Flexible parametric survival models for registry data: How much freedom do we have in selecting the degrees of freedom?

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Excess mortality and Relative survival

In population-based cancer data, problems are caused because of the inaccuracy or non-availability of death certificates that result in incomplete or false information on cause of death.

Excess mortality

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

Relative survival

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

- Relative survival estimates survival in a hypothetical scenario where the cancer of interest is the only possible cause of death (net survival).
- Net survival is a useful measure for comparing survival between different populations.

Flexible parametric survival models

The survival function of a Weibull distribution can be written as

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

Transforming this to the log cumulative hazard scale gives a linear function of log-time

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

By including covariates in the model

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

Flexible parametric survival models (II)

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

Basic Idea

In flexible parametric survival models, rather than assuming linearity with $\ln t$ we use restricted cubic splines for $\ln t$.

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Basic Idea

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Splines

- *Splines* are flexible mathematical functions defined by piecewise polynomials and *knots* are the points at which the polynomials join.
- The most common used splines are the *cubic spines*. The function is forced to follow constraints to ensure it is smooth.
- Extension is *restricted cubic splines* which are forced to be linear before the first knot and after the final knot.

Flexible parametric survival models (III)

A flexible parametric model with knots k_0 for the log baseline cumulative hazard is given by

$$\ln\left[H(t|\boldsymbol{x})\right] = s(\ln(t)|\gamma, \boldsymbol{k_0}) + \boldsymbol{x}\beta$$

$$\ln\left[H(t|\boldsymbol{x})\right] = \ln\left[H_0(t)\right] + \boldsymbol{x}\beta$$

- We model on the log cumulative hazard scale.
- This is a proportional hazards model.

It is easy to incorporate time-dependent effects

$$\ln\left[H(t|\boldsymbol{x})\right] = s(\ln(t)|\gamma, \boldsymbol{k_0}) + \boldsymbol{x}\beta + \sum_{i=1}^{D} s(\ln(t)|\boldsymbol{\delta_i}, \boldsymbol{k_i})\boldsymbol{x}_i$$

Motivation

A number of recent studies using population-based cancer data have focused on the development and application of flexible parametric models.

An important issue on flexible parametric survival models is the number of knots (degrees of freedom) used for the splines and whether this makes it impractical to perform analyses across a wide range of cancer sites with a pre-specified analysis.

- How many knots to use?
- Are the fitted values sensitive to the number of the knots?
- Is it possible to have a default model?

Data

Table 1: Number of patients diagnosed between 1986-90 in England & Wales, per cancer type.

Cancer type	Males	Females
Liver	2,253	1,413
Lung	101,688	44,387
Colon	31,651	36,830
Oesophagus	12,162	8,568
Stomach	27,294	16,291
Melanoma	5,964	9,976
Pancreas	11,214	11,603
Prostate	51,910	-
Breast	-	117,739
Ovary	-	21,241

Sensitivity analysis

We assessed the reliability of estimates by using data for a range of cancer types.

- Sixty flexible parametric survival models were fitted to each site with varying degrees of freedom to model
    - the baseline excess hazard: 3,4,5,6,7
    - the main effect of age: 3,4,5
    - the time dependent effect of age: 2,3,4,5

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  - the baseline excess hazard: 3,4,5,6,7
  - the main effect of age: 3,4,5
  - the time dependent effect of age: 2,3,4,5
- Predicted age-specific and internally age-standardised relative survival estimates were obtained from each of the models.
  - Age standardised estimate at a certain time is a weighted average of the relative survival in each age group. In internal age standardisation, the weights are based on the age distribution within the study population.

Sensitivity analysis (II)

- The Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) were calculated in order to compare the models.

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- We developed web-based interactive graphs, where users can compare the estimates for a range of models.

