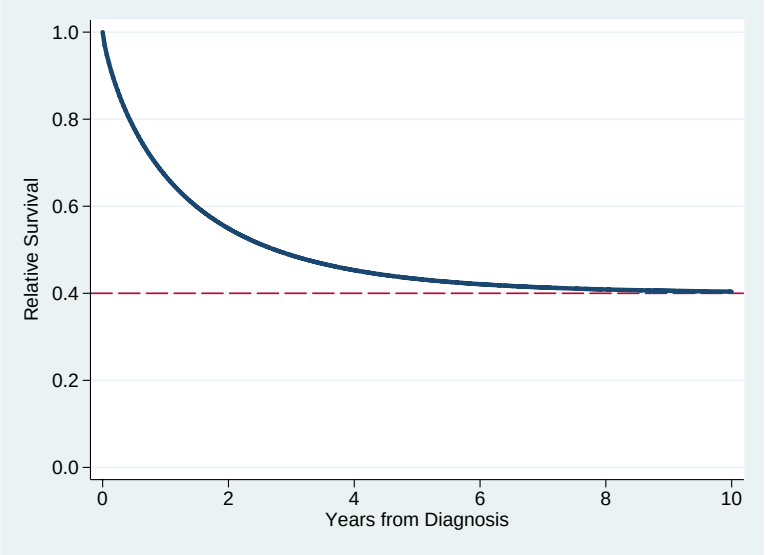
$$\lambda(t) = h(t) - h^*(t)$$

$$\begin{array}{ccccc} \text{Excess} & & \text{Observed} & & \text{Expected} \\ \text{Mortality Rate} & = & \text{Mortality Rate} & - & \text{Mortality Rate} \end{array}$$

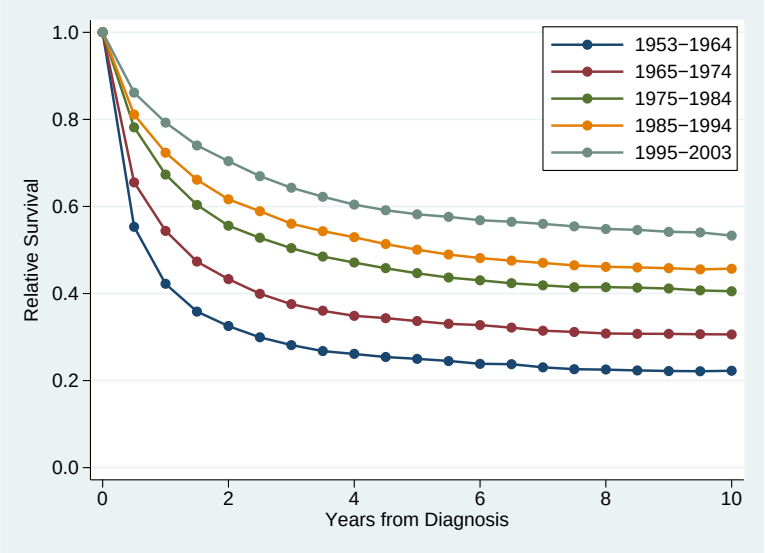
Definition of Cure (1)

- For many cancers the excess mortality (hazard) rate returns to the same level as that in the general population.
- When this occurs the relative survival curve is seen to reach a plateau.
- This is Population or Statistical Cure.
- Information of cure at the individual level not available.
- For the 'uncured' we can obtain a summary measure of survival.

Definition of Cure (2)



