Proportion cured models applied to a large data set of 23 cancer sites

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Outline of this talk

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- Modeling approaches
  - Mixture vs non-mixture model
- Practical examples:
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What is cure?

- Medical cure
  - determined on the basis of lack of specific symptoms of the individual, achieved when all cancerous cells in the body have been eradicated
  - Impossible to determine ‘cure’ with certainty on an individual level

- Statistical cure
  - defined as the proportion of survivors who as a group, exhibit the same mortality as observed in the general population.

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Estimating the cure proportion

- For a majority of cancer sites, the relative survival function will reach a plateau at some point after diagnosis; this plateau represents the proportion of survivors for whom, as a group, there is no longer any excess mortality compared with the general cancer free population (for given age and sex).

- The value of the function at the time point when this plateau is reached can be taken as an estimate of the proportion of patients who are (statistically) cured of their disease.

- This approach refers to a population, not to cancer patients on an individual level.

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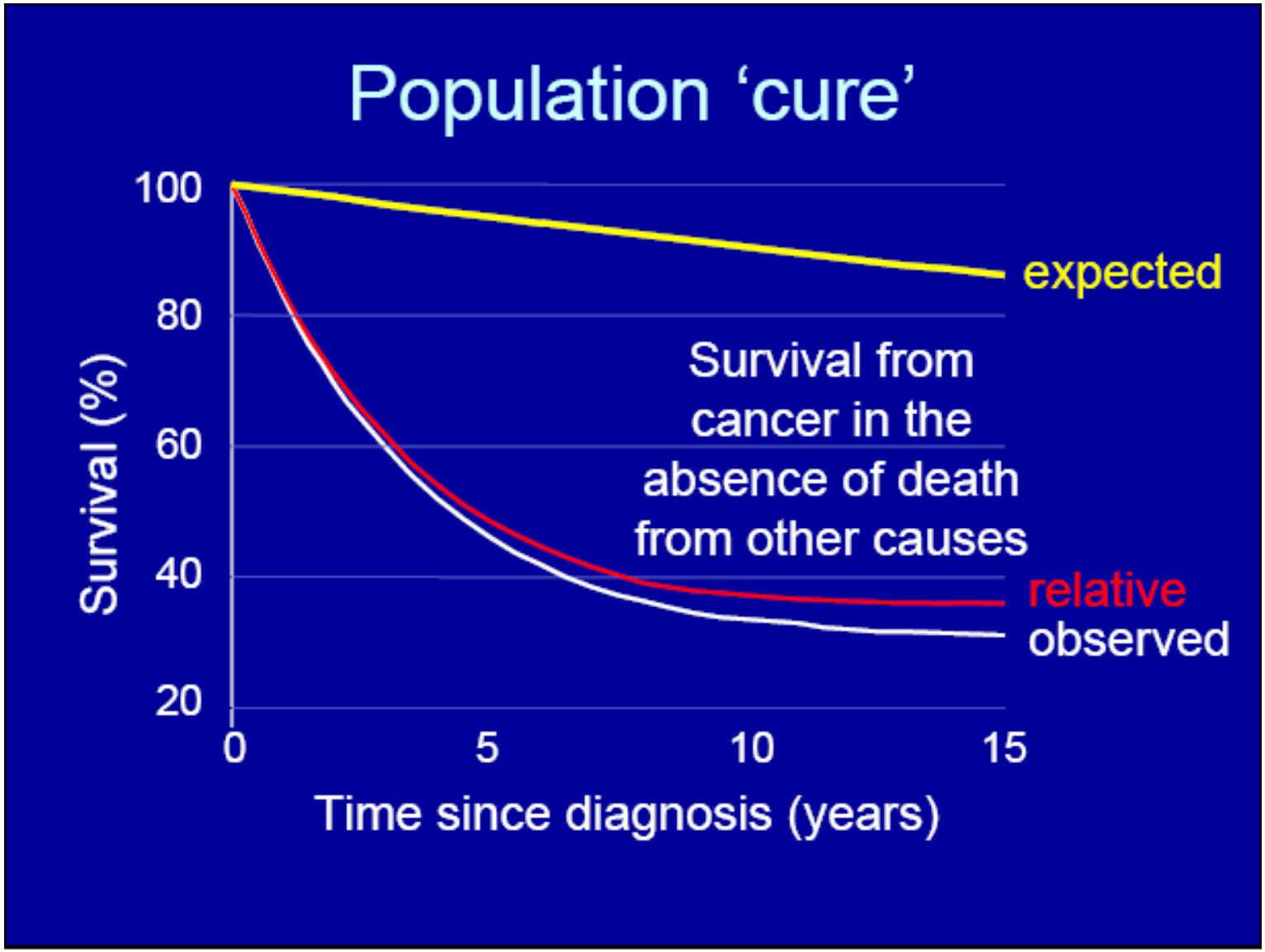