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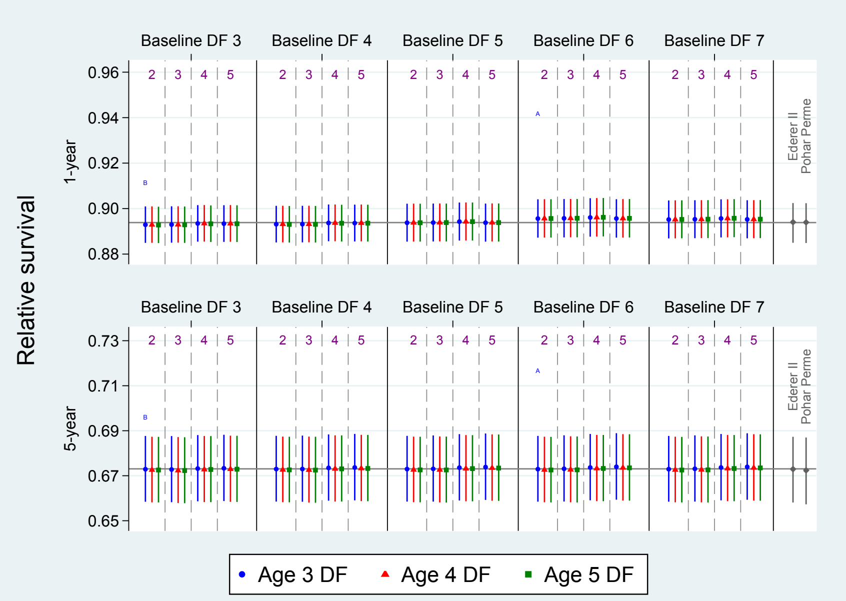
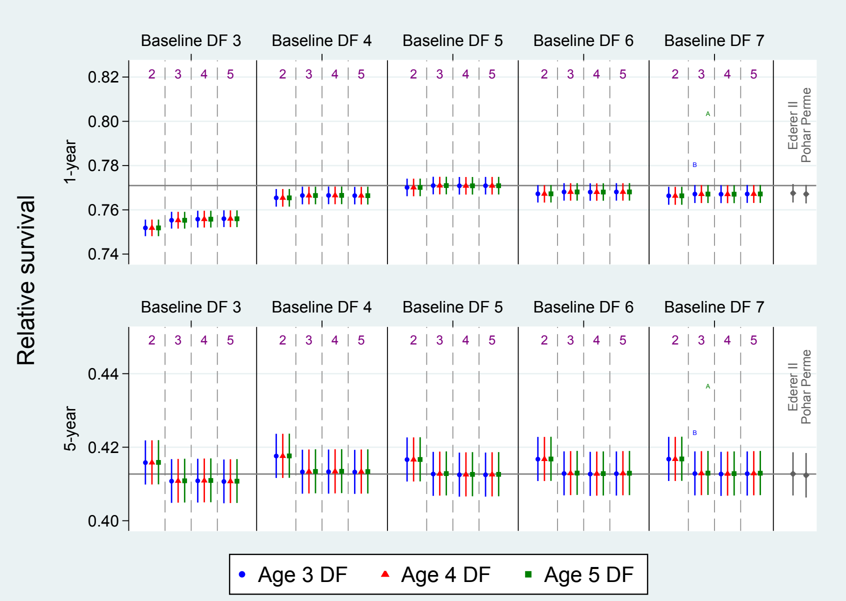
Reference model

The model with 5, 3 and 3 degrees of freedom for the baseline hazard, the main and the time dependent effect of age respectively is used as the reference model in the plots.

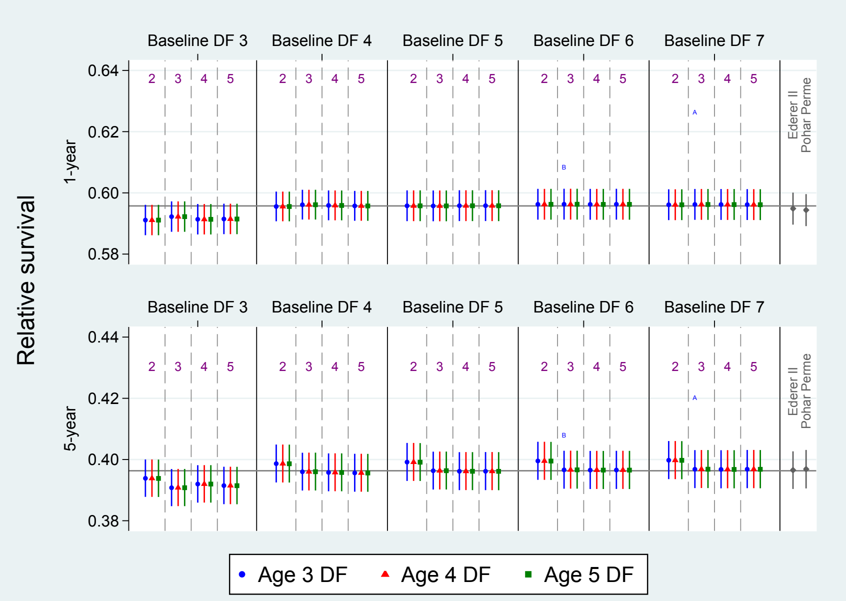
Age-standardised estimates for males with melanoma