Relative Survival for Cancer of the Colon in Finland



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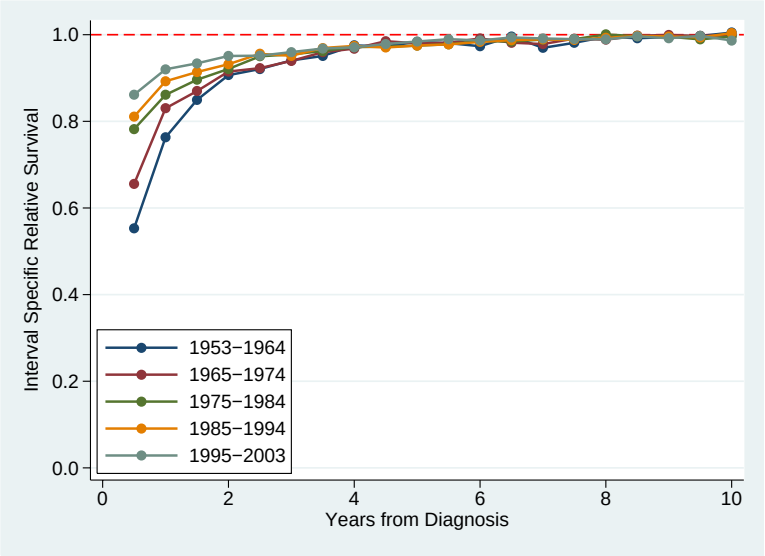

Relative Survival Models and Cure Models

Relative Survival Models

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

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

- When modelling cure we define an asymptote at the cure fraction, π, for the relative survival function, $R(t)(4; 5)$.

Mixture Cure Model

$$S(t) = S^*(t)(\pi + (1 - \pi)S_u(t))$$

Survival for the 'Uncured'

- As well as the cure fraction, summaries of the 'uncured' (those 'bound to die') are potentially useful.
- For example, mean or median survival or some other percentile of the survival distribution.
- We need to choose parametric form for $S(t)$.
- For many scenarios the Weibull distribution provides a good fit.

Interpreting changes over time

Adapted from Verdeccia (1998)

(a) General Improvement
(b) Selective Improvement
(c) Improved palliative care
(d) Inclusion of subjects with no excess risk

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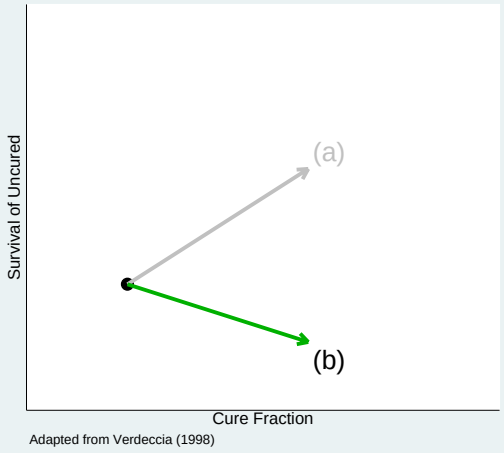

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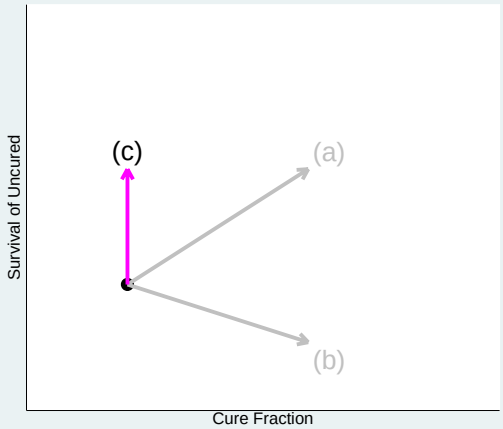

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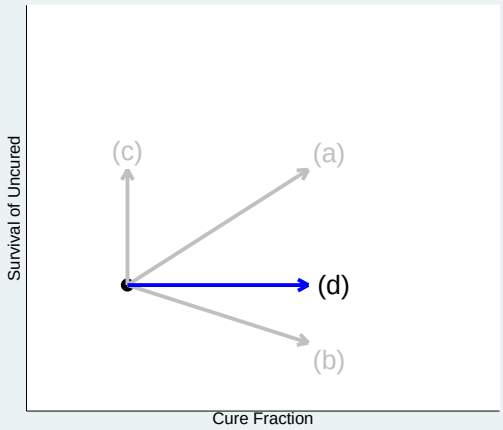

