EUROPEAN JOURNAL OF CANCER 44 (2008) 2661–2667

available at www.sciencedirect.com

journal homepage: www.ejconline.com

# How to interpret the relative survival ratios of cancer patients

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ARTICLE INFO

*Article history:*
Received 29 July 2008
Received in revised form
5 August 2008
Accepted 11 August 2008
Available online 24 September 2008

*Keywords:*
Epidemiologic methods
Models
Neoplasms
Prognosis
Survival
Age-standardisation

ABSTRACT

It is common in population-based cancer registries to use the relative survival ratio to estimate patients' probabilities of surviving if their cancer were the only cause of death. Results from the recently proposed new methods of age-standardisation can be interpreted as ratios between the observed and expected survival proportions. Like the non-standardised ratios, these age-standardised relative survival ratios have, however, the desired probability interpretation only under a specific condition.

The condition involved is the survival with respect to other causes up to the given point of follow-up. With different lengths of follow-up, this condition is also different. As a consequence, the non-standardised relative survival ratios and those standardised with the two newest methods produce, for different lengths of follow-up, mutually incomparable estimates with respect to age. Not accounting for this may, for example, lead to erroneous conclusions about the cure of the patients. The traditional method of age-standardisation does not have this problem of incomparability. Results of relative survival analyses of data from the Finnish Cancer Registry are used to illustrate this issue.

To avoid overinterpretation and confusion, the different interpretations of the relative survival ratios, both non-standardised and age-standardised, must be known. For example, the very popular cumulative relative survival curves, consisting of consecutive cumulative relative survival ratios, should not be produced for the non-standardised ratios or for ratios age-standardised with the two newest methods. In practical applications, it is crucial to know which method of standardisation, and not only which standard population, has been in use.



## 1. Introduction

The relative survival rate[1] is supposed to give an estimate of the net survival probability of the patients, i.e. the survival probability if the cancer of the patients was the only cause of death. Actually, the relative survival rate is a ratio between the observed proportion of survivors among the patients and that expected in a group of the general population, comparable with the patients at the beginning of the follow-up period concerned, with respect to sex, age, calendar period and sometimes even to region, social class and race.

Fairly little attention has been paid to the fact that this interpretation is valid only when survival with respect to cancer and that with respect to other causes are independent. If the patient group is heterogeneous with respect to age, both the cancer-related survival and that related to other causes often tend to be low at the same time in old patients and high in young patients. The cure for this is a stratified analysis by age and a summary of the age-specific results as a weighted

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0959-8049/$ - see front matter 
doi:10.1016/j.ejca.2008.08.016

average[2], an age-standardised ratio[3] or a result based on statistical modelling.[4] A recently proposed method of age-standardisation[5] is not based on stratification by age. Thus, it is natural to question whether the original interpretation of the relative survival ratio is valid for the age-standardised relative survival ratio by using this method. In the following, this issue will be investigated for all three proposed methods[3,5,6] of age-standardisation of the relative survival ratios as well as for the non-standardised relative survival ratio. Survival analysis data from the Finnish Cancer Registry are used for illustration of the methods and their interpretations.

## 2. Materials and methods

Patients diagnosed in Finland with cancer at one of 21 major sites from 1955–1974 and 1985–2004 and followed-up for death and emigration until the end of 2005 were used as the practical material. Altogether, 154,281 and 323,352 patients were diagnosed from 1955–1974 and 1985–2004, respectively (Table 1). The Finnish Cancer Registry has a virtually complete coverage[7], and only 456 patients, less than 0.1%, 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.[8]

The three methods of age-standardisation of the relative survival ratios[3,5,6] as well as the obtaining of the non-standardised ratios, are all described in a uniform way in detail in the Appendix. Non-standardised and age-specific 5-, 10- and 15-year relative survival ratios were calculated for each site and time period for the five groups 0–44, 45–54, 55–64, 65–74 and 75 years and over. Age-standardised cumulative relative survival ratios were derived with the general population mortality in one period as the standard using each of the three methods. Both the patients' own age distribution at diagnosis (internal standardisation) and the patients' age distribution from the other period (external standardisation) were employed as the standard. Changes between the 5-, 10- and 15-year relative survival ratios were compared both age-specifically and using the non-standardised and the age-standardised figures.