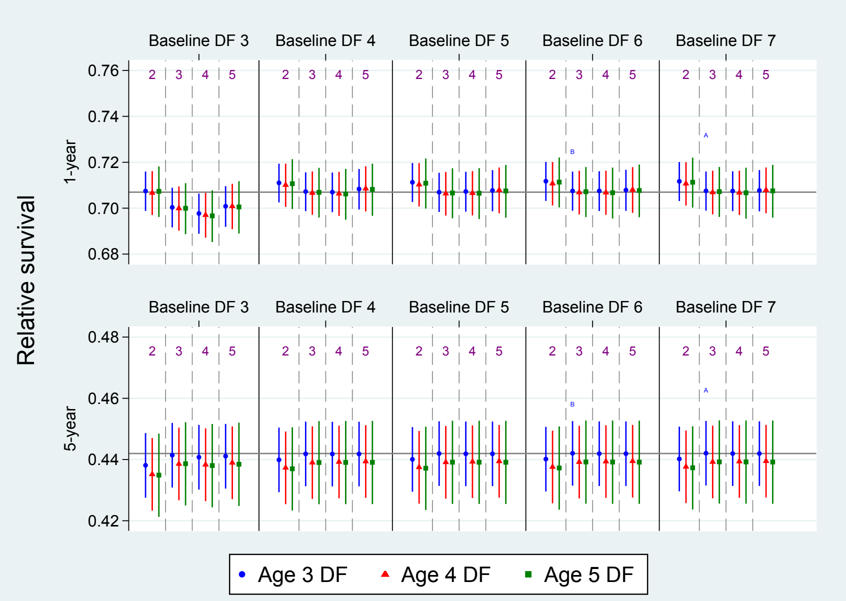
Age-standardised estimates for males with prostate cancer



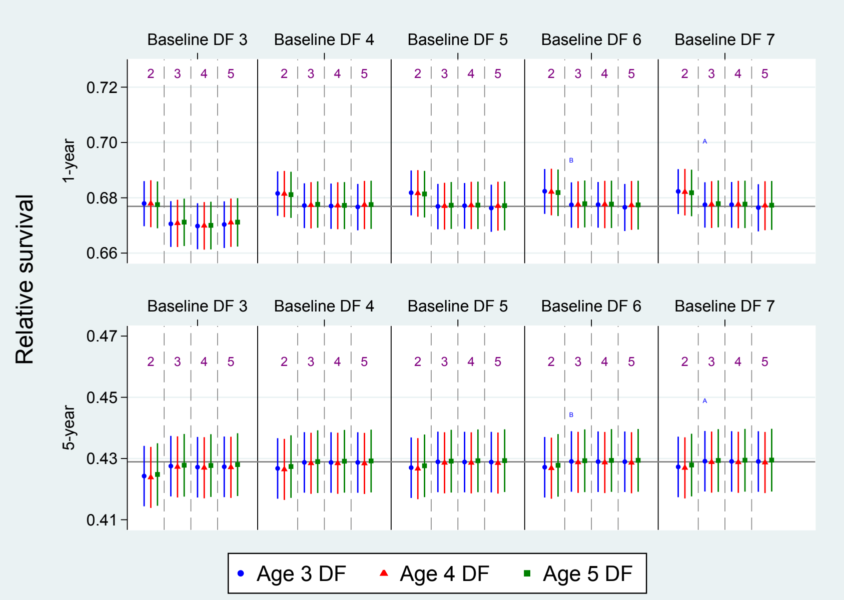
Age-standardised estimates for females with colon cancer