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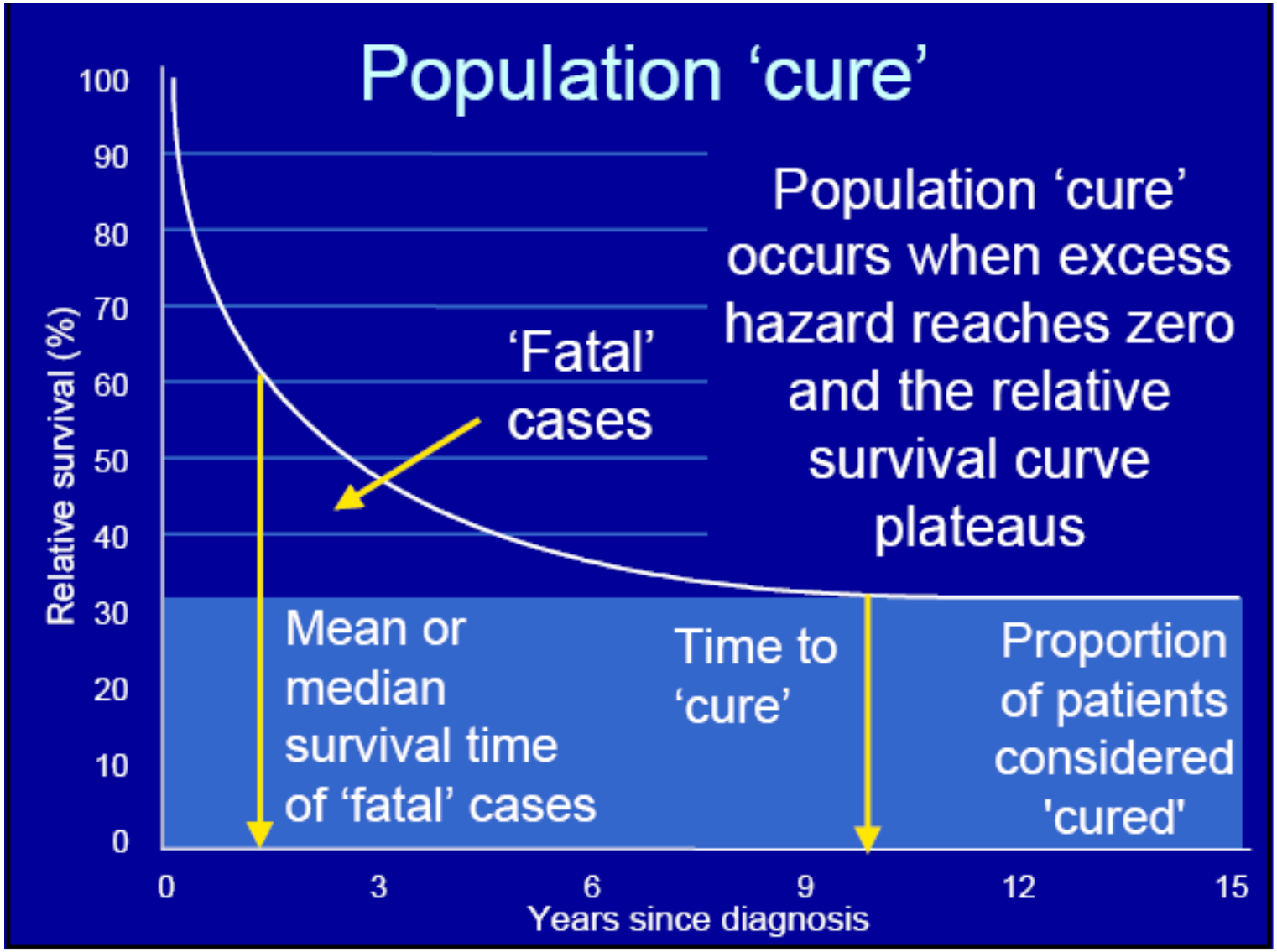

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Modeling ‘cure’

- First suggested by Boag (1949)

- Two types of models have been used
  - Mixture model
  - Non-mixture model

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Modeling cure (mixture model)

$$S(t) = S^*(t)[\pi + (1 - \pi)Su(t)]$$

- S^* is the expected survival,
- π is the proportion cured (the cure fraction),
- $(1 - \pi)$ is the proportion 'uncured' (or those 'bound to die' fatal cases)
- Su(t) is the survival function for the uncured individuals.