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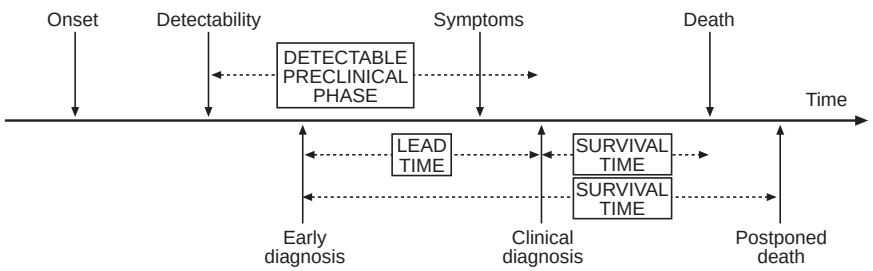
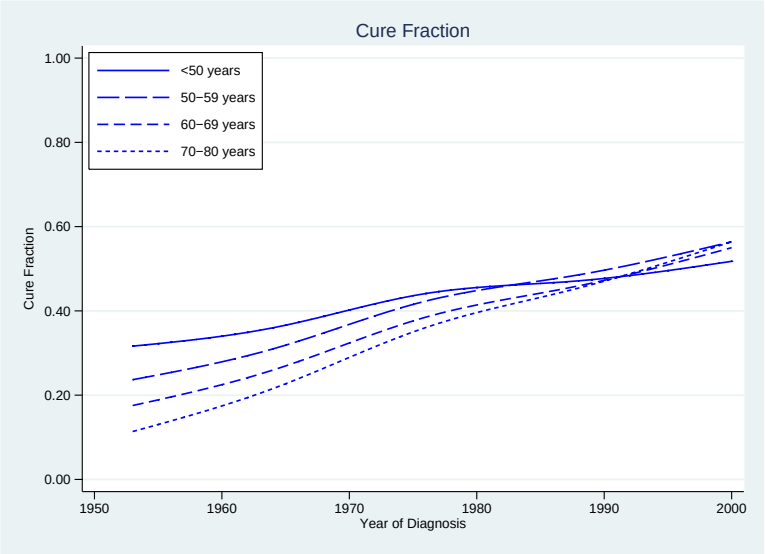
The cure proportion is not affected by lead time



Time Trends for Cancer of the Colon



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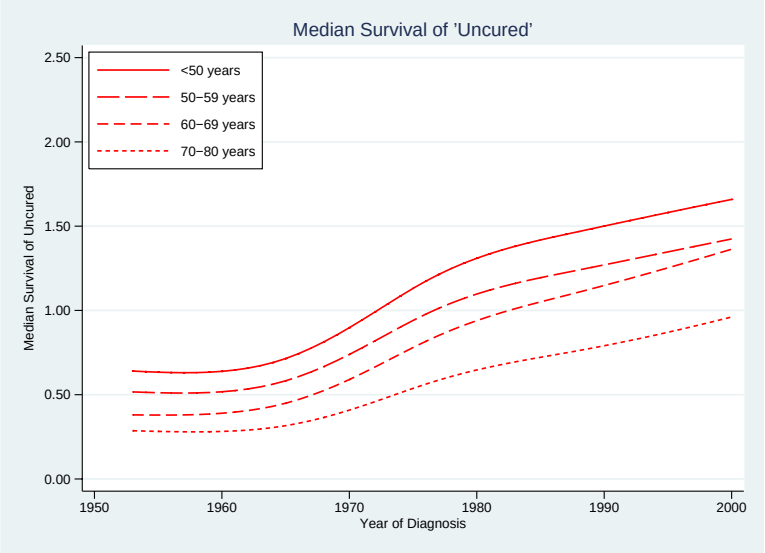
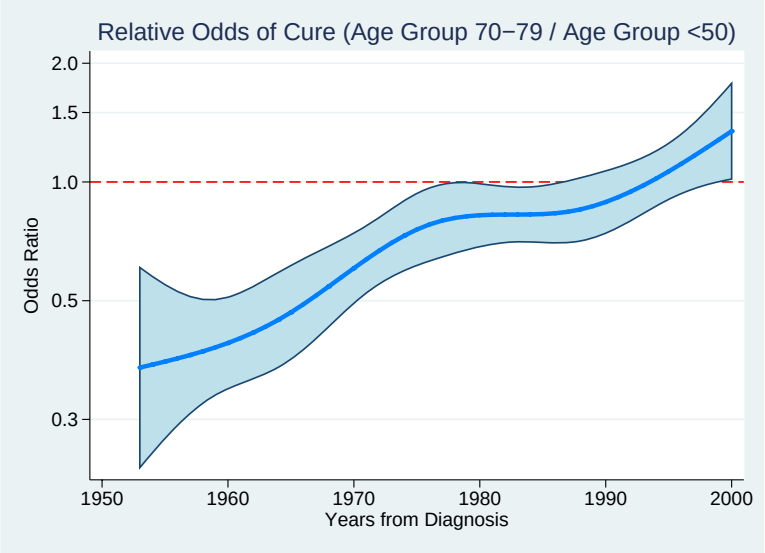