**Table 1 – Numbers of cancer patients in Finland in 1955–1974 and 1985–2004 and included in population-based survival analysis by site**

| Site | 1955–1974 | | 1985–2004 | |
|---|---|---|---|---|
| | Males | Females | Males | Females |
| Salivary glands | 271 | 323 | 553 | 607 |
| Oesophagus | 2354 | 2696 | 2374 | 1801 |
| Stomach | 16576 | 13116 | 9957 | 8776 |
| Colon | 2838 | 4502 | 10024 | 13146 |
| Rectum | 2901 | 3558 | 7728 | 7120 |
| Liver | 697 | 562 | 2463 | 1897 |
| Pancreas | 3252 | 2919 | 6316 | 7517 |
| Nose | 443 | 347 | 411 | 353 |
| Lung | 28745 | 2448 | 31805 | 8684 |
| Skin melanoma | 1154 | 1417 | 5677 | 5699 |
| Other skin | 1587 | 1585 | 5581 | 6290 |
| Breast | – | 18121 | – | 60224 |
| Cervix uteri | – | 7235 | – | 3092 |
| Corpus uteri | – | 5484 | – | 12362 |
| Ovary | – | 5011 | – | 9171 |
| Prostate | 7916 | – | 49197 | – |
| Testis | 497 | – | 1692 | – |
| Kidney | 1946 | 1795 | 7263 | 5876 |
| Urinary bladder | 3156 | 1005 | 10737 | 3452 |
| Thyroid gland | 449 | 1442 | 1337 | 4916 |
| Leukaemia | 3109 | 2824 | 4868 | 4386 |
| Total | 77891 | 76390 | 157983 | 165369 |

When the potential censoring does not differ between age groups, all the methods can be represented as weighted averages of the age-specific relative survival ratios, even the non-standardised ratio and the ratio standardised by the most recent method[5] (cf. Appendix). The weights used in the standardisation, however, differ. They are as follows for patients followed-up up to $t$ years since the beginning of follow-up:

*Traditional method:* proportion of patients belonging to the age group at the beginning of follow-up in the standard population.

*Non-standardised ratio:* expected proportion of patients under follow-up at $t$ belonging to the age group given that the patients were subject to their own general population mortality.

*Brenner and Hakulinen (2003)[6]:* expected proportion of patients under follow-up at $t$ belonging to the age group in the standard population given that the patients were subject to the general population mortality in the standard population.

*Brenner and colleagues (2004)[5]:* expected proportion of patients under follow-up at $t$ belonging to the age group in the standard population given that the patients were subject to their own general population mortality.

A comparison between these weights reveals the following:

a. Only non-standardisation does not take into account the age distribution of patients in the standard population. In this respect, all the standardisation methods do standardise.
b. Only the traditional method gives the same set of weights for all values of follow-up time $t$. Thus, only the traditional method standardises for age when relative survival ratios for different lengths of follow-up are compared.
c. The non-standardisation and the method by Brenner and colleagues (2004) are confounded by age-specific differences in patients' own general population mortality, as this is included in the weights for the age-specific relative survival ratios.