Su(t) is modeled with a chosen distribution with two shape parameters λ and γ:

$$Su(t) = \exp(-\lambda t^{\gamma})$$

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Modeling cure (cont)

- For practical purposes cure is assumed to be reached when the relative survival function of the ‘uncured’ group is below a stated amount; 1% in our study.

- Estimation of the cure model parameters is obtained using maximum likelihood on the individual level data.

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Data sources

- The data used in this study was extracted from The Cancer Registry of Norway, which is national and population based

- Incidence data on all cancers recorded at the Registry for diagnoses 1963–2007 were obtained, together with follow-up on matching vital status with the Deaths Registry at Statistics Norway.

- A total of 23 most common cancers were selected for analysis

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Data sources: chosen cancer sites

- Bladder
- CNS
- Rectum
- Colon
- Leukemia
- Kidney
- Non-Hodgkin lymphoma
- Mouth, pharynx
- Ovary
- Stomach
- Gallbladder
- Lung, trachea
- Oesophagus
- Liver
- Pancreas
- Breast
- Prostate
- Cervical
- Endometrial
- Testicular
- Thyroid
- Hodgkin cancers
- Melanoma of the skin

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Methods

- *Changes in trends in survival*

  - To estimate temporal trends between 1965–2007 in the proportion of cured patients, and the median survival of fatal cases
  - the complete approach was used, whereby all diagnosed cases over the period irrespective of the length of their follow-up were used in the estimations.
  - The main focus was on estimating changes in trends for patients diagnosed at different five-year time periods; hence period of diagnosis was modeled as a categorical variable with the 5-year periods as the categories.
  - The model was fitted using a three-year moving window.

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Methods

- *Up-to-date proportion cured*

  - To model the most up-to-date estimates of the proportion of cured patients and the median survival of those uncured, we used period approach with a 3-year window (2005-2007) and a 15-year relative survival

  - the follow up was set to 15-years but there were no restraints in the model concerning when in time the statistical cure is to be reached.

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Results

- both mixture and non-mixture models were fitted with Weibull, lognormal and Gamma distribution and identity, logit and log-log link.

- All 23 cancer sites were modeled using these eighteen models

- It was not possible to fit the cure fraction for eight (breast, prostate, cervical, endometrial, testicular, thyroid, Hodgkin cancers and melanoma of the skin) of the 23 cancer sites

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Results (cont)

- When we compared the up-to-date estimates of long term relative survival and the proportion cured derived from the cure models, the proportion cured fitted well for all the 15 cancer sites where convergence was reached except for Non-Hodgkin lymphoma and mouth and pharynx.

