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The validity of the mortality to incidence ratio as a proxy for site-specific cancer survival

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Background: The complement of the cancer mortality to incidence ratio [1 – (*M*/*I*)] has been suggested as a valid proxy for 5-year relative survival. Whether this suggestion holds true for all types of cancer has not yet been adequately evaluated. **Methods:** We used publicly available databases of cancer incidence, cancer mortality and relative survival to correlate relative survival estimates and 1 – (*M*/*I*) estimates from Denmark, Finland, Iceland, Norway, Sweden, the USA and the Netherlands. We visually examined for which tumour sites 5-year relative survival cannot simply be predicted by the 1 – (*M*/*I*) and evaluated similarities between countries. **Results:** Country-specific linear regression analyses show that there is no systematic bias in predicting 5-year relative survival by 1 – (*M*/*I*) in five countries. There is a small but significant systematic underestimation of survival from prognostically poor tumour sites in two countries. Furthermore, the 1 – (*M*/*I*) overestimates survival from oral cavity and liver cancer with >10% in at least two of the seven countries. By contrast, the proxy underestimates survival from soft tissue, bone, breast, prostate and oesophageal cancer, multiple myeloma and leukaemia with >10% in at least two of the seven countries. **Conclusion:** The 1 – (*M*/*I*) is a good approximation of the 5-year relative survival for most but not all tumour sites.

Keywords: cancer, incidence, mortality, prediction, survival

Introduction

With around 7 million deaths from cancers worldwide annually (12% of the nearly 56 million deaths from all causes), cancer is one of the most devastating diseases.[1] Because of the ageing of the population, and trends towards earlier diagnosis and better survival, cancer poses enormous challenges for health-care systems in high and low-resource countries alike. A variety of occurrence and outcome parameters are being used to quantify the burden of cancer. These parameters, i.e. prevalence, incidence, mortality and survival, are important for assessing the current situation, for predictions of developments into the future, and for allocation of resources for different control strategies. Survival estimates are being used for the monitoring of disease aggressiveness, treatment efficacy and burden on health-care systems with respect to periodic check-ups. The optimal way to assess cancer survival rates is to actively follow cohorts of cancer patients, registered in population-based cancer registries. An alternative for such active follow-up is linkage of population-based cancer registries to population-based vital statistics registries.

Both active follow-up and linkage with vital statistics registries may be problematic because of financial and logistical constraints, particularly in low- and medium-resource countries. Such limitations may prohibit the calculation of survival parameters. A proxy indicator for survival is the complement of the mortality (M) to incidence (I) ratio [$1-(M/I)$]. This ratio is synonymous to the complement of the fatality rate (or lethality rate) and defined as the complement of the ratio of the number of deaths from a specific type of disease within a specified period of time to the number of new cases of the same disease during the same period of time. Some studies have previously used this method either to estimate the 5-year survival of cancer patients or to evaluate the completeness of a cancer registry.[2,3] However, in these previous studies, the validity was examined for a single country only. This means there is only a possibility to examine systematic bias from the perfect regression line $Y=X$ of relative survival regressed on $1-(M/I)$ for all tumour sites. All deviant points (i.e. tumour sites) from that line would automatically be interpreted as random deviations, while they may be consistent 'random errors' in different registries and therefore systematic after all. As far as we know, this is the first study to examine the validity of the proxy using several data sets. We regressed 5-year relative survival on $1-(M/I)$ for 32 cancer sites in 7 different countries and visually inspected for which tumour sites the proxy is invalid.