The interpretation of the differently standardised ratios is as follows, provided that the excess mortality hazard of the patients compared to the corresponding general population hazard can be attributed to patients' cancer:

*Unconditional probability:* The traditional age-standardisation method gives an estimate of the net probability of survival of the patients up to any time $t$ given that the cancer of the patients was the only cause of death and the patients had at the beginning of follow-up the same age distribution as the standard population. This interpretation is in keeping with the original one for the relative survival ratio.[1]

*Conditional probabilities:* The method by Brenner and Hakulinen (2003) gives an estimate of the net probability of survival of the patients up to $t$ for those able to survive the general population mortality of the standard population for that long given that the patients had at the beginning of follow-up the same age distribution as the standard population. The method by Brenner and colleagues (2004) gives an estimate of the net probability of survival of the patients up to $t$ for those able to survive the patients' own general population mortality for that long given that the patients had at the beginning of follow-up the same age distribution as the standard population. The non-standardised relative survival ratio has the same interpretation as that standardised by the method by Brenner and colleagues (2004), with the exception that the patients have their own age distribution at the beginning of the follow-up, rather than that of the standard population. These interpretations as conditional probabilities are different from the classical interpretation of the relative survival ratio. The conditional probability interpretations, particularly that for the method by Brenner and Hakulinen (2003), may well be useful, as has been mooted by Brenner and Hakulinen.[6]

In the following, the focus of attention will be on studying whether it matters, in practice, that standardisation can produce unconditional or conditional net survival probability estimates, by looking at the relative survival ratios pertaining to different lengths of follow-up. The issue of additional confounding, introduced for the Brenner and colleagues (2004) method due to differences in the general population mortality between populations, has been dealt with in another paper.[9]

## 3. Results

Fig. 1 shows some examples on how the crude (non-standardised) cumulative relative survival ratio ($r(t)$ Appendix) summarises the age-specific cumulative relative survival ratios. In general, there is a tendency that the cumulative relative survival looks more favourable than the age-specific cumulative relative survival: in stomach cancer, it increases with follow-up time after about 5 years of follow-up. An increase can also be observed in cancer of the thyroid but much earlier. In corpus uteri and ovarian cancers, the cumulative relative survival stabilises around 5 years which, in general, is not true for the age-specific survival.

The differences in crude relative survival between 5 and 10 and between 10 and 15 years seem to have a tendency of being smaller than those in age-specific relative survival. Thus, the crude relative survival does not summarise the age-specific relative survival in an appropriate way. The traditional age-standardised relative survival ($r_T(t)$, Appendix) with the patients' age distribution at diagnosis as the standard does not share this problem (WRR in Fig. 1).

Let us then look at how the age-standardised relative survival ratios, derived from the three methods, summarise the age-specific ratios. The simplest way to do the standardisation is to use the age distribution of each patient group at the beginning of the follow-up as standard (the so-called internal standardisation). Table 2 reports for females by site how many of the five age-specific relative survival curves have a less or more favourable course than each age-standardised curve calculated by different methods. For example, for female patients diagnosed with oesophageal cancer in 1985–2004 and followed up between 5 and 10 years after diagnosis, the traditional age-standardisation method gave, in three age groups, a more favourable course in relative survival than the age-specific relative survival, whereas in two age groups the age-specific relative survival had a more favourable course than the age-standardised relative survival. For the two newest methods of age-standardisation, in four out of five age groups the age-standardised relative survival gave a more favourable course than the age-specific relative survival. The line is left blank for the sites where no age-specific relative survival could be calculated.