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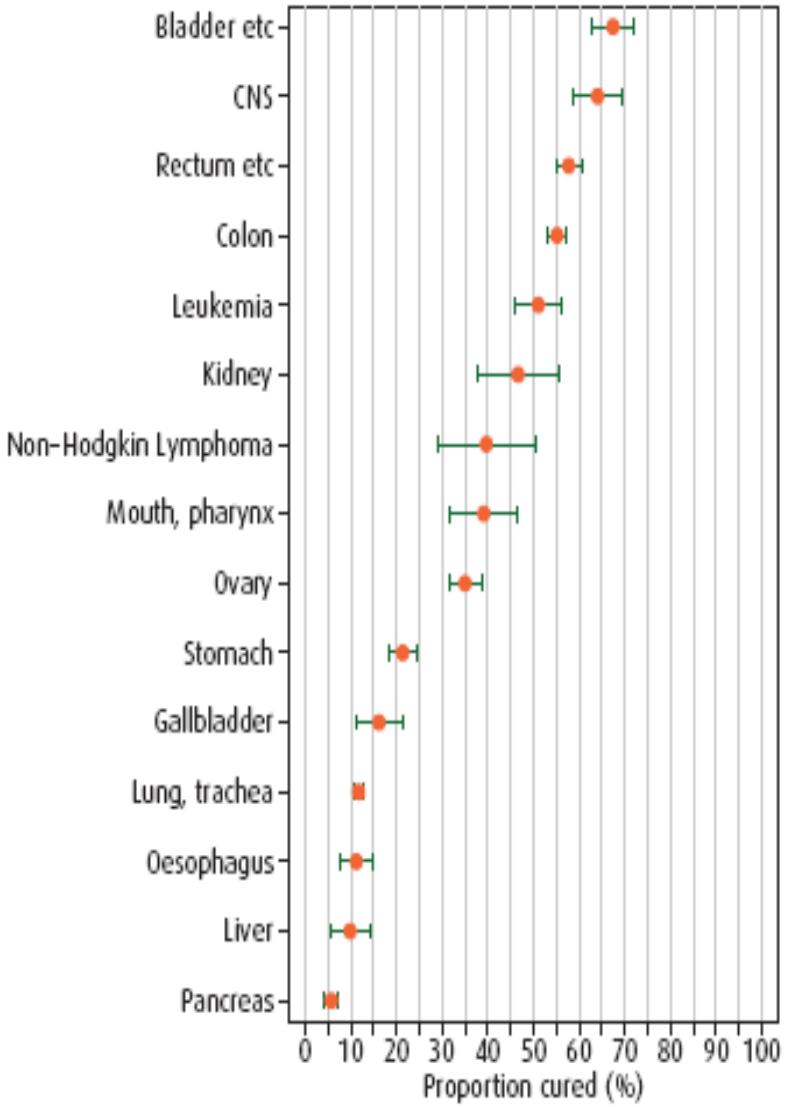
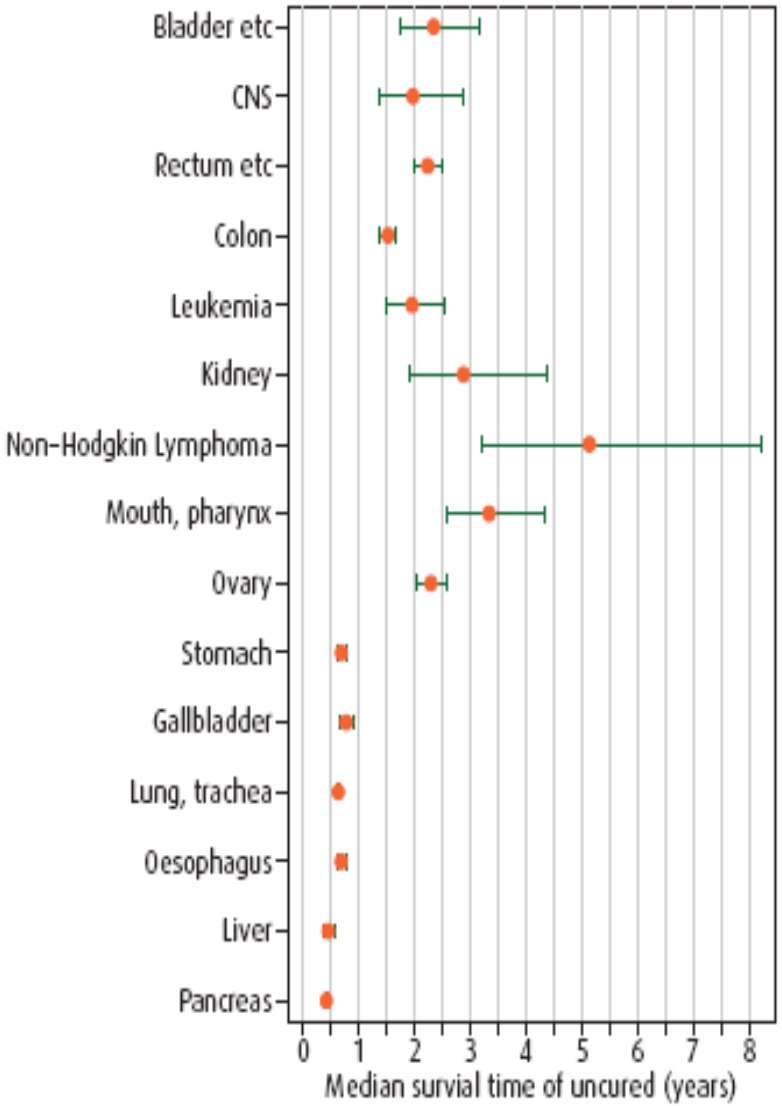
