available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

Age-standardisation of relative survival ratios of cancer patients in a comparison between countries, genders and time periods

Arun Pokhrel[a,b,*], *Timo Hakulinen*[a]

[a]*Finnish Cancer Registry, Institute for Statistical and Epidemiological Cancer Research, Pieni Roobertinkatu 9, FI-00130 Helsinki, Finland*
[b]*Central Bureau of Statistics, Kathmandu, Nepal*

ARTICLE INFO

Article history:
Received 19 September 2008
Received in revised form
3 October 2008
Accepted 16 October 2008
Available online 8 December 2008

Keywords:
Epidemiologic methods
Models
Neoplasms
Prognosis
Survival
Age-standardisation

ABSTRACT

A recent method of age-standardisation of relative survival ratios for cancer patients does not require calculation of age-specific relative survival ratios, as ratios of age-specific proportions between the standard population and study group at the beginning of the follow-up are used to substitute the original individual observations. This method, however, leads to direct age-standardisation with weights that are different for each patient group if the general population mortality patterns for the groups are different. This is the case in international comparisons, and in comparisons between genders and time periods.

The magnitude of the bias caused by the differences in general population mortality is investigated for comparisons involving European countries and the USA. Patients in each country are assumed to have exactly the same age-specific relative survival ratios as those diagnosed in Finland in 1985–2004. An application of a properly functioning age-standardisation method should then give exactly equal age-standardised relative survival ratios for each country. However, the recent method shows substantial differences between countries, with highest relative survival for populations, where the general population mortality in the oldest ages is the highest.

This source of error can thus be a serious limitation for the use of the method, and other methods that are available should then be employed.

1. Introduction

The relative survival rate[1] gives an estimate of the net survival probability of the patients, i.e. the survival probability when the cancer of the patients is considered as the only cause of death. The relative survival rate is actually a ratio between two proportions, also historically called rates, the observed survival rate of the patients and an expected survival rate in the general population group, comparable to the patients with respect to sex, age and calendar period of observation. Factors even more than these three, e.g. region, may be involved in the comparability. The relative survival ratios are used by population-based cancer registries universally.[2–4] In this text, the term relative survival ratio is used hereafter.

The relative survival ratios of cancer patients usually depend on age.[5] It is common that the relative survival is lower for older patients, and thus in populations where the proportion of older patients is larger, the relative survival ratios tend

* *Corresponding author:* Address: Finnish Cancer Registry, Institute for Statistical and Epidemiological Cancer Research, Pieni Roobertinkatu 9, FI-00130 Helsinki, Finland. Tel.: +358 9 135 331; fax: +358 9 135 5378.
E-mail address: arun.pokhrel@cancer.fi (A. Pokhrel).
0959-8049/$ - see front matter
doi:10.1016/j.ejca.2008.10.034

to be lower. It is possible to age-standardise these ratios by the same approach as that used for the incidence rates.

As the relative survival ratios describe the fate of patients and not that of the general population, the weights used in taking weighted averages for age-standardisation should be relevant for patient populations. This means that older age groups should get more relative weight in a standard population for survival than in a standard population for incidence. The age-standardised relative survival ratios for the patient populations should then have an interpretation as relative survival ratios if each of them had the same age distribution as the standard patient population.

The age-standardised incidence rates become equal to the crude (non-standardised) incidence rates when the patients' own age structure is used as the standard. This is also true for the relative survival ratios age-standardised using the two newest methods, the BH[6] and BA[7] methods, respectively.[8] For the BH method, however, this is true only if the potential censoring does not depend on age.[8]

The BA method does not require calculation of age-specific relative survival ratios. However, this method leads to direct age-standardisation with a set of weights that is different for each patient group to be compared, if the patterns of general population mortality for the patient groups are different.[8] These patterns are typically different for patient groups in international comparisons and in comparisons between genders and time periods.

Direct age-standardisation should be made with the same fixed set of age-specific weights for all patient groups. Thus, in principle, the fact that the set is not the same for all patient groups implies a bias in comparisons. The age-standardised relative survival is then confounded by differences in expected survival.

