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A Greenwood formula for standard error of the age-standardised relative survival ratio

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ABSTRACT

The age-standardised relative survival ratio is used to compare population-based cancer survival patterns when the population age structures differ. Traditionally, the direct standardisation method based on age-specific relative survival ratios has been used. In a new method [Brenner H, Arndt V, Gefeller O, Hakulinen T. An alternative approach to age adjustment of cancer survival rates. *Eur J Cancer* 2004;**40**:2317–22], weighted observations depending on the age structures of the study and standard populations are used to substitute the patients leading to a use of weighted counts. The relative survival ratio is then calculated in the conventional way. However, no standard error of the age-standardised relative survival estimate has been reported. In this paper, we introduce a generalisation of the well-known Greenwood formula for that purpose. This method is also applicable for the observed survival and particularly when the observed survival probabilities of the patient population differ by age stratum. The traditional Greenwood formula is a special case of the method when no specific weights are used and the observed survival probability is the same in each stratum. Data from the Finnish Cancer Registry are used for illustration.

1. Introduction

The relative survival ratio over a given follow-up period has been defined as the ratio of the observed survival proportion of a group of patients (with disease such as cancer) to the expected survival proportion in a subgroup of the general population similar to the group of patients at the beginning of the period of follow-up with respect to age, sex and calendar time of diagnosis.[1] Since this ratio reflects the survival of the group of patients that are free of other causes of death, other than the particular cancer of interest, it has been widely used as a measure of 'net survival' by cancer registries. As the age distributions of the cancer patients often vary between different populations or within the same population over different time periods, age-standardised relative survival ratios are presented for comparative studies instead of the crude or non-standardised ratios.[2]

Traditionally, the age-standardised relative survival ratio has been derived as the weighted average of age-specific relative survival ratios, weights being the proportions of patients from the standard population at the beginning of follow-up. However good the method is in theory, the traditionally standardised relative survival ratio cannot be calculated in practice for the long-term as it depends on the age-specific relative survival ratios and it is not often possible to get long-term relative survival ratio for the oldest patient group.[3] Moreover, the traditional age-standardised estimates are generally lower than the non-standardised or crude estimates

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even if the standardisation is made with the study population itself as a standard.[4] As an alternative to the traditional standardisation, another method has been proposed[5] which does not require age-specific relative survival estimates. In this method, age-specific weights based on ratios between proportions of patients in the standard and the study population are first assigned to each patient of the respective age group leading to the use of weighted counts. The relative survival ratios are then calculated in the conventional way. Let us denote this as the 'Brenner II' method for simplicity throughout this paper (the age-standardisation method given in Ref. [4] can be denoted as the 'Brenner I' method).

The standard error of any estimate indicates the extent to which the estimate may have been influenced by random variation and also provides the confidence interval with which it becomes easier to interpret the result. In epidemiological or other observational studies, estimates are usually given with confidence intervals. Standard errors of observed survival proportions have been estimated using Greenwood's method[6] whereas those for the relative survival ratios are calculated simply by dividing the standard errors of the observed survival proportions by the expected survival proportions, without taking consideration of the standard errors of the expected survival proportions as the latter are usually based on large populations.[1] Although the standard errors of the Brenner II age-standardised relative survival ratios have been calculated by the bootstrap method,[7] a straightforward formula for this purpose was lacking. In this paper, we derive this formula (Appendix 1) and illustrate the new formula using data from the nationwide Finnish Cancer Registry.

2. The principles of the standard error calculation

The basis for the need of age-standardisation is that the relative survival ratios are different by age group. In relative survival analysis, only the numerator of the ratio, the observed survival proportion, is really assumed to have random error. The denominator, the expected survival proportion, being based on larger counts in the general population, is considered to be a fixed value, without random error. In this text, these assumptions will be followed.