Quantifying Differences



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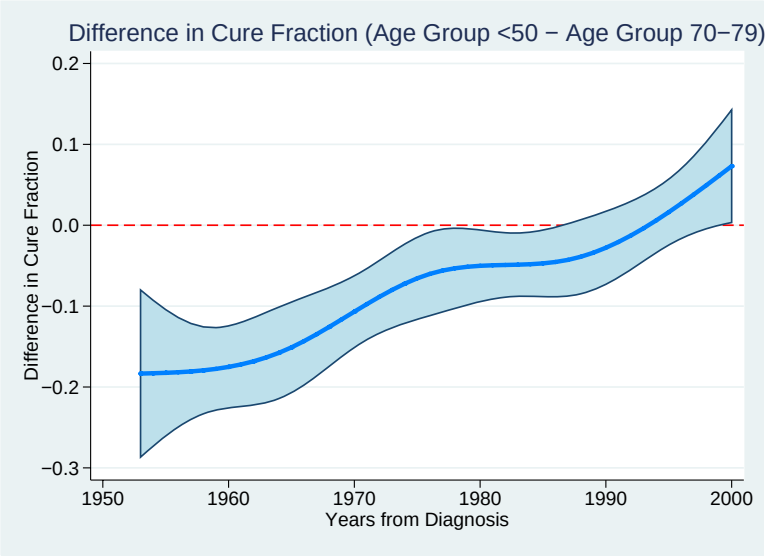
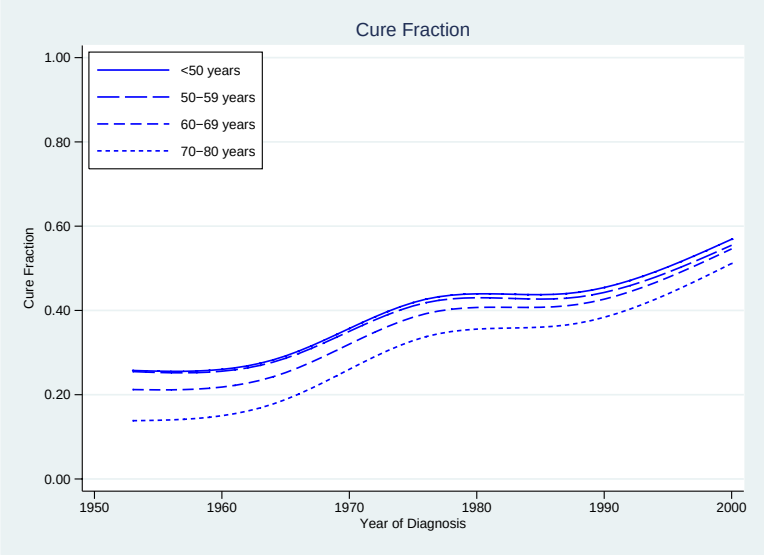