The bias may be serious in international comparisons where the general mortality patterns vary by country. This is investigated in the following for European countries and the USA. The idea is to assume that each of the countries would have the same age-specific relative survival ratios but their own general mortality patterns.

2. Material and methods

The countries chosen for the comparative study were Austria, Belarus, Belgium, Bulgaria, Czech Republic, Denmark, England, Estonia, Finland, France, West and East Germany (defined as if they existed even in 2000–2004), Hungary, Iceland, Italy, the Netherlands, Norway, Portugal, Russia, Slovakia, Sweden, Switzerland, the Ukraine and the USA. The general mortality to be used in the age-specific weights of the BA method was obtained for calendar periods 1965–1969 and 2000–2004.[9]

The relative survival ratios for each country were adopted from those for patients diagnosed in Finland with a major cancer in 1985–2004. Twenty-one sites were included in the study, and 323,352 patients were followed-up for death and emigration until the end of 2005 (Table 1). Various checks have indicated that the Finnish Cancer Registry has a virtually complete coverage.[10] Only 277 patients, 0.09%, were lost from follow-up before the end of 2005. The expected survival proportions were based on general population mortality by 5-year calendar period, sex and 1-year age group available from Statistics Finland.[11]

Table 1 – Numbers of cancer patients in Finland in 1985–2004 and included in population-based survival analysis by site.

Site	Males	Females
Salivary gland	553	607
Oesophagus	2374	1801
Stomach	9957	8776
Colon	10,024	13,146
Rectum	7728	7120
Liver	2463	1897
Pancreas	6316	7517
Nose	411	353
Lung	31,805	8684
Skin melanoma	5677	5699
Skin non-melanoma	5581	6290
Breast	–	60,224
Cervix uteri	–	3092
Corpus uteri	–	12,362
Ovary	–	9171
Prostate	49,197	–
Testis	1692	–
Kidney	7263	5876
Urinary bladder	10,737	3452
Thyroid gland	1337	4916
Leukaemia	4868	4386
Total	157,983	165,369

Age-specific 5-, 10- and 15-year relative survival ratios were calculated for each site using the Hakulinen method.[12] The age groups were 0–44, 45–54, 55–64, 65–74 and 75 years and over. Age-standardised cumulative relative survival ratios based on the BA method[8] were derived using the age distribution 1 of the Corazziari and colleagues standard cancer patient populations.[13]

For each country, the gender and age-specific relative survival ratios in the two calendar periods were kept fixed to those observed in Finland in 1985–2004. In order to control for the patient selection by age within the age groups[14], each age group was represented in the calculations of the expected survival by a central value (40, 50, 60, 70 and 80 years).

3. Results

Fig. 1 illustrates the typical effect of age. In patients with cervix uteri cancer diagnosed in 1985–2004, the relative survival was lower the older the patients were at diagnosis. These age-specific relative survival ratios were assumed to apply for each of the 24 countries in both the time periods. For 1965–1969, this produced clearly higher cumulative relative survival for Austria than for Belarus (Fig. 1).

The age-standardised 5-year relative survival ratios for cervical cancer patients based on the BA method by Brenner and colleagues[7] varied between 55.1% and 56.6%, 10-year ratios from 50.5% to 53.7% and 15-year ratios from 49.2% to 53.4% (Table 2), when the general population mortality of each country included in the weights of the standardisation was from females in 2000–2004. Table 2 indicates that the BA