Traditionally, the standard error of the observed survival proportion has been obtained by the Greenwood formula.[6] The formula for the cumulative observed survival proportion $P(t)$ at the end of follow-up time interval t is

$$\mathrm{SE}\{P(t)\} = P(t)\sqrt{\sum_{i=1}^{t} \frac{d(i)}{l'(i)\{l'(i) - d(i)\}}},$$

where $d(i)$ is the number of deaths during the follow-up interval i and $l'(i)$ is the effective number of persons at risk of dying at the beginning of follow-up interval i. The formula actually assumes that the same binomial probability of observed death applies to all patients at risk at the beginning of each interval. Even if this were true with respect to the risk of dying from the cancer of the patients, this is not true as far as the other causes of death of the patients are concerned. The risk of dying from other causes will be higher the older the patient is. Thus, a stratified analysis by age is called for.

If there is a complete follow-up for all patients, there is no need to make a stratified analysis by age in order to obtain unbiased estimates for observed survival. This is also true if patients' (potential) censoring does not depend on age. In both cases, the censoring does not imbalance the age distribution of patients under follow-up.[3,8]

The basic idea of the Brenner II method is that no stratification by age will be done in the analysis phase. The only stratification needed is for obtaining the patient-specific weights by age group. Let there be m age groups and let the proportions u_a and w_a of the standard and study populations, respectively, at the beginning of follow-up belong to age group a, $a = 1, 2, 3, \ldots, m$. Each patient belonging to the age group a is then substituted by a weight defined by the ratio $g_a = \frac{u_a}{w_a}$. After that, the analysis will be continued for the weighted observations in the same way as usual.

This principle works well for point estimation, but for interval estimation, the basis of describing random variation must be on full counts with a specified binomial error structure. The random errors related to the weighted observations have to properly take into account that the binomial counts have been adjusted by a set of constant weights.

3. The generalised Greenwood method

The details of how to derive the new method and formulae are given in Appendix 1. The new formulae for the standard error of the numerator of the Brenner II age-standardised relative survival ratio, the Brenner II age-standardised observed survival proportion (formula (4) in Appendix 1) becomes also a generalisation of the Greenwood formula when it cannot be assumed that the observed survival would be the same in all age groups. The exact Greenwood formula will be obtained when this assumption can be done. This would, however, almost never be true with patients differing greatly with respect to age.

A computer program (Appendix 2) was developed in STATA (version 9) to compute the standard errors using the new formulae. It can be used in connection with other software for the relative survival in STATA.[9]

4. Empirical illustration

The data for this study were obtained from the nationwide Finnish Cancer Registry, which is well known for its high quality and completeness.[10] Female oesophageal, colon, rectum, breast, bladder and thyroid cancer patients diagnosed in Finland during 1960–1989 and followed up until 31st December 2005 were included in the study material. The sites chosen represent those of different levels of cancer incidence and survival. On the basis of age at the time of diagnosis, the patients were classified into five age groups: 0–44, 45–54, 55–64, 65–74 and 75+ as done in the EUROCARE studies.[11] Patients diagnosed during the periods 1960–1974 and 1975–1989 were treated separately to implement the age-standardisation.

The age distribution of the cancer patients has changed over time. The proportion of oldest patients was larger in the later period except for thyroid cancer where the proportion of youngest patients had increased (Table 1). The Hakulinen method[8] was used in the estimation of relative

Table 1 – Number (N) and age-specific proportions (p1, p2 in %) of cancer patients by period of diagnosis and site in female cancer patients diagnosed in 1960–1974 and 1975–1989 in Finland

Site	1960–1974 (*p*1)						1975–1989 (*p*2)					
	N	0–44	45–54	55–64	65–74	75+	*N*	0–44	45–54	55–64	65–74	75+
Oesophagus	1998	1.6	7.2	18.3	35.0	37.9	1680	0.9	2.9	13.3	33.2	49.6
Colon	3786	7.8	10.0	20.6	33.9	27.8	7091	6.5	7.1	15.0	31.2	40.2
Rectum	3002	4.3	11.2	22.9	35.1	26.5	4385	3.6	8.0	17.8	32.4	38.2
Breast	14806	14.9	24.2	26.7	22.3	11.9	27900	13.9	20.9	22.8	23.1	19.3
Bladder	861	2.7	9.5	25.0	34.0	28.8	1808	2.4	5.9	18.6	30.5	42.5
Thyroid	1205	27.5	17.0	20.3	21.4	13.8	2669	37.1	17.0	16.0	16.5	13.4

survival. Standard errors of the Brenner II age-standardised relative survival ratios were computed using formula (5) of Appendix 1 and compared to those derived from the traditional Greenwood formula by directly inserting the weighted counts (6).