Time Trends for Cancer of the Rectum



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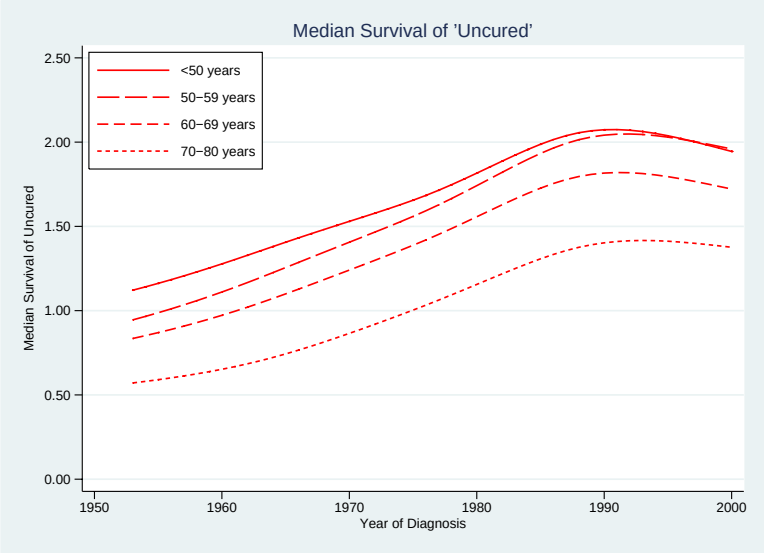


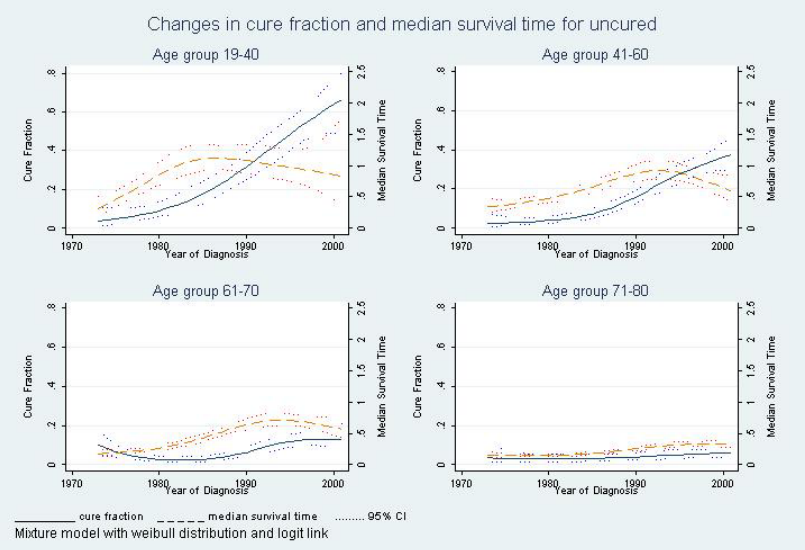
Factors contributing to improvements

- Surgical and anaestesiological techniques have become more aggressive and sophisticated over time.
- The age of the patient at which surgeons are prepared to operate has increased over time, which may explain the reduced differences in the proportion cured between age groups.
- Better awareness among the public and doctors about the importance of early diagnosis for cure.
- Some of the trends over time are likely to be due to the "learning period" when gradually introducing new techniques within and between hospitals.

Greater improvements for rectal than colon cancer

- Rectal cancer surgery is much more demanding than colon cancer surgery, and the general improvements in anaesthesiology and postoperative care seen in the late 1960s/early 1970s were relatively much more important for rectal than colon cancer.
- The steep increase during the 1990s seen in all age groups likely reflects the marked decrease in the risk of a local failure after rectal cancer surgery seen after the introduction of total mesorectal excision (TME) and increased use of preoperative radiotherapy or postoperative radiochemotherapy.
- A local failure is a much less clinical problem in cancer of the colon than in cancer of the rectum.
- Metastatic disease has been the predominant cause of death among colon cancer patients.
- The natural course of local failure is longer than that of metastatic disease (which often involves the liver).