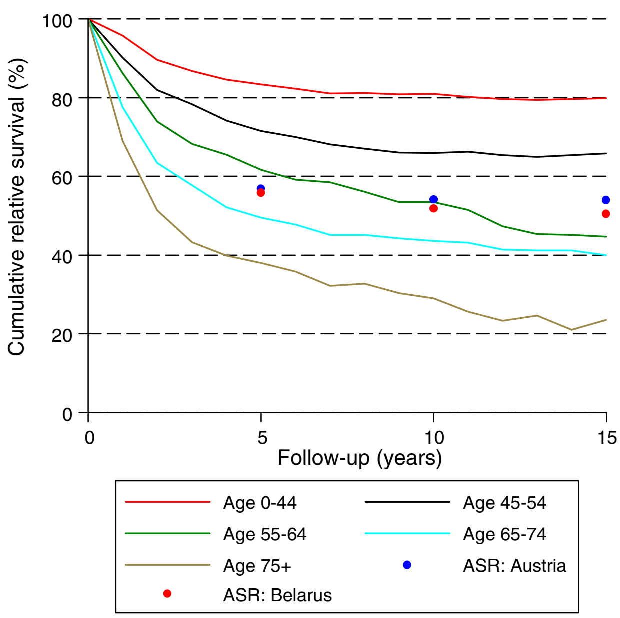

Fig. 1 – Age-specific cumulative relative survival ratios of patients with cancer of the cervix uteri diagnosed in Finland in 1985–2004 and age-standardised 5-, 10- and 15-year cumulative relative survival ratios for Austria and Belarus in 1965–1969 using the method by Brenner and colleagues[7] by assuming that these age-specific relative survival ratios would apply for both the countries. The Corazziari and colleagues standard no. 1[13] was used as the standard age distribution of patients at diagnosis.

method produced varying age-standardised relative survival ratios by country on the basis of constant age-specific relative survival ratios also for all the other 20 sites considered. This was clearly observable already for the 5-year follow-up, but the variation usually became larger when the follow-up period became longer.

An assumption that the same Finnish age-specific relative survival ratios applied in all the countries during both 1965–1969 and 2000–2004 leads also to trends in the age-standardised relative survival ratios based on the BA method. In Austria, the 5-year relative survival ratio of cervical cancer patients decreased from 56.8% in 1965–1969 to 55.5% in 2000–2004, whereas an increase from 55.8% to 56.5% would have been observed in Belarus (Table 3). In 10- and 15-year relative survival ratios, these decreases and increases were even larger (Table 3). If the women had had the general mortality equal to that in the corresponding male populations, all the age-standardised relative survival ratios would have been clearly even higher, with an increasing difference compared to females by the length of the follow-up.

Similar results (not shown) were obtained for all the different sites considered and also for males. For most countries, a downward trend in the age-standardised relative survival would have been observed. Upward trends would have been observed for Belarus, Russia and the Ukraine. The same age-specific relative survival ratios assumed for males always gave higher age-standardised relative survival ratios than for females, as also shown in the example of Table 3.

Table 2 – The mean, minimum and maximum age-standardised 5-, 10- and 15-year relative survival ratios in females in 24 countries based on the method by Brenner and colleagues[7] by assuming the age-specific relative survival ratios of Finnish patients in 1985–2004 for each of the countries and using for each country its own general population mortality in females for 2000–2004 to obtain the weights in standardisation (SD = standard deviation). The Corazziari and colleagues standard no. 1[13] was used as the standard age distribution of patients at diagnosis.