The standard errors of the age-standardised relative survival ratios increased with the follow-up (Tables 2 and 3). A direct substitution of the adjusted counts into the traditional Greenwood formula often gave very similar but slightly conservative standard error estimates compared to the new formula.

5. Discussion

The Greenwood formula (8) in Appendix 1 has been used for estimation of standard errors of the relative survival ratios by assuming that the death probabilities are the same in each age stratum. This assumption does not hold in practice as the death probabilities are, in general, higher in older patients. When age-specific weights are also applied to each individual, the Greenwood formula with weighted counts (6) does not necessarily give the correct estimates of standard error of the Brenner II age-standardised relative survival ratios (or

Table 2 – Crude and Brenner II age-standardised relative survival ratios (R, in %) with standard errors (Sn) by site and follow-up year in female cancer patients diagnosed in 1960–1975 and 1975–1989 and followed up to the end of 2005

Site/follow-up (years)	1960–1974						1975–1989		
	Crude			Standardised			Crude		
	R	Sn	Sg	R	Sn	Sg	R	Sn	Sg
Oesophagus									
5	5.8	0.61	0.66	4.8	0.56	0.64	8.1	0.77	0.84
10	4.8	0.66	0.75	4.0	0.63	0.76	7.7	0.91	1.01
15	4.5	0.77	0.91	3.9	0.77	0.98	7.9	1.11	1.30
Colon									
5	33.4	0.90	0.92	31.7	0.95	0.95	47.7	0.72	0.73
10	33.0	1.06	1.09	31.8	1.17	1.17	45.7	0.88	0.90
15	33.1	1.25	1.30	32.2	1.41	1.44	45.9	1.08	1.11
Rectum									
5	33.7	1.01	1.03	31.8	1.06	1.06	45.3	0.90	0.91
10	31.3	1.17	1.20	30.3	1.26	1.28	41.7	1.07	1.10
15	32.6	1.41	1.46	31.9	1.56	1.61	42.4	1.32	1.36
Breast									
5	60.5	0.46	0.46	60.0	0.50	0.48	75.0	0.32	0.32
10	48.6	0.52	0.52	48.3	0.56	0.55	62.7	0.39	0.39
15	43.0	0.56	0.57	42.9	0.61	0.61	56.5	0.44	0.45
Bladder									
5	42.2	2.00	2.07	39.3	2.15	2.14	62.3	1.49	1.50
10	39.5	2.37	2.48	37.0	2.63	2.68	58.8	1.91	1.95
15	40.2	2.87	3.06	37.9	3.21	3.42	55.6	2.37	2.46
Thyroid									
5	67.9	1.47	1.58	72.0	1.34	1.51	83.3	0.82	0.88
10	67.9	1.76	1.86	72.4	1.59	1.77	84.1	1.00	1.05
15	69.7	2.05	2.16	74.3	1.82	2.02	85.4	1.19	1.24

The patients diagnosed in 1975–1989 have been used as the standard population. The estimates (Sg) derived by the direct substitution of weighted counts into the traditional Greenwood formula have been given for comparison. The larger standard errors have been italicised.

Table 3 – Crude and Brenner II age-standardised relative survival ratios (R, in %) with standard errors (Sn) by site and follow-up year in female cancer patients diagnosed in 1960–1975 and 1975–1989 and followed up to the end of 2005