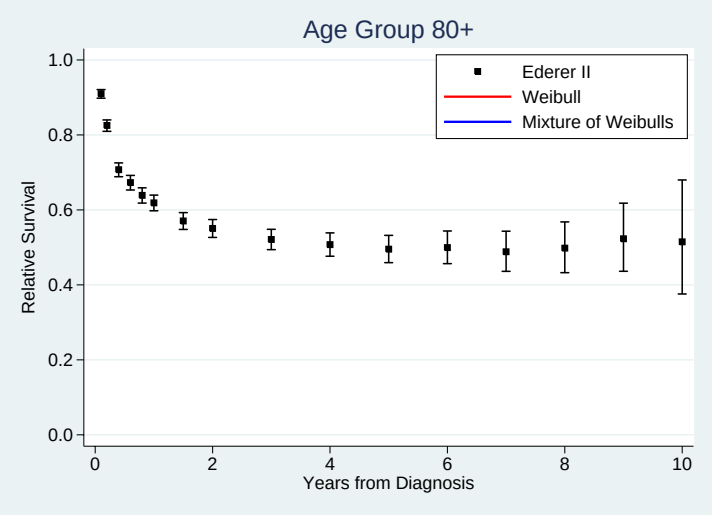
Time Trends for AML in Sweden



Challenges and current/future research

- How to assess goodness-of-fit? Standard methods not appropriate.
- How do the models behave when cure is not reached (e.g., female breast cancer).
- Preliminary evidence suggests the models perform best when mortality is neither high nor low.

Cure models may fit poorly when early mortality is high: Cancer of the Colon: Weibull and Mixture of Weibulls



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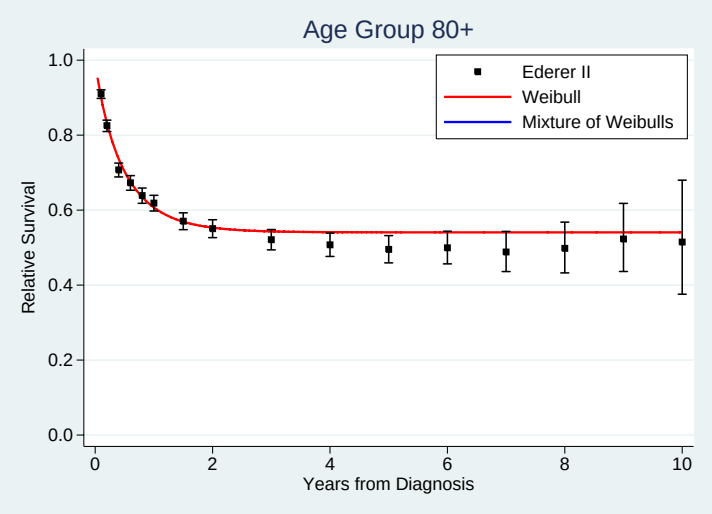

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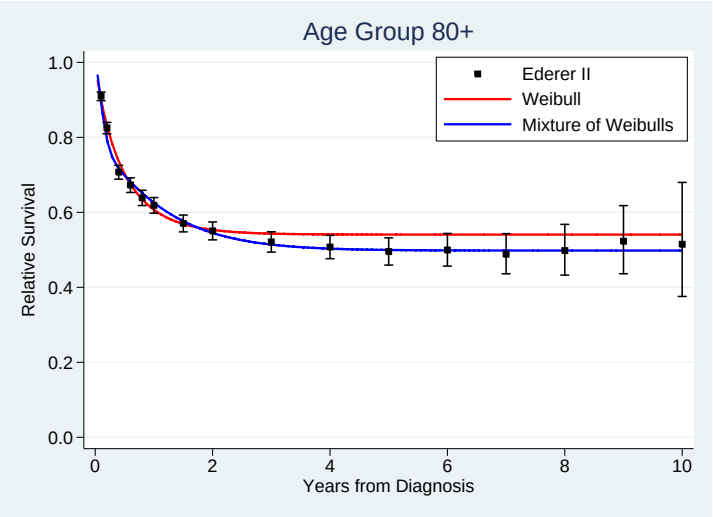

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[2] Ederer F, Axtell LM, Cutler SJ. The relative survival rate: A statistical methodology. *National Cancer Institute Monograph* 1961;**6**:101–121.

[3] Ederer F, Heise H. The effect of eliminating deaths from cancer on general population survival rates. Methodological note No. 11, End Results Evaluation Section, National Cancer Institute, Bethesda MD, 1959.

[4] Lambert PC, Dickman PW, Osterlund P, Andersson T, Sankila R, Glimelius B. Temporal trends in the proportion cured for cancer of the colon and rectum: A population-based study using data from the finnish cancer registry. *Int J Cancer* Nov 2007;**121**:2052–2059.

[5] Lambert PC, Thompson JR, Weston CL, Dickman PW. Estimating and modeling the cure fraction in population-based cancer survival analysis. *Biostatistics* Jul 2007;**8**:576–594.