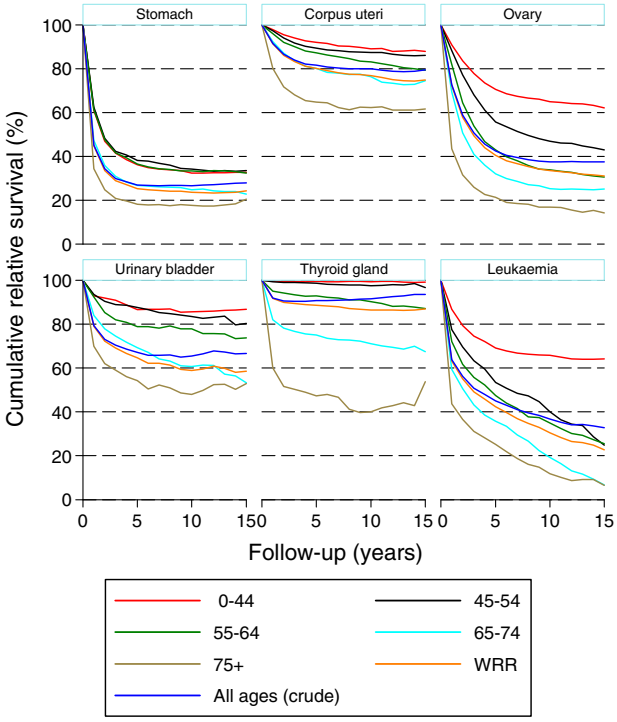


**Fig. 1 – Age-specific and crude (non-standardised) cumulative relative survival ratios (%) for female patients diagnosed in Finland in 1985–2004 with cancer at selected sites: stomach, corpus uteri, ovary, urinary bladder, thyroid and leukaemia. The traditionally age-standardised ratios are also given, with the patients' age distribution at diagnosis as the standard (WRR).**

A similar analysis was also done for males and with the so-called external standardisation, by using the 1985–2004 age distributions as standards for patients diagnosed in 1955–1974 and vice versa. The results (not shown) are very similar to those obtained for internal standardisation. The overall pattern is that the two newest methods give, on average, a more favourable course than the age-specific relative survival (Table 3). A more favourable course is given as a summary 2–3 times as often as a less favourable course. The traditional method does not have a systematic favour in this respect.

It should, nevertheless, be noted that, for example, for cancers of the nose and lung (15-year follow-up only) the relative survival estimates were not always available for all age

**Table 2 – Number of times the differences in age-standardised relative survival ratios between 10 and 5, and 15 and 10 years of follow-up are higher (+) or lower (–) than the corresponding differences in age-specific relative survival ratios by method of age-standardisation, period of diagnosis and site, females**