Site	5-year				10-year				15-year			
	Mean	SD	Min	Max	Mean	SD	Min	Max	Mean	SD	Min	Max
Salivary gland	74.0	0.6	73.2	75.2	73.0	0.7	72.1	74.2	67.9	1.0	66.5	69.8
Oesophagus	15.4	0.2	15.1	15.9	13.7	0.2	13.4	14.2	14.1	0.1	13.9	14.3
Stomach	29.6	0.3	29.2	30.1	28.7	0.4	28.1	29.5	29.4	0.5	28.7	30.3
Colon	58.3	0.2	58.0	58.7	55.9	0.4	55.4	56.6	55.1	0.6	54.3	56.3
Rectum	55.7	0.3	55.3	56.3	51.3	0.5	50.6	52.1	51.9	0.4	51.2	52.7
Pancreas	4.3	0.1	4.2	4.5	3.4	0.1	3.2	3.7	3.4	0.2	3.1	3.8
Liver	7.9	0.2	7.7	8.1	–	–	–	–	–	–	–	–
Nose	44.8	0.3	44.4	45.3	32.9	0.9	31.7	34.6	–	–	–	–
Lung	13.3	0.2	13.0	13.6	10.0	0.3	9.5	10.6	8.6	0.4	8.1	9.3
Melanoma	83.4	0.2	83.1	83.8	81.3	0.3	80.9	81.9	80.5	0.7	79.6	81.8
Other skin	92.3	0.1	92.1	92.5	88.9	0.4	88.3	89.6	87.2	0.9	85.9	89.0
Breast	82.1	0.2	81.9	82.5	72.8	0.4	72.2	73.6	67.5	0.6	66.6	68.6
Cervix uteri	55.7	0.5	55.1	56.6	51.8	1.0	50.5	53.7	51.0	1.3	49.2	53.4
Corpus uteri	80.6	0.4	80.2	81.3	79.4	0.6	78.6	80.6	79.5	0.7	78.5	80.7
Ovary	38.7	0.5	38.1	39.6	34.1	0.8	33.0	35.7	34.7	1.0	33.2	36.6
Kidney	58.4	0.4	57.9	59.2	52.2	0.8	51.0	53.7	48.8	1.2	47.2	50.9
Bladder	72.2	0.4	71.7	73.1	70.2	0.9	68.9	72.0	70.1	1.2	68.5	72.3
Thyroid	78.5	0.7	77.6	79.9	79.5	1.5	77.4	82.3	83.5	1.4	81.5	86.1
Leukaemia	41.5	0.4	41.0	42.3	30.8	0.9	29.6	32.6	24.2	1.3	22.4	26.6

The symbol–indicates that not all the age-specific relative survival ratios are available.

Table 3 – Age-standardised 5-, 10- and 15-year relative survival ratios of cervical cancer patients in Austria (A) and Belarus (B) based on the method by Brenner and colleagues[7] by assuming the age-specific relative survival ratios of Finnish patients in 1985–2004 for both the countries and using different sets of general population mortality to obtain the weights in the standardisation. The 'male mortality' indicates the assumption that the general population mortality in females had been equal to that observed in males. The Corazziari and colleagues standard no. 1[13] was used as the standard age distribution of patients at diagnosis.

Mortality	5-year		10-year		15-year	
	A	B	A	B	A	B
Female mortality						
1965–1969	56.8	55.8	54.1	51.8	54.0	50.5
2000–2004	55.5	56.5	51.4	53.3	50.4	52.9
Male mortality						
1965–1969	57.6	56.4	55.6	53.0	56.3	52.5
2000–2004	56.1	57.3	52.7	54.9	52.4	55.4

4. Discussion

The examples were constructed in a way that a properly functioning age-standardisation should not have produced any differences between countries, genders or time periods as the age-specific relative survival was not assumed to vary by these factors.

To understand the background of the differences and trends observed, it is useful to look at the developments of the expected survival over time, which, for example, shows that in Austria, as in most of the countries considered, the expected survival has raised much more in older ages than in younger ages (Table 4). As the expected survival is lower in the older ages than in younger ages, there is mathematically much more room for rise in the older ages. The relative weight of older patients in the standardisation using the BA method usually becomes larger when a recent calendar time is considered. As the relative survival for older patients is lower than that for younger patients and as it gets a larger weight in the latter period, a downward trend in the age-standardised relative survival will be observed when the age-specific relative survival ratios are held constant over time.

The three countries of the former Soviet Union make an exception in this respect. There the expected survival has deteriorated more in the older ages than in younger ages. Thus, for the relative survival in the latter period, the low age-specific relative survival in the higher ages will get less weight in the calculation of the age-standardised survival. This will lead to an artificial observation of an improvement in the age-standardised relative survival.

The differences by gender are also explained by a smaller weight of higher ages in the expected survival in males compared to females. For international comparisons, most importantly, all the age-specific weights also differ from country to country.