Site/follow-up (years)	1960–1974			1975–1989					
	Crude			Crude			Standardised		
	R	Sn	Sg	R	Sn	Sg	R	Sn	Sg
Oesophagus									
5	5.8	0.61	0.66	8.1	0.77	0.84	9.1	0.86	0.85
10	4.8	0.66	0.75	7.7	0.91	1.01	8.5	0.97	0.98
15	4.5	0.77	0.91	7.9	1.11	1.30	8.7	1.13	1.20
Colon									
5	33.4	0.90	0.92	47.7	0.72	0.73	49.2	0.71	0.70
10	33.0	1.06	1.09	45.7	0.88	0.90	46.6	0.83	0.83
15	33.1	1.25	1.30	45.9	1.08	1.11	46.5	0.99	1.00
Rectum									
5	33.7	1.01	1.03	45.3	0.90	0.91	47.1	0.90	0.88
10	31.3	1.17	1.20	41.7	1.07	1.10	42.9	1.03	1.03
15	32.6	1.41	1.46	42.4	1.32	1.36	43.3	1.23	1.23
Breast									
5	60.5	0.46	0.46	75.0	0.32	0.32	75.5	0.30	0.30
10	48.6	0.52	0.52	62.7	0.39	0.39	63.2	0.37	0.37
15	43.0	0.56	0.57	56.5	0.44	0.45	57.0	0.42	0.42
Bladder									
5	42.2	2.00	2.07	62.3	1.49	1.50	65.2	1.41	1.41
10	39.5	2.37	2.48	58.8	1.91	1.95	60.8	1.77	1.77
15	40.2	2.87	3.06	55.6	2.37	2.46	57.1	2.17	2.16
Thyroid									
5	67.9	1.47	1.58	83.3	0.82	0.88	80.4	0.95	0.93
10	67.9	1.76	1.86	84.1	1.00	1.05	80.8	1.17	1.13
15	69.7	2.05	2.16	85.4	1.19	1.24	82.0	1.40	1.34

The patients diagnosed in 1960–1975 have been used as the standard population. The estimates (Sg) derived by the direct substitution of weighted counts into the traditional Greenwood formula have been given for comparison. The larger standard errors have been italicised.

observed survival proportions). A new formula (5) has been now developed for this purpose.

The empirical illustration shows that a direct substitution of the weighted observations into the traditional Greenwood formula yields very similar results to those given by the new formula. This is, of course, a feature of the data at hand and cannot, without further studies, be generalised to other materials and settings. It would be desirable that this simple substitution could work as then it would be a simple matter to use the existing software in a modified fashion to produce the standard errors, without the need of calculation of the age-specific observed survival proportions. The latter feature, the lack of need to calculate the age-specific figures, is an advantage of the Brenner II method, and a similar advantage could be wished for calculation of the standard error by using that method. The applicability of a direct substitution into the Greenwood formula is however dependent on the differences between the age-specific death (or survival) probabilities and between the age distributions of the patients and the standard population.

In summary, the traditional Greenwood method (with weighted counts) should not in principle be used for the estimation of standard errors of relative survival ratios (or the observed survival proportions) when the individuals in the study population are substituted by the weighted observations. When no weights are applied, the proposed new method also gives a generalisation of the traditional Greenwood method that accounts for the patients' different death probabilities by age both for the evaluation of the observed and the relative survival.

The drawback of the proposed method is the need of the stratum-specific relative (or observed) survival estimates, which were not needed for the estimation of age-standardised relative survival ratio itself. In the era of computers this does not need to be such a serious drawback. The availability of standard error formula should, in any case, facilitate the further use of the Brenner II method in the age-standardisation of the observed and relative survival.

Conflict of interest statement

None declared.

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Appendix 1. Derivation of the standard error formula

Let $l_a(i)$ be the number of patients in the age group a ($a = 1,2,3,\ldots,m$) at the beginning of follow-up interval i ($i = 1,2,3,\ldots,t$). Let $d_a(i)$ patients amongst $l_a(i)$ die during the interval. If there is no censoring, $d_a(i)$ can be assumed to follow a binomial distribution with parameters $\{l_a(i), 1 - p_a(i)\}$. Otherwise, $l_a(i)$ can be substituted with the effective number of patients at risk $l'_a(i) = l_a(i) - \frac{c_a(i)}{2}$, where $c_a(i)$ denotes the age-specific number of patients censored during interval i.

Let u_a and w_a be the age-specific proportions of patients in the standard and the study populations, respectively, at the time of diagnosis (i.e. at the beginning of follow-up). In the Brenner II standardisation method, the weights based on the ratios $g_a = \frac{u_a}{w_a}$ are used to substitute each patient of the corresponding age group. Since $d_a(i)$ is a binomial variable, the variance of $g_a d_a(i)$ is $(g_a)^2 l_a(i) p_a(i)\{1 - p_a(i)\}$.