| Follow-up year/site | 1955–1974 | | | | | | 1985–2004 | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Traditional | | BH | | BA | | Traditional | | BH | | BA | |
| | + | – | + | – | + | – | + | – | + | – | + | – |
| *5–10 years* | | | | | | | | | | | | |
| Salivary glands | 2 | 3 | 2 | 3 | 2 | 3 | 4 | 1 | 4 | 1 | 4 | 1 |
| Oesophagus | 3 | 2 | 4 | 1 | 4 | 1 | 3 | 2 | 4 | 1 | 4 | 1 |
| Stomach | 3 | 2 | 4 | 1 | 4 | 1 | 4 | 1 | 5 | 0 | 5 | 0 |
| Colon | 4 | 1 | 5 | 0 | 5 | 0 | 4 | 1 | 4 | 1 | 4 | 1 |
| Rectum | 2 | 3 | 4 | 1 | 4 | 1 | 4 | 1 | 4 | 1 | 4 | 1 |
| Nose | 1 | 4 | 2 | 3 | 2 | 3 | 2 | 3 | 2 | 3 | 2 | 3 |
| Lung | 3 | 2 | 4 | 1 | 4 | 1 | 2 | 3 | 4 | 1 | 4 | 1 |
| Skin melanoma | 2 | 3 | 3 | 2 | 3 | 2 | 2 | 3 | 4 | 1 | 4 | 1 |
| Other skin | 1 | 4 | 3 | 2 | 3 | 2 | 1 | 4 | 2 | 3 | 2 | 3 |
| Breast | 3 | 2 | 3 | 2 | 3 | 2 | 3 | 2 | 3 | 2 | 3 | 2 |
| Cervix uteri | 3 | 2 | 5 | 0 | 5 | 0 | 3 | 2 | 4 | 1 | 4 | 1 |
| Corpus uteri | 3 | 2 | 4 | 1 | 4 | 1 | 2 | 3 | 5 | 0 | 5 | 0 |
| Ovary | 2 | 3 | 3 | 2 | 3 | 2 | 2 | 3 | 4 | 1 | 4 | 1 |
| Kidney | 2 | 3 | 3 | 2 | 3 | 2 | 2 | 3 | 3 | 2 | 3 | 2 |
| Bladder | 2 | 3 | 5 | 0 | 5 | 0 | 2 | 3 | 3 | 2 | 3 | 2 |
| Thyroid | 4 | 1 | 5 | 0 | 5 | 0 | 3 | 2 | 5 | 0 | 5 | 0 |
| Leukaemia | 2 | 3 | 2 | 3 | 2 | 3 | 4 | 1 | 4 | 1 | 4 | 1 |
| Total | 42 | 43 | 61 | 24 | 61 | 24 | 47 | 38 | 64 | 21 | 64 | 21 |
| *10–15 years* | | | | | | | | | | | | |
| Salivary glands | 3 | 2 | 2 | 3 | 2 | 3 | 2 | 3 | 3 | 2 | 4 | 1 |
| Oesophagus | 3 | 2 | 3 | 2 | 3 | 2 | 3 | 2 | 4 | 1 | 2 | 3 |
| Stomach | 2 | 3 | 5 | 0 | 5 | 0 | 4 | 1 | 4 | 1 | 4 | 1 |
| Colon | 1 | 4 | 5 | 0 | 5 | 0 | 2 | 3 | 4 | 1 | 5 | 0 |
| Rectum | 4 | 1 | 5 | 0 | 5 | 0 | 3 | 2 | 5 | 0 | 4 | 1 |
| Nose | 3 | 2 | 3 | 2 | 3 | 2 | | | | | | |
| Lung | | | | | | | 2 | 3 | 4 | 1 | 4 | 1 |
| Skin melanoma | 3 | 2 | 3 | 2 | 3 | 2 | 1 | 4 | 4 | 1 | 4 | 1 |
| Other skin | 1 | 4 | 4 | 1 | 4 | 1 | 1 | 4 | 2 | 3 | 2 | 3 |
| Breast | 2 | 3 | 4 | 1 | 4 | 1 | 1 | 4 | 4 | 1 | 4 | 1 |
| Cervix uteri | 3 | 2 | 5 | 0 | 5 | 0 | 3 | 2 | 5 | 0 | 5 | 0 |
| Corpus uteri | 2 | 3 | 5 | 0 | 5 | 0 | 1 | 4 | 4 | 1 | 5 | 0 |
| Ovary | 2 | 3 | 4 | 1 | 4 | 1 | 4 | 1 | 4 | 1 | 5 | 0 |
| Kidney | 2 | 3 | 3 | 2 | 3 | 2 | 2 | 3 | 3 | 2 | 3 | 2 |
| Bladder | 2 | 3 | 5 | 0 | 5 | 0 | 3 | 2 | 3 | 2 | 3 | 2 |
| Thyroid | 3 | 2 | 5 | 0 | 5 | 0 | 4 | 1 | 4 | 1 | 4 | 1 |
| Leukaemia | 3 | 2 | 3 | 2 | 3 | 2 | 3 | 2 | 4 | 1 | 4 | 1 |
| Total | 39 | 41 | 64 | 16 | 64 | 16 | 39 | 41 | 61 | 19 | 62 | 18 |

The age distribution of patients at the beginning of follow-up has been used as a standard for each patient group separately (internal age-standardisation). Here: BH = Brenner and Hakulinen (2003), BA = Brenner and colleagues (2004).

**Table 3 – Number of times the differences in age-standardised relative survival ratios between 10 and 5, and 15 and 10 years of follow-up by site and sex are higher (+) or lower (–) than the corresponding differences in age-specific relative survival ratios by method of standardisation, period of diagnosis, internal and external standardisation**

| Method | Standardisation | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Internal | | | | External | | | |
| | 1955–1974 | | 1985–2004 | | 1955–1974 | | 1985–2004 | |
| | + | – | + | – | + | – | + | – |
| Traditional | 137 | 138 | 148 | 142 | 146 | 129 | 152 | 138 |
| BH | 201 | 74 | 210 | 80 | 203 | 72 | 198 | 92 |
| BA | 201 | 74 | 213 | 77 | 207 | 68 | 193 | 97 |

BH = Brenner and Hakulinen (2003), BA = Brenner and colleagues (2004).

groups (Table 2). Thus, only the relative survival ratios given by the Brenner and colleagues,[5] method are available.

