Estimating and modelling relative survival

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Overview

- Introduction to relative survival; comparison with cause-specific survival.
- Estimating relative survival using a period (as opposed to cohort) approach
- Modelling
  - Additive (excess mortality) models
  - Multiplicative (relative mortality) models
  - Extending standard models

Introduction to relative survival

- Relative survival, the survival analogue of excess mortality, is commonly used in population-based studies of cancer patient survival although its utility is not restricted to this area.
- I will focus on application of relative survival to cancer registry data.
- Our interest is typically in net survival rather than all-cause survival, that is, we are interested in mortality due to cancer.
- Cause-specific survival is commonly estimated in cancer clinical trials — only those deaths which can be attributed to the cancer in question are considered to be events, while all other deaths are considered censorings.

Potential disadvantages of cause-specific survival

- Using cause-specific survival to estimate net survival 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 or suicide?
- Consider a man diagnosed with prostate cancer and treated with estrogen who dies following a myocardial infarction. Do we classify this death as 'due entirely to prostate cancer' or 'due entirely to other causes'?
- Welch *et al.* [1] studied deaths among surgically treated cancer patients that occurred within one month of diagnosis. They found that 41% of deaths were not attributed to the coded cancer.

Relative survival

- Can instead 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.
- It is usual to estimate the expected survival proportion from nationwide (or statewide) population life tables stratified by age, sex, calendar time, and, where applicable, race [2].
- Although these tables include the effect of deaths due to the cancer being studied, Ederer *et al.* [3] showed that this does not, in practice, affect the estimated survival proportions.

- A major advantage of relative survival (excess mortality) is that information on cause of death is not required, thereby circumventing problems with the inaccuracy [4] or nonavailability of death certificates.
- We obtain a measure of the excess mortality experienced by patients diagnosed with cancer, irrespective of whether the excess mortality is directly or indirectly attributable to the cancer.
- Deaths due to treatment complications or suicide are examples of deaths which may be considered indirectly attributable to cancer.

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

Women diagnosed Jan 1994 - June 2001 with follow-up to June 2002

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

Issues with relative survival

- The central issue in estimating relative survival is defining a 'comparable group from the general population' and estimating expected survival.
- If not all of the excess mortality is due to the cancer then the relative survival ratio will underestimate net survival (overestimate excess mortality).
- For example, patients diagnosed with smoking-related cancers will experience excess mortality, compared to the general population, due to both the cancer and other smoking related conditions.
- Should the patients be a selected group from the general population, for example, with respect to social class, the national population might not be an appropriate comparison group.

Statistical cure

- The life table is a useful tool for describing the survival experience of the patients over a long follow-up period.
- In particular, an interval-specific relative survival ratio equal to one indicates that, during the specified interval, mortality in the patient group was equivalent to that of the general population.
- The attainment and maintenance of an interval-specific RSR of one indicates that there is no excess mortality due to cancer and the patients are assumed to be 'statistically cured'.
- An individual is considered to be medically cured if he or she no longer displays symptoms of the disease.
- Statistical cure applies at a group, rather than individual, level.

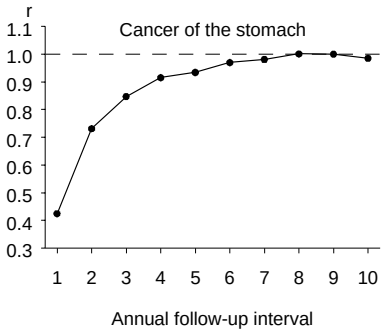

Figure 1: Plots of the annual (interval-specific) relative survival ratios (r) for males and females diagnosed with cancer of the stomach in Finland 1985–1994 and followed up to the end of 1995.

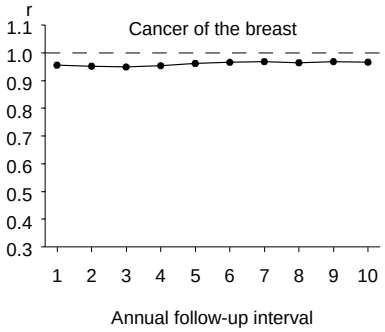

Figure 2: Plots of the annual (interval-specific) relative survival ratios (r) for females diagnosed with cancer of the breast in Finland 1985–1994 and followed up to the end of 1995.

- Plots of the interval-specific RSR are also useful for assessing the quality of follow-up.
- If the interval-specific RSR levels out at a value greater than 1, this generally indicates that some deaths have been missed in the follow-up process.
- An interval-specific relative survival ratio of unity is generally not achieved for smoking-related cancers, such as cancer of the lung and kidney.
- Compared to the general population, these patients are subject to excess mortality due to the cancer in addition to excess mortality due to other conditions caused by smoking, such as cardiovascular disease.

Estimating relative survival using a period approach

- In 1996 Hermann Brenner suggested estimating cancer patient survival using a period, rather than cohort, approach [5].
- This suggestion was initially met with scepticism although studies based on historical data [6] have shown that
  - period analysis provides very good predictions of the prognosis of newly diagnosed patients; and
  - highlights temporal trends in patient survival sooner than cohort methods.

Modelling excess mortality (relative survival)

- The hazard at time since diagnosis t for persons diagnosed with cancer is modelled as the sum of the known baseline hazard, $\lambda^*(t)$, and the excess hazard due to a diagnosis of cancer, $\nu(t)$ [7, 8, 9, 10, 11].