The estimated survival probability using the weighted age-specific counts during interval i is

$$p(i) = \frac{\sum_{a=1}^{m} g_a\{l_a(i) - d_a(i)\}}{\sum_{a=1}^{m} g_a\{l_a(i)\}} \tag{1}$$

and the variance of $p(i)$ is

$$\mathrm{Var}[p(i)] = \frac{\sum_{a=1}^{m} (g_a)^2 l_a(i) p_a(i)\{1 - p_a(i)\}}{\left[\sum_{a=1}^{m} g_a l_a(i)\right]^2}. \tag{2}$$

Using the 'delta method',[12]

$$\begin{aligned}\mathrm{Var}[\log\{p(i)\}] &\approx \frac{1}{[p(i)]^2}\mathrm{Var}\{p(i)\} \\ &= \frac{\sum_{a=1}^{m}[(g_a)^2 l_a(i) p_a(i)\{1 - p_a(i)\}]}{\left[\sum_{a=1}^{m} g_a\{l_a(i) - d_a(i)\}\right]^2}.\end{aligned} \tag{3}$$

The cumulative Brenner II age-standardised observed survival proportion is $P_{BII}(t) = \prod_{i=1}^{t} p(i)$, where $p(i)$ is given in (1).

Taking log of both sides,

$$\log[P_{BII}(t)] = \sum_{i=1}^{t} \log\{p(i)\}.$$

$$\mathrm{Var}[\log\{P_{BII}(t)\}] = \sum_{i=1}^{t} \mathrm{Var}[\log\{p(i)\}].$$

From (3),

$$\mathrm{SE}[P_{BII}(t)] \approx [P_{BII}(t)]\sqrt{\sum_{i=1}^{t} \frac{\sum_{a=1}^{m}\left[(g_a)^2\left\{\frac{d_a(i)}{l_a(i)}\right\}\{l_a(i) - d_a(i)\}\right]}{\left[\sum_{a=1}^{m} g_a\{l_a(i) - d_a(i)\}\right]^2}}. \tag{4}$$

The corresponding age-standardised cumulative expected survival proportion $P^*_{BII}(t)$ can be calculated either using the Ederer II or the Hakulinen method using the same patient-specific weights.[8]

The standard error of the age-standardised relative survival ratio by the Brenner II method is

$$\begin{aligned}\mathrm{SE}[R_{BII}(t)] &= \frac{\mathrm{SE}[P_{BII}(t)]}{P^*_{BII}(t)} \\ &= R_{BII}(t)\sqrt{\sum_{i=1}^{t} \frac{\sum_{a=1}^{m}(g_a)^2\left\{\frac{d_a(i)}{l_a(i)}\right\}\{l_a(i) - d_a(i)\}}{\left[\sum_{a=1}^{m} g_a\{l_a(i) - d_a(i)\}\right]^2}}.\end{aligned} \tag{5}$$

The traditional Greenwood formula using the weighted counts gives

$$\mathrm{SE}_{GW}[R_{BII}(t)] = [R_{BII}(t)] \times \sqrt{\sum_{i=1}^{t} \frac{\sum_{a=1}^{m} g_a d_a(i)}{\left[\left\{\sum_{a=1}^{m} g_a l_a(i)\right\}\left\{\sum_{a=1}^{m} g_a\{l_a(i) - d_a(i)\}\right\}\right]}}. \tag{6}$$

When $u_a = w_a$ but $p_a(i) \neq p(i)$, the standard error of the cumulative observed survival proportion $P(t)$ can be calculated in three different ways.

From the new formula derived in (4)

$$\mathrm{SE}_{NEW}[P(t)] = P(t)\sqrt{\sum_{i=1}^{t} \frac{\sum_{a=1}^{m}\left\{\frac{d_a(i)}{l_a(i)}\right\}\{l_a(i) - d_a(i)\}}{\left[\sum_{a=1}^{m}\{l_a(i) - d_a(i)\}\right]^2}}. \tag{7}$$

From the Greenwood formula (for weighted counts) in (6),

$$\mathrm{SE}_{GW}[P(t)] = P(t)\sqrt{\sum_{i=1}^{t} \frac{\sum_{a=1}^{m} d_a(i)}{\left[\left\{\sum_{a=1}^{m} l_a(i)\right\}\left\{\sum_{a=1}^{m}\{l_a(i) - d_a(i)\}\right\}\right]}}. \tag{8}$$

The cumulative observed survival proportion can also be estimated as $P(t) = \sum_{a=1}^{m} w_a P_a(t)$ (stratified method).