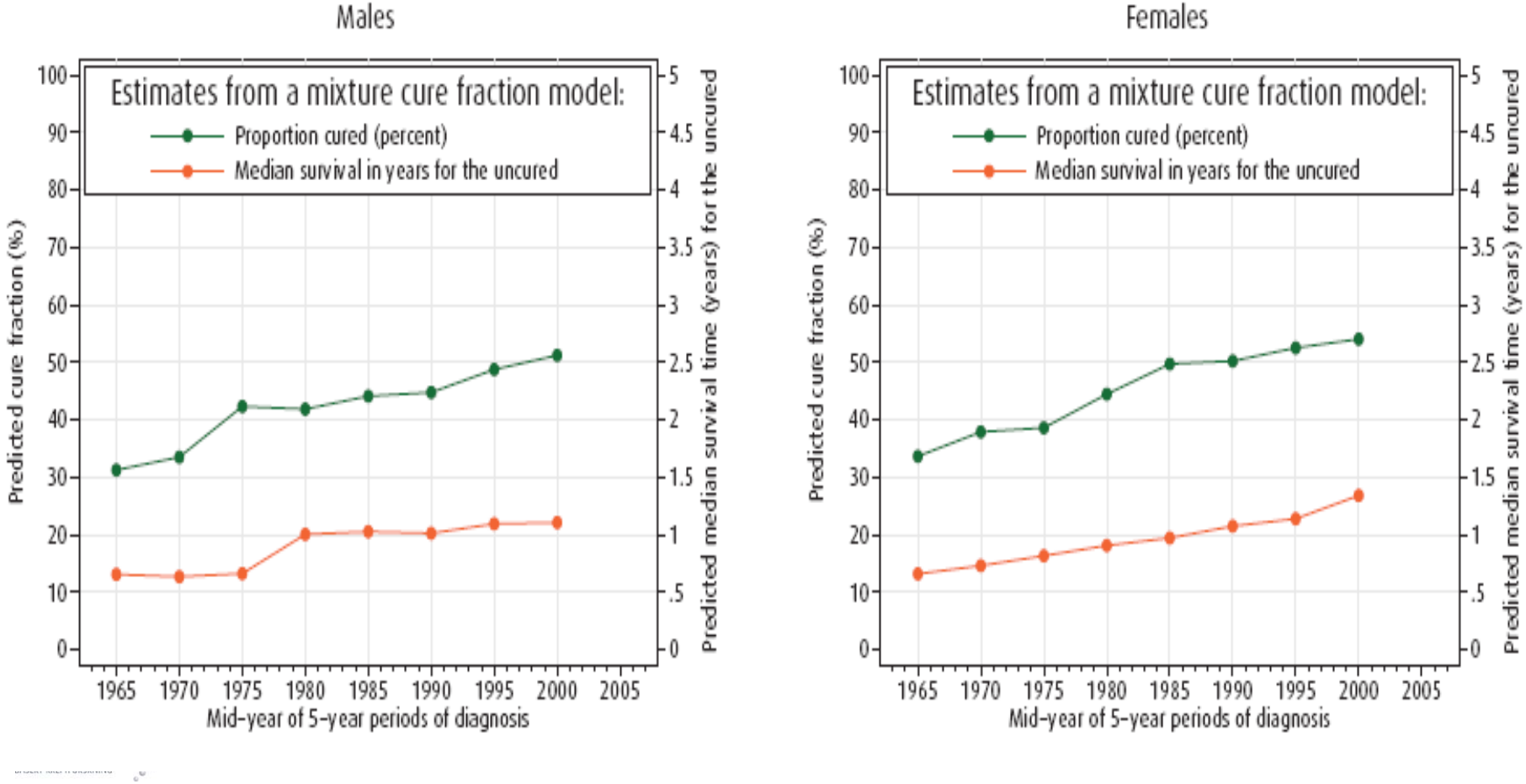
Proportion cured (left) and median survival of fatal cases (right)