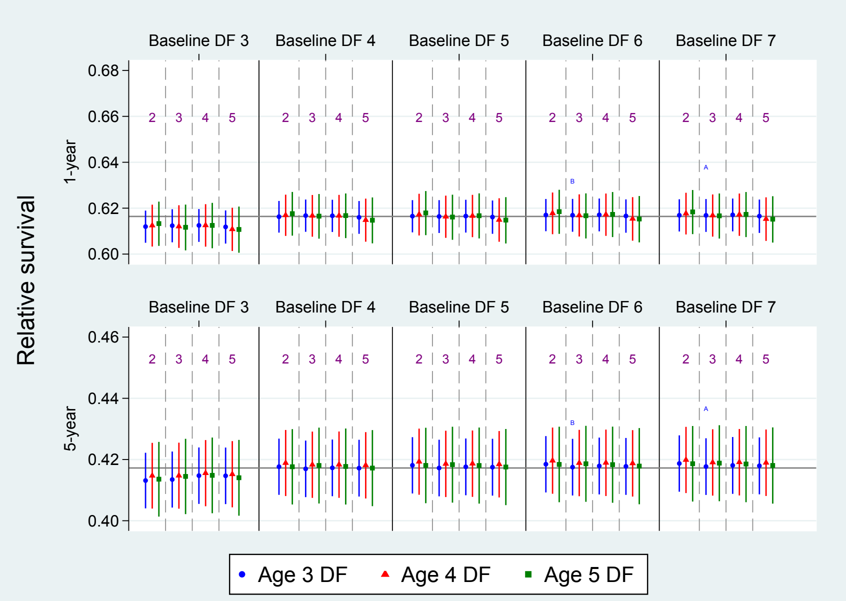
Estimates for 55-year old females with colon cancer



Estimates for 65-year old females with colon cancer



Estimates for 75-year old females with colon cancer



Estimates for 85-year old females with colon cancer

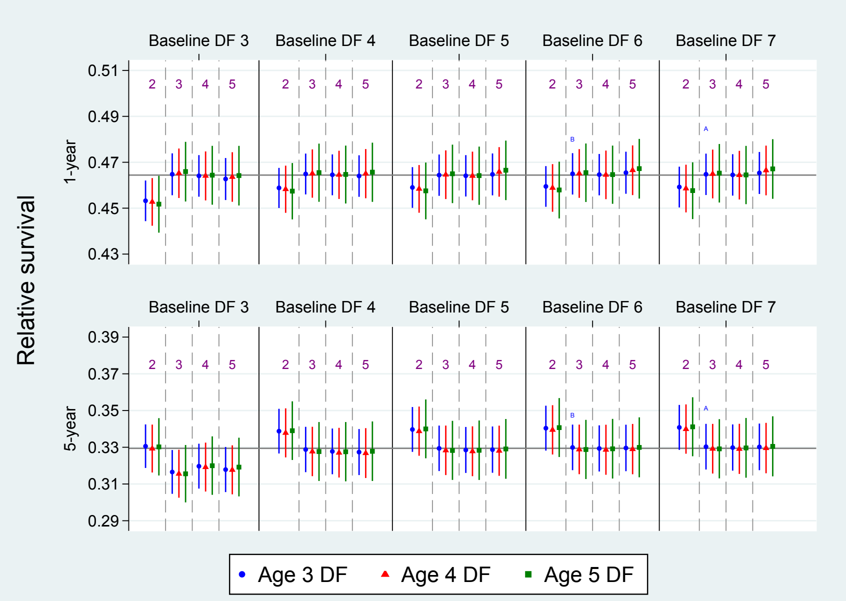


Table 2: Differences between the estimates of survival of the reference model with the one with the minimum AIC and BIC respectively, for men aged 55, 65, 75 and 85 by type of cancer.