## 4. Discussion

Hakulinen[2] showed some 30 years ago that the overall cumulative non-standardised relative survival ratio converges with follow-up time towards that of the youngest age group. With an increasing length of follow-up it is the youngest people that are both observed and expected to survive, and thus the ratio of their observed and expected survival proportions will give the relative survival ratio when the follow-up time is sufficiently long. Even if this phenomenon is known and to various degrees present in all non-standardised cumulative relative survival curves, these curves are continuously shown in world literature as estimates of patient survival curves as far as the cancer of the patients is concerned. This convergence property is shared by the age-standardised cumulative relative survival ratios derived from the two newest methods.[5,6]

The age-specific cumulative relative survival ratios do not have this convergence tendency, particularly if the age range within each age group is not very broad. If the independence assumption between cancer-related survival and survival in a comparable general population group is valid within these age groups, the age-specific cumulative relative survival curves as in Fig. 1 can well be interpreted as the patients' net survival curves by age, in as far as the cancer of the patients was the only cause of death. For narrow enough age groups, these estimates, up to any follow-up time *t*, are the same for patients at the beginning of follow-up and for those patients at the beginning of follow-up that could survive with respect to comparable general population mortality up to point *t*. The age-specific unconditional and conditional cumulative relative survival ratios are thus the same.

However, even in this situation, the overall (all ages combined) unconditional and conditional estimates are not the same. The traditional method of age-standardisation summarises the age-specific unconditional cumulative relative survival ratios whereas the two newer methods of age-standardisation do not do this equally well for the same age-specific (conditional) cumulative relative survival ratios.

It is, of course, not that clear a priori, whether a method of age-standardisation should give a summary of the age-specific relative survival over follow-up time. It should do that, if it were desirable that the age-standardised relative survival ratio should have an interpretation as an estimate of net survival probability of the patients without any conditions or if these ratios should be comparable over follow-up time with respect to age.

On the other hand, as long-term survival may be regarded a rather theoretical possibility for the oldest patients, it is arguable and defensible to look at this net probability on the condition that people in the comparable general population could live for that long.[6] However, this condition then imposes differences in the age distributions when cumulative relative survival ratios related to different lengths of follow-up are concerned. For a 5-year follow-up, it is still rather common to survive in the general population in the age group 75 years or more at the beginning of follow-up, whereas this is rather uncommon when the follow-up is 15 years. Thus, it can be argued that for age-standardisation between patient populations, this oldest age group should get much less weight when the follow-up is 15 years than when the follow-up is 5 years.[6] It is also notable that the non-standardised cumulative relative survival ratio has this same property and interpretation as a conditional net probability estimate.

One useful way to interpret the conditional cumulative relative survival ratios is the simple ratio. A conditional cumulative relative survival ratio expresses which proportion of the theoretically maximal survival probability (in the general background population) has been attained by the patient group at hand. This interpretation also easily accommodates the possibility that the patients can survive better than the general population group, as the ratio can exceed 100%.

Originally, the net probability estimate to be given by the relative survival analysis was supposed to be unconditional.[1,10] If that is desired, the traditional age-standardisation is a must even when comparisons are done within a single group of patients but between relative survival ratios related to different lengths of follow-up. For these single-group standardised analyses, a concept of internal age-standardisation is useful. Otherwise, the patients may erroneously be interpreted to have a better survival than the comparable general population group or to have a too early point of cure after which the relative survival stabilises at a constant level (see examples in Fig. 1).

Age-standardisation of the relative survival ratios should make the relative survival ratios observed in different populations or calendar periods comparable. It is another issue whether age-standardisation should also make the cumulative relative survival ratios related to different lengths of follow-up comparable with respect to age. It is well acceptable that not all methods need to do this, but it is also well understood that there has to be at least one method for that, too, which is the traditional method.