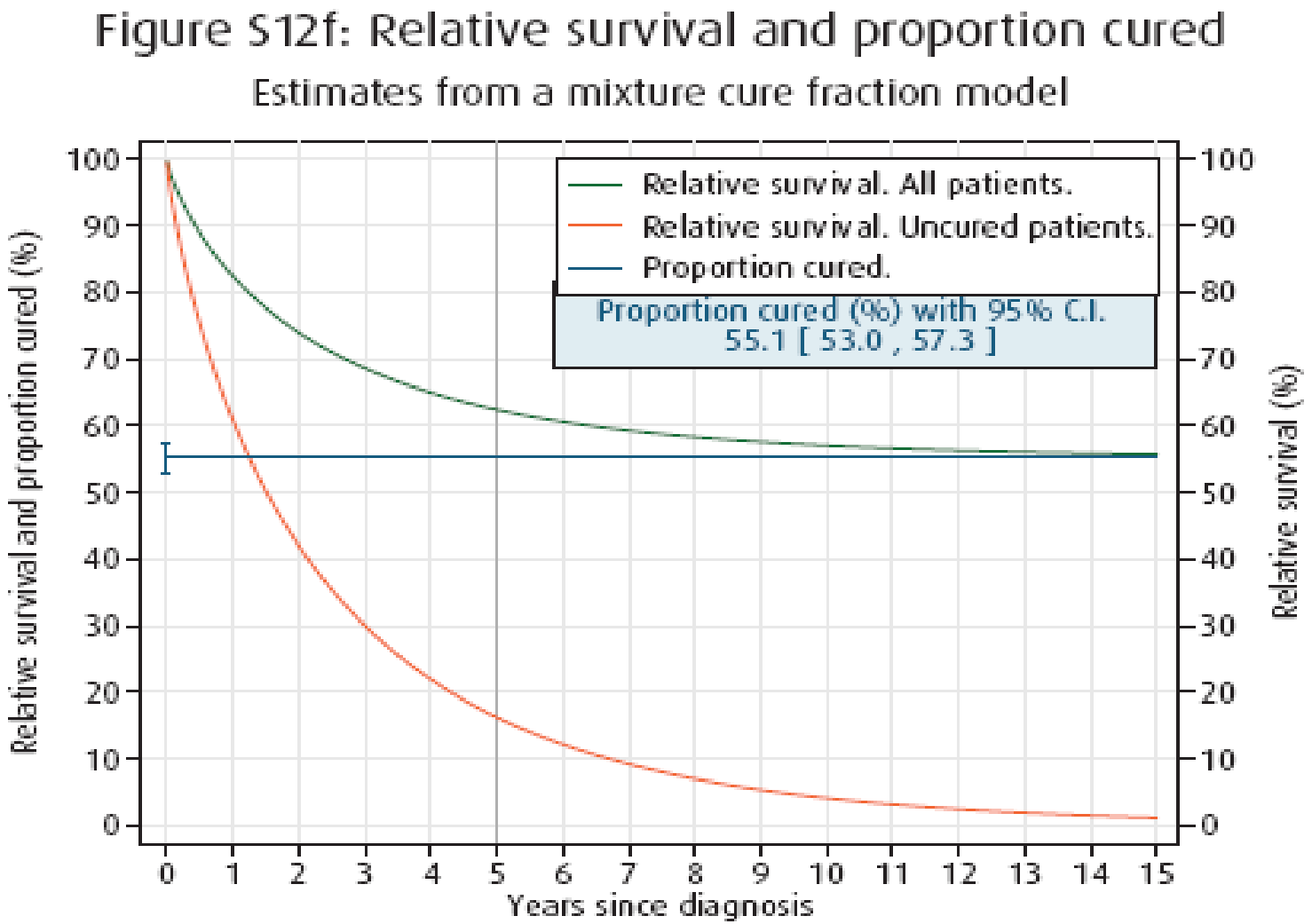


Example: colon ca.

Figure S12c: Estimates of trends in the proportion cured and the median survival time for the uncured



Example: colon ca.



Mixture vs non-mixture models

- very small differences between estimates
- Overall, the non-mixture model estimates were slightly lower compared to those from the mixture model concerning proportion cured and marginally higher when estimating median time of fatal cases.
- The models converged most often when using the logit link regardless the choice of distribution and for both mixture and non-mixture models

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Mixture vs non-mixture models (summary)

- According to the literature, in most cases it does not matter if one uses the mixture or non-mixture models. Our comparison of different distributions and link functions confirmed this finding.

- However, the mixture models are easier to explain and provide estimates of the survival function of the ‘uncured’ group.

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Conclusion

- Proportion cured models are useful when monitoring progress in cancer care; however they must be applied and interpreted with caution.

- The existence of a cured and an uncured group of patients is a necessary but rather strong assumption underlying the mixture model.

- The absolute estimates of the cured fraction are speculative, particularly for cancer sites where a cure is not clearly indicated.

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References

- Småstuen M, Aagnes B, Johannesen TB, Møller B, Bray F. Long-term cancer survival: patterns and trends in Norway 1965-2007 (http://www.kreftregisteret.no/Global/Publikasjoner%20og%20rapporter/CIN2007_del2.pdf)

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

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