Then, the standard error of the cumulative observed survival proportion is

$$\mathrm{SE}_{ST}[P(t)] = \sqrt{\sum_{a=1}^{m} (w_a)^2 \mathrm{Var}_{GW}\{P_a(t)\}}. \tag{9}$$

When, in addition, $p_a(i) = p(i)$, (7) gives the Greenwood formula (8).

Appendix 2. STATA code for standard error of the Brenner II age-standardised observed survival proportion (available at http://www.cancerregistry.fi/eng/general/links.html)

```
capture program drop secosr
program define secosr
version 8.0


syntax, age(varname) start(varname) endf(varname)
status(varname) [stan_v(name) outfile(name)]
// stan_v(varname): HAS TO BE coded 1 = standard
group 2 = study group
// age(varname)
// outfile, optional, saves listed ouput to stata
file


quietly {
preserve


if "`stan_v'" != "" {
   inspect `age'
   local nage = r(N_unique)
   count if `stan_v'==1
   local Nsta = r(N)
```

```
   count if `stan_v'==2
   local Nstu = r(N)

   forvalues i = 1/`nage' {

      count if `stan_v'==1 & `age'==`i'
      local nsta = r(N)
      count if `stan_v'==2 & `age'==`i'
      local nstu = r(N)
      local g`i' = (`nsta'/`Nsta')/ (`nstu'/`Nstu')
   }
keep if `stan_v'==2
   }


gen id=_n
stset `endf', origin(`start') failure(`status')
scale(365.25) id(id)
stsplit fu, at(0(1)max)
rename _d D
gen L = 1
collapse (sum) L D, by(fu `age')
sort `age' fu
bysort `age': gen W = L[_n] - L[_n+1] - D[_n]
replace W = L - D if W==.
gen P = 1 - D/(L-W *.5)
bysort `age': gen CP = exp(sum(ln(P)))


gen g=.
forvalues i = 1/`nage' {
replace g = `g`i'' if `age'==`i'


      }


gen Qik = D/(L-(W*.5))
bysort fu: egen _nomi = sum(g*D)
bysort fu: egen _deno = sum(g*D(L-W*.5) )
bysort fu: gen qk = _nomi/_deno
drop _nomi _deno
bysort fu: egen _nomi = sum((g^2)*(L-W*.5)*Qik*(1-
Qik))
bysort fu: egen _deno_1 = sum(g*((L-W*.5)-D) )
bysort fu: replace _deno = _deno_1^2
bysort fu: gen Bk = _nomi/_deno
gen nomi_Bk = _nomi
gen deno_Bk = _deno
sort fu `age'


drop _nomi _deno
bysort fu: egen _deno = sum( g*(L-W*.5) )
bysort fu: egen _A = sum( g*((L-W*.5)-D) )
bysort fu: replace _deno = _deno*_A
bysort fu: egen _nomi = sum( g*D )
bysort fu: gen Bk_p = _nomi/_deno
sort fu agegrp
bysort fu: gen _i = _n
bysort fu: keep if _i==_N
gen COSR = exp(sum(ln(1-qk) ) )
gen seCOSR = sqrt( COSR^2 * sum(Bk) )
gen sepCOSR = sqrt( COSR^2 * sum(Bk_p) )


}


list fu COSR seCOSR sepCOSR


if "`outfile'" != "" {
   keep fu COSR seCOSR sepCOSR
   save `outfile', replace
   }



restore
end


////APPLICATION


use data, clear
gen status_exit = 1 if lstatus==1
replace status_exit = 0 if lstatus==0


replace status_exit = 0 if lstatus==2
gen standard = 1 if period==2
replace standard = 2 if period==1


secosr, age(agegrp) start(dx) endf(exit)
status(status_exit)///
     stan_v(standard) outfile(output)
```

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