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

- It is common to assume that the excess hazards are piecewise constant and proportional.
- The model can be easily estimated in the framework of generalised linear models using standard statistical software (e.g., SAS, Stata, R).
- Non-proportional excess hazards are common but can be incorporated by introducing follow-up time by covariate interaction terms.
- Giorgi *et al.* [12] use B-splines to model the excess hazard ratio as a flexible function of time.

A multiplicative rather than additive model

- Other authors [13, 14, 15] have explored multiplicative (relative mortality) rather than additive (excess mortality) models

$$\lambda(t) = \lambda^*(t) \times \nu(t)$$

- Professor Stare will shortly present an innovative approach to estimating and modelling relative mortality [16].
- Mixture models, which include the additive and multiplicative models as special cases, have also been considered [13, 14, 17].
- As with most areas of statistics there is not a uniformly best model; recent attention has focussed on model diagnostics and goodness-of-fit.

Other areas of research

- Survival of patient with multiple cancers [18, 19, 20, 21].
- Age standardised estimates of relative survival [22].
- Modelling period survival; this afternoon Dr. Lambert will present 'a comparison of models with additive and relative effects of covariates'.
- Simultaneously estimating the probability of cure and the survival proportion for patients bound to die [23].
- Cumulative cause-specific mortality [24].

Software

- SAS macros by Hermann Brenner and colleagues
  `www.imbe.med.uni-erlangen.de/issan/SAS/period/period.htm`
- SAS and Stata macros by Paul Dickman and colleagues
  `http://www.pauldickman.com/rsmodel/index.php`
- Seer*Stat (from the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute)
  `http://seer.cancer.gov/seerstat/`

References

[1] Welch HG, Black WC. Are deaths within 1 month of cancer-directed surgery attributed to cancer? *J Natl Cancer Inst* 2002;**94**:1066–70.

[2] Berkson J, Gage RP. Calculation of survival rates for cancer. *Proceedings of Staff Meetings of the Mayo Clinic* 1950;**25**:270–286.

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

[4] Percy CL, Stanek E, Gloeckler L. Accuracy of cancer death certificates and its effect on cancer mortality statistics. *American Journal of Public Health* 1981;**71**:242–250.

[5] Brenner H, Gefeller O. An alternative approach to monitoring cancer patient survival. *Cancer* 1996;**78**:2004–2010.

[6] Brenner H, Gefeller O, Hakulinen T. Period analysis for 'up-to-date' cancer survival data: theory, empirical evaluation, computational realisation and applications. *European Journal of Cancer* 2004;**40**:326–35.

[7] Dickman PW, Sloggett A, Hills M, Hakulinen T. Regression models for relative survival. *Stat Med* Jan 2004;**23**:51–64.

[8] Estève J, Benhamou E, Croasdale M, Raymond L. Relative survival and the estimation of net survival: Elements for further discussion. *Statistics in Medicine* 1990;**9**:529–538.

[9] Hakulinen T, Tenkanen L. Regression analysis of relative survival rates. *Applied Statistics* 1987;**36**:309–317.

[10] Berry G. The analysis of mortality by the subject-years method. *Biometrics* 1983; **39**:173–184.

[11] Pocock S, Gore S, Kerr G. Long term survival analysis: the curability of breast cancer. *Stat Med* 1982;**1**:93–104.

[12] Giorgi R, Abrahamowicz M, Quantin C, Bolard P, Esteve J, Gouvernet J, Faivre J. A relative survival regression model using B-spline functions to model non-proportional hazards. *Stat Med* Sep 2003;**22**:2767–84.

[13] Price DL, Manatunga AK. Modelling relative survival using transformation methods. *Stat Med* Aug 2004;**23**:2463–77.

[14] Andersen PK, Væth M. Simple parametric and nonparametric models for excess and relative mortality. *Biometrics* 1989;**45**:523–535.

[15] Buckley JD. Additive and multiplicative models for relative survival rates. *Biometrics* 1984; **40**:51–62.

[16] Stare J, Henderson R, Pohar M. An individual measure of relative survival. *JRSS C* 2005; (to appear).

[17] Oksanen H. *Modelling the Survival of Prostate Cancer Patients*. Ph.D. thesis, University of Tampere, Finland, 1998. Acta Universitatis Tamperensis, vol 615.

[18] Heinävaara S, Hakulinen T. Relative survival of patients with subsequent cancer. *J Cancer Epidemiol Prev* 2002;**7**:173–9.

[19] Heinävaara S, Hakulinen T. Parametric mixture model for analysing relative survival of patients with multiple cancers. *J Cancer Epidemiol Prev* 2002;**7**:147–53.

[20] Heinävaara S, Teppo L, Hakulinen T. Cancer-specific survival of patients with multiple cancers: an application to patients with multiple breast cancers. *Stat Med* Nov 2002; **21**:3183–95.

[21] Heinävaara S, Sankila R, Storm H, Langmark F, Hakulinen T. Relative survival of patients with prostate cancer as a first or subsequent tumor–a Nordic collaborative study. *Cancer Causes Control* Nov 2002;**13**:797–806.

[22] Brenner H, Hakulinen T. On crude and age-adjusted relative survival rates. *J Clin Epidemiol* Dec 2003;**56**:1185–91.

[23] De Angelis R, Capocaccia R, Hakulinen T, Söderman B, Verdecchia A. Mixture models for cancer survival analysis: Application to population-based data with covariates. *Statistics in Medicine* 1999;**18**:441–454.

[24] Cronin K, Feuer E. Cumulative cause-specific mortality for cancer patients in the presence of other causes: a crude analogue of relative survival. *Stat Med* Jul 2000;**19**:1729–40.