		55		**65**		**75**		**85**	
		AIC	BIC	AIC	BIC	AIC	BIC	AIC	BIC
Liver	1	0.00340	-0.00445	0.00281	0.00220	0.00202	0.00705	0.00160	-0.00096
	5	-0.00098	0.00278	-0.00100	-0.00187	-0.00091	-0.00338	-0.00055	0.00184
Lung	1	0.00148	0.00045	-0.00139	-0.00111	-0.00095	-0.00209	-0.00885	-0.00539
	5	0.00349	-0.00092	-0.00311	-0.00160	0.00193	-0.00131	-0.00090	0.00089
Colon	1	0.00271	0.00004	0.00083	0.00030	-0.00112	0.00047	0.00053	0.00009
	5	0.00019	-0.00021	-0.00046	-0.00048	-0.00230	-0.00080	-0.00039	-0.00067
Prostate	1	0.01670	0.00273	-0.00702	0.00281	0.01030	0.00351	0.00289	0.00560
	5	0.01233	-0.00029	-0.00986	-0.00024	0.00088	-0.00022	0.00362	0.00018
Oesophagus	1	-0.00663	-0.00663	-0.00483	-0.00483	-0.00214	-0.00214	0.00089	0.00089
	5	0.00011	0.00011	-0.00026	-0.00026	-0.00191	-0.00191	-0.00374	-0.00374
Stomach	1	-0.00263	-0.00626	-0.00225	-0.00260	-0.00188	-0.00164	-0.00150	0.00355
	5	-0.00040	0.00021	-0.00073	-0.00064	-0.00101	-0.00102	-0.00129	-0.00673
Melanoma	1	-0.00284	-0.00025	-0.00243	0.00040	-0.00262	0.00103	-0.00397	0.00128
	5	-0.00044	-0.00023	-0.00054	-0.00028	0.00064	0.00045	0.00313	0.00199
Pancreas	1	0.00582	0.00582	0.00582	0.00582	0.00506	0.00506	0.00365	0.00365
	5	-0.00240	-0.00240	-0.00240	-0.00240	-0.00241	-0.00241	-0.00307	-0.00307

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		AIC	BIC	AIC	BIC	AIC	BIC	AIC	BIC
Liver	1	0.00340	-0.00445	0.00281	0.00220	0.00202	0.00705	0.00160	-0.00096
	5	-0.00098	0.00278	-0.00100	-0.00187	-0.00091	-0.00338	-0.00055	0.00184
Lung	1	0.00148	0.00045	-0.00139	-0.00111	-0.00095	-0.00209	-0.00885	-0.00539
	5	0.00349	-0.00092	-0.00311	-0.00160	0.00193	-0.00131	-0.00090	0.00089
Colon	1	0.00271	0.00004	0.00083	0.00030	-0.00112	0.00047	0.00053	0.00009
	5	0.00019	-0.00021	-0.00046	-0.00048	-0.00230	-0.00080	-0.00039	-0.00067
Prostate	1	0.01670	0.00273	-0.00702	0.00281	0.01030	0.00351	0.00289	0.00560
	5	0.01233	-0.00029	-0.00986	-0.00024	0.00088	-0.00022	0.00362	0.00018
Oesophagus	1	-0.00663	-0.00663	-0.00483	-0.00483	-0.00214	-0.00214	0.00089	0.00089
	5	0.00011	0.00011	-0.00026	-0.00026	-0.00191	-0.00191	-0.00374	-0.00374
Stomach	1	-0.00263	-0.00626	-0.00225	-0.00260	-0.00188	-0.00164	-0.00150	0.00355
	5	-0.00040	0.00021	-0.00073	-0.00064	-0.00101	-0.00102	-0.00129	-0.00673
Melanoma	1	-0.00284	-0.00025	-0.00243	0.00040	-0.00262	0.00103	-0.00397	0.00128
	5	-0.00044	-0.00023	-0.00054	-0.00028	0.00064	0.00045	0.00313	0.00199
Pancreas	1	0.00582	0.00582	0.00582	0.00582	0.00506	0.00506	0.00365	0.00365
	5	-0.00240	-0.00240	-0.00240	-0.00240	-0.00241	-0.00241	-0.00307	-0.00307

Table 3: Differences between the estimates of survival of the reference model with the one with the minimum AIC and BIC respectively, for women aged 55, 65, 75 and 85 by type of cancer.