The relative survival ratio should give an estimate of cancer patients' (net) survival probability as far as the cancer of the patients is concerned as a cause of death. The BH and BA methods of age-standardisation[6,7] actually compare cumulative relative survival for those who with respect to other causes would survive for a sufficiently long period (Appendix).[8] The probability of surviving with respect to other causes varies between populations, and should consequently also be subject to standardisation. This problem has been solved in the BH method of age-standardisation,[6] as

Table 4 – The expected 5-, 10- and 15-year survival probabilities of those aged 40, 50, 60, 70 and 80 years in Austria in 1965–69 and 2000–04 by gender based on the human mortality database[9] and the ratios between the two time periods by gender and age.

Gender/age	5-year			10-year			15-year		
	1965–69	2000–04	Ratio	1965–69	2000–04	Ratio	1965–69	2000–04	Ratio
Males									
40	0.98033	0.98949	1.01	0.95073	0.97215	1.02	0.90757	0.94366	1.04
50	0.95461	0.97070	1.02	0.88095	0.92770	1.05	0.76541	0.86895	1.14
60	0.86884	0.93667	1.08	0.68987	0.84307	1.22	0.48742	0.70973	1.46
70	0.70654	0.84184	1.19	0.41851	0.63456	1.52	0.18489	0.39326	2.13
80	0.44179	0.61974	1.40	0.13005	0.27386	2.11	0.02097	0.06790	3.24
Females									
40	0.98915	0.99445	1.01	0.97215	0.98542	1.01	0.94709	0.97108	1.03
50	0.97422	0.98546	1.01	0.93571	0.96405	1.03	0.87555	0.93444	1.07
60	0.93570	0.96928	1.04	0.83348	0.92295	1.11	0.67642	0.84546	1.25
70	0.81156	0.91603	1.13	0.56317	0.77599	1.38	0.29652	0.55907	1.89
80	0.52652	0.72046	1.37	0.18386	0.37732	2.05	0.03588	0.11823	3.30

the expected survival from the standard population instead of that from the study population is included in the weights of the standardisation. The fact that both the BH and BA methods actually produce age-standardised relative survival ratios with a different, conditional, interpretation compared to the traditional method[2] is more extensively reviewed in another study.[8]

The BA method can give very different results from those obtained by the BH method on the same data. For example, the upper age-standardised cumulative relative survival ratios of Fig. 1 will be produced for the Belarus women using the BH method when the standard population mortality is based on the Austrian women. The BA method will give the lower age-standardised cumulative relative survival ratios.

The additional dependence of the BA method on age-specific differences in potential censoring[15] was not investigated in this study. This dependence is similar to that of the crude, non-standardised ratios' dependence on the same differences.[12]

For practical applications, it is good to be aware of the confounding introduced by differences in the expected survival and the potential censoring, when the BA method[7] is employed. Differences in the expected survival by country, gender and time period as sources of confounding may have large effects in national and international comparisons. It may then be safer to use the other methods available for age-standardisation.

Conflict of interest statement

None declared.

Acknowledgements

The work of Arun Pokhrel was supported by the Finnish Ministry of Education (Doctoral Programmes in Public Health) and by a grant from the Cancer Society of Finland.

Appendix: The two new methods of age-standardisation of relative survival

The BH method[6] uses standardisation weights proportional to the expected age distribution of persons surviving in the standard population up to the given time point t given that the standard population were only subject to the respective general population mortality:

$$r_{BH}(t) = \frac{\sum_{a=1}^{m} w_{as} p_{as}^{*}(t) r_a(t)}{\sum_{a=1}^{m} w_{as} p_{as}^{*}(t)},$$

where w_{as} is the proportion of persons in the standard population belonging to age group a at the beginning of the follow-up and the $p_{as}^{*}(t)$ is the expected proportion of survivors at time t based on the general population mortality for the standard population. This method gives the non-standardised relative survival ratio $r(t)$ when the patient group itself with a proper general population mortality is used as a standard, provided that there is no censoring, or at least, that the potential censoring is the same in all age groups:

$$r_{BHp}(t) = \frac{\sum_{a=1}^{m} w_a p_a^{*}(t) r_a(t)}{\sum_{a=1}^{m} w_a p_a^{*}(t)}.$$

Here, w_a is the proportion of persons in the study population belonging to age group a at the beginning of the follow-up and $p_a^{*}(t)$ is the expected proportion of survivors at time t based on the general population mortality in the study population.