In practical applications, it is good to be aware of the additional confounding introduced by differences in the expected survival and potential censoring, when the newest age-standardisation method[5] is employed. These sources of confounding may have large effects in truly international comparisons. Clearly, differences by age in the expected survival between countries, genders and time periods do not cancel out in calculations.[9]

From a theoretical viewpoint, it would be reasonable to recommend the use of traditional age-standardised cumulative relative survival estimates and curves to show unconditional cumulative relative survival estimates and to make comparisons over follow-up time. The use of the method by Brenner and Hakulinen[6] could also be recommended to show conditional cumulative relative survival estimates as simple ratios between the expected and observed survival but not as survival curves.

If the age-specific relative survival ratio for the oldest age group cannot be estimated precisely, or even at all, then the method by Brenner and colleagues[5] may be the method of choice. The alternatives to this method may be the use of statistical modelling for the age-specific relative survival[4] or perhaps the omission of the oldest age group entirely. Modelling may be also an alternative solution when data are sparse.[11]

It may be regarded undesirable that there are so many alternatives and problems in the age-standardisation of relative survival. On the other hand, properly used, the age-standardisation methods for relative survival provide unusually rich possibilities of looking at the different aspects of patient survival. An (internal) age-standardisation of relative survival ratios can be important even when no relative survival comparisons between populations are attempted, simply in order to maintain comparability of these ratios over the follow-up time.

The age-standardisation of relative survival ratios is not only a matter of feasibility of calculation, maximisation of precision or choosing the age structure for standard. It should be decided what is the desired interpretation of the age-standardised relative survival ratio. The major demarcation lies between the unconditional and the conditional probability estimates. The goals of age-standardisation should be defined and taken into account when choosing the method to be applied.

## Conflict of interest statement

None declared.

## Acknowledgement

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 A. Methods related to age-standardisation of relative survival ratios

### A.1. Traditional method

The traditional method of age-standardising relative survival[12,3] is to take a weighted average of the age-specific relative survival ratios $r_a(t)$, a= 1,2,...,m, with weights proportional to the age distribution of the standard patient population, $w_{as}$, at the beginning of the follow-up

$$r_T(t) = \frac{\sum_{a=1}^{m} w_{as} r_a(t)}{\sum_{a=1}^{m} w_{as}}.$$

The weights of the traditional standardisation do not depend on the follow-up time or expected survival.

### A.2. Non-standardised ratio

The crude, non-standardised relative survival ratio can also be written as a weighted average of the age-specific relative survival ratios when the potential censoring patterns do not differ between age groups[2]:

$$r(t) = \frac{\sum_{a=1}^{m} w_a p_a^*(t) r_a(t)}{\sum_{a=1}^{m} w_a p_a^*(t)} = \frac{\sum_{a=1}^{m} W_a(t) r_a(t)}{\sum_{a=1}^{m} W_a(t)},$$

where $w_a$ is the proportion of patients belonging to age group $a$ at the beginning of follow-up and $p_a^*(t)$ is the expected proportion of survivors in age group $a$ at time $t$ according to general population mortality. Differences in the patterns of potential censoring by age group further affect the non-standardised ratio.[13]

It is assumed that the age groups are narrow enough so that the expected and relative survivals are independent. Note that unlike in the traditional age-standardisation, the weights $W_a(t) = w_a p_a^*(t)$ depend on follow-up time $t$ through the expected survival $p_a^*(t)$. Thus, if in the traditional standardisation the age distribution of patients at the beginning of follow-up is taken as standard (i.e.,$w_{as} = w_a$), $r_T(t)$ becomes

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

It can easily be seen that in general $r(t)$ is not equal to $r_{Tp}(t)$ so that the traditional age-standardisation does not give the non-standardised relative survival ratio as a special case when the age-distribution of the patients (at the beginning of follow-up) is used as the standard. This is different from what happens in the direct standardisation of incidence rates, where a non-standardised rate is obtained as a special case when the patients' own age distribution is used as a standard.[14]