		55		**65**		**75**		**85**	
		AIC	BIC	AIC	BIC	AIC	BIC	AIC	BIC
Liver	1	-0.00388	-0.00388	-0.00283	-0.00283	0.00121	0.00121	0.00107	0.00107
	5	0.00184	0.00184	0.00112	0.00112	-0.00051	-0.00051	-0.00101	-0.00101
Lung	1	0.00026	-0.00013	-0.00025	-0.00063	-0.00298	-0.00247	-0.00756	-0.00652
	5	-0.00084	-0.00077	-0.00151	-0.00149	-0.00079	-0.00098	0.00183	0.00126
Colon	1	-0.00056	-0.00053	-0.00059	-0.00056	-0.00048	-0.00054	-0.00036	-0.00057
	5	-0.00011	-0.00007	-0.00022	-0.00014	-0.00047	-0.00028	-0.00089	-0.00050
Breast	1	0.00134	-0.00201	0.00346	0.00588	-0.00895	-0.00845	-0.00157	-0.00027
	5	0.00656	-0.00286	0.00564	0.01303	-0.01063	-0.01422	0.00738	0.00745
Oesophagus	1	-0.00368	-0.00652	-0.00359	0.00286	-0.00282	0.00179	-0.00202	-0.00098
	5	-0.00032	0.00216	-0.00053	-0.00117	-0.00095	-0.00070	-0.00076	0.00059
Stomach	1	-0.00232	-0.00799	-0.00202	-0.00457	-0.00169	0.00102	-0.00136	0.00315
	5	-0.00011	0.00177	-0.00035	0.00102	-0.00075	-0.00121	-0.00093	-0.00299
Melanoma	1	-0.00157	-0.00157	0.00065	0.00065	0.00195	0.00195	-0.00036	-0.00036
	5	-0.00157	0.00000	0.00043	0.00043	0.00078	0.00078	0.00087	0.00087
Ovary	1	-0.00750	-0.00803	-0.00343	-0.00249	0.00685	0.00425	0.00122	0.00231
	5	0.00342	-0.00010	-0.01188	-0.00066	0.01239	0.00108	-0.00660	0.00485
Pancreas	1	0.01022	0.00111	0.00942	0.00487	0.00547	0.00579	0.00040	0.00667
	5	-0.00288	0.00023	-0.00386	-0.00128	-0.00227	-0.00232	-0.00047	-0.00580

Table 3: Differences between the estimates of survival of the reference model with the one with the minimum AIC and BIC respectively, for women aged 55, 65, 75 and 85 by type of cancer.

		55		**65**		**75**		**85**	
		AIC	BIC	AIC	BIC	AIC	BIC	AIC	BIC
Liver	1	-0.00388	-0.00388	-0.00283	-0.00283	0.00121	0.00121	0.00107	0.00107
	5	0.00184	0.00184	0.00112	0.00112	-0.00051	-0.00051	-0.00101	-0.00101
Lung	1	0.00026	-0.00013	-0.00025	-0.00063	-0.00298	-0.00247	-0.00756	-0.00652
	5	-0.00084	-0.00077	-0.00151	-0.00149	-0.00079	-0.00098	0.00183	0.00126
Colon	1	-0.00056	-0.00053	-0.00059	-0.00056	-0.00048	-0.00054	-0.00036	-0.00057
	5	-0.00011	-0.00007	-0.00022	-0.00014	-0.00047	-0.00028	-0.00089	-0.00050
Breast	1	0.00134	-0.00201	0.00346	0.00588	-0.00895	-0.00845	-0.00157	-0.00027
	5	0.00656	-0.00286	0.00564	0.01303	-0.01063	-0.01422	0.00738	0.00745
Oesophagus	1	-0.00368	-0.00652	-0.00359	0.00286	-0.00282	0.00179	-0.00202	-0.00098
	5	-0.00032	0.00216	-0.00053	-0.00117	-0.00095	-0.00070	-0.00076	0.00059
Stomach	1	-0.00232	-0.00799	-0.00202	-0.00457	-0.00169	0.00102	-0.00136	0.00315
	5	-0.00011	0.00177	-0.00035	0.00102	-0.00075	-0.00121	-0.00093	-0.00299
Melanoma	1	-0.00157	-0.00157	0.00065	0.00065	0.00195	0.00195	-0.00036	-0.00036
	5	-0.00157	0.00000	0.00043	0.00043	0.00078	0.00078	0.00087	0.00087
Ovary	1	-0.00750	-0.00803	-0.00343	-0.00249	0.00685	0.00425	0.00122	0.00231
	5	0.00342	-0.00010	-0.01188	-0.00066	0.01239	0.00108	-0.00660	0.00485
Pancreas	1	0.01022	0.00111	0.00942	0.00487	0.00547	0.00579	0.00040	0.00667
	5	-0.00288	0.00023	-0.00386	-0.00128	-0.00227	-0.00232	-0.00047	-0.00580

Conclusions

- Through sensitivity analysis, we showed that age-standardised estimates were very insensitive to the exact choice of the number of knots for the splines.
- Age-specific survival is also very stable with negligible differences between models except for the youngest and oldest, of whom there are very few.
- Both the age-specific and age-standardised estimates of relative survival are not over-sensitive to the specified number of knots.
- Too few knots for the splines should be avoided, as they can result in a poor fit. It is better to overfit!

Selected References

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