This age-standardised relative survival ratio can be interpreted as an estimate of the probability of surviving the extra mortality hazard related to cancer on the condition that the person would survive with respect to general population mortality hazard in the standard population for that long.

The BA method, proposed by Brenner and colleagues[7], is apparently not based on the use of age-specific relative survival ratios. Each patient in a particular relative survival analysis is substituted with a weighted count, the ratio between w_{as} and w_a. If the potential censoring is not depending on age, the result, the age-standardised relative survival ratio, is

$$r_{BA}(t) = \frac{\sum_{a=1}^{m} w_{as} p_a^{*}(t) r_a(t)}{\sum_{a=1}^{m} w_{as} p_a^{*}(t)}.$$

This formula gives the non-standardised relative survival ratio when the patient group itself is used as a standard ($w_{as} = w_a$). On the other hand, this is very similar to the $r_{BH}(t)$ but includes another source of confounding. The weights are not the same for all patient groups being compared unless these patient groups come from the same general population. For that, the $p_a^{*}(t)$ has to be equal to the $p_{as}^{*}(t)$ for all groups under comparison. This is a serious theoretical limitation if the method is to be used in international comparisons[3] or in comparisons between genders or over time in the same population.

REFERENCES

1. Berkson J, Gage RP. Calculation of survival rates for cancer. *Proc Staff Meet Mayo Clin* 1950;**25**:270–86.
2. Sankaranarayanan R, Black RJ, Parkin DM, editors. Cancer survival in developing countries. IARC Scientific Publications No. 145, Lyon; 1998.
3. Berrino F, Capocaccia R, Coleman MP, et al. Survival of cancer patients in Europe; the EUROCARE-3 study. *Ann Oncol* 2003;**14**(Suppl 5):v1–v155.
4. Ries LAG, Eisner MP, Kosary CL, et al. SEER cancer statistics review, 1975–2001. National Cancer Institute, Bethesda, MD, <http://seer.cancer.Gov/csr/1975_2001/>; 2004.
5. Dickman PW, Hakulinen T, Luostarinen T, et al. Survival of cancer patients in Finland 1955–1994. *Acta Oncol* 1999;**38**(Suppl 12):1–103.
6. Brenner H, Hakulinen T. On crude and age-adjusted relative survival rates. *J Clin Epidemiol* 2003;**56**:1185–91.

7. 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.
8. Pokhrel A, Hakulinen T. How to interpret the relative survival ratios of cancer patients. *Eur J Cancer* 2008;**44**: 2661–7.
9. Human Mortality Database, University of California, Berkeley (USA), and Max Planck Institute for Demographic Research (Germany). www.mortality.org (data downloaded on May, 2008).
10. Teppo L, Pukkala E, Lehtonen M. Data quality and quality control of a population-based cancer registry. *Acta Oncol* 1994;**33**:365–9.
11. Statistics Finland. <http://www.stat.fi/tup/tasaarvo/tilastotietoa_en.html>.
12. Hakulinen T. Cancer survival corrected for heterogeneity in patient withdrawal. *Biometrics* 1982;**38**:933–42.
13. Corazziari I, Quinn M, Capocaccia R. Standard cancer patient population for age standardizing survival ratios. *Eur J Cancer* 2004;**40**:2307–16.
14. Hakulinen T. On long-term relative survival rates. *J Chron Dis* 1977;**30**:431–43.
15. Pokhrel A. Age-standardization of relative survival ratios for cancer patients. Acta Universitatis Tamperensis 1278, Tampere; 2007. <http://acta.uta.fi/pdf/978-951-44-7145-2.pdf>.