### A.3. Brenner and Hakulinen (2003)

Brenner and Hakulinen[6] and Brenner and colleagues[5] have proposed methods to avoid this apparent drawback. The first one of these methods uses, instead of the age distribution of standard population at the beginning of follow-up, the expected age distribution of persons surviving in the standard population up to the given time point $t$ given that the standard population was 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 $p_{as}^*(t)$ 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 proper general population mortality, is used as a standard, provided that there is no censoring or, at least, that potential censoring is the same in all age groups:

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

Thus, $r_{BHp}(t) = r(t)$. 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 for that long.

### A.4. Brenner and colleagues (2004)

The method proposed by Brenner and colleagues[5] is apparently not based on the use of age-specific relative survival ratios. Each patient in a particular relative survival analysis is substituted with an adjusted count, the ratio between $w_{as}$ and $w_a$. The result, the age-standardised relative survival

ratio according to this method, assuming that the patterns of potential censoring do not differ between age groups, 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 are related to the same general population ($p_a^*(t)$ has to be equal to $p_{as}^*(t)$ for all groups under comparison). This is a theoretical limitation if the method is to be used in international comparisons[15] or comparisons over calendar time or between genders (and is studied further in another paper[9]). Like the non-standardised ratio, the ratio standardised by the Brenner et al. method[5] also depends on differences in patterns of potential censoring between age groups.[16]

## REFERENCES


1. Berkson J, Gage RP. Calculation of survival rates for cancer. *Proc Staff Meet Mayo Clin* 1950;**25**:270–86.
2. Hakulinen T. On long-term relative survival rates. *J Chron Dis* 1977;**30**:431–43.
3. Corazziari I, Quinn M, Capocaccia R. Standard cancer patient population for age standardizing survival ratios. *Eur J Cancer* 2004;**40**:2307–16.
4. Dickman PW, Sloggett A, Hills M, Hakulinen T. Regression models for relative survival. *Stat Med* 2004;**23**:51–64.
5. 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.
6. Brenner H, Hakulinen T. On crude and age-adjusted relative survival rates. *J Clin Epidemiol* 2003;**56**:1185–91.
7. Teppo L, Pukkala E, Lehtonen M. Data quality and quality control of a population-based cancer registry. *Acta Oncol* 1994;**33**:365–9.
8. Statistics Finland. http://www.stat.fi/tup/tasaarvo/tilastotietoa_en.html.
9. Pokhrel A, Hakulinen T. Age-standardisation in a comparison of relative survival ratios of cancer patients between countries, genders and time periods. Eur J Cancer (submitted for publication 2008).
10. Ederer F, Axtell LM, Cutler SJ. The relative survival rate: a statistical methodology. *Natl Cancer Inst Monogr* 1961;**6**:101–21.
11. Gondos A, Parkin DM, Chokunonga E, Brenner H. Calculating age-adjusted cancer survival estimates when age-specific data are sparse: an empirical evaluation of various methods. *Br J Cancer* 2006;**96**:450–4.
12. Black RJ, Bashir SA. World standard cancer patient populations; a resource for comparative analysis of survival data. In: Sankaranarayanan R, Black RJ, Parkin DM, editors. *Cancer survival in developing countries*. No. 145, Lyon: IARC Scientific Publications; 1998. p. 9–11.
13. Hakulinen T. Cancer survival corrected for heterogeneity in patient withdrawal. *Biometrics* 1982;**38**:933–42.
14. Fleiss JL. *Statistical methods for rates and proportions*. New York: Wiley; 1973.
15. 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.
16. Pokhrel A. Age-standardization of relative survival ratios for cancer patients. Tampere: Acta Universitatis Tamperensis 1278; 2007. Also available at: http://acta.uta.fi/pdf/978–951-44–7145-2.pdf.