Methods

Data sources

For this study, publicly-available data were derived from seven population-based cancer registries, i.e. the Surveillance, Epidemiology and End Results (SEER) programme of the USA, the nationwide Netherlands Cancer Registry (NCR), and the national cancer registries of the Nordic countries Denmark, Finland, Iceland, Norway and Sweden. From the SEER registry, incidence, mortality and survival data were taken for the calendar year 2000.[4] For the Netherlands, we used data on incidence, mortality and survival from the NCR for the years 2002–06.[5] Incidence and mortality data from Denmark, Finland, Iceland, Norway and Sweden were obtained from the NORDCAN database for the period 1995–99.[6] The NORDCAN database contains data on incidence and mortality from five Northern European Countries. For these Nordic countries, survival data were derived from the EUROCARE-4 project.[7] Because data on cancer-specific survival was not available, we used relative survival, which is calculated as the absolute survival rate among patients divided by the expected survival rate of the general population with the same sex and age structure. A maximum of 32 types of cancer were used from the seven data sets for the purpose of this study. Because of different definitions used for 'brain cancer' for incidence (NORDCAN) and survival (EUROCARE), brain cancer was excluded from the analyses of the Nordic data sets. Tumour sites that were used for analyses are listed in table 1.

Data analysis

Mortality to incidence ratio (M/I ratio) is usually calculated by dividing crude rates or numbers of deaths by crude incidence rates or numbers of incident cases. Because crude rates or numbers were not publicly available for all selected countries, the M/I ratio for each cancer site was calculated by dividing the standardized mortality rate by the standardized incidence rate in a similar calendar period. For the six European countries, rates were standardized with the European standard population. The incidence and mortality rates reported by the SEER were standardized using the US standard population. The $1-(M/I)$ ratio is a number typically (although not necessarily) between 0 and 100%, where 0% points to an extremely poor survival and 100% to an excellent survival. Observed $1-(M/I)$ ratios smaller than 0% (i.e. in a specific calendar period, more patients die from a specific cancer than the number of patients that is newly diagnosed with the disease) were bounded to 0% because relative survival is bounded at 0% as well.

Due to a lack of publicly available sex-specific survival data from the NORDCAN registries, we did not differentiate between males and females for all countries. Sex-specific analyses were performed for the SEER database only in order to see whether the lack of gender-specific analyses for all countries could have influenced the results.

Before we evaluated the $1-(M/I)$ ratio as a proxy for relative survival in all data sets, we used data from The Netherlands (1998–2002) and SEER (1990–94) in order to see whether the proxy is better for shorter (3 years), medium (5 years) or

Table 1 Tumour sites analysed in data sets from different countries and results of the comparisons between the 1-(M/I) ratio and 5-year relative survival

	Tumour site[a]	Denmark	Finland	Iceland	Norway	Sweden	The Netherlands	USA
1	Lip	√	√	NI	√	√	√	NI
2	Oral cavity	↑(15%)	↑(11%)	↑(12%)	√	↑(11%)	↑(15%)	↑(12%)
3	Salivary glands	√	√	NI	√	√	√	NI
4	Pharynx	NI	NI	NI	NI	NI	√	NI
5	Oesophagus	√	↓(11%)	↑(25%)	√	NI	√	↓(17%)
6	Stomach	√	√	√	√	√	√	↑(25%)
7	Small intestine	√	√	√	↓(11%)	√	√	↑(15%)
8	Colon	√	√	√	√	√	√	√
9	Anus	NI	NI	NI	NI	NI	↑(17%)	NI
10	Liver	√	↑(11%)	√	√	√	↓(13%)	↑(13%)
11	Gallbladder	NI	√	NI	√	↓(10%)	√	↑(25%)
12	Pancreas	√	√	√	√	√	√	√
13	Nasal cavity	NI	NI	NI	NI	NI	↑ (12%)	NI
14	Lung and brunch	√	√	√	√	↓(13%)	√	√
15	Larynx	√	√	↑(26%)	√	√	√	√
16	Soft tissue	√	√	↓(38%)	↑(10%)	↓(10%)	√	↓(11%)
17	Bone	↓(23%)	√	NI	√	↓(16%)	↓(25%)	↓(24%)
18	Breast	↓(13%)	√	↓(19%)	↓(10%)	√	↓(12%)	↓(11%)
19	Cervix	√	√	√	√	√	√	√
20	Corpus uteri	√	√	↑(16%)	√	√	√	√
21	Ovary	√	√	√	√	√	↓(20%)	√
22	Prostate	√	√	√	↓(12%)	↓(12%)	↓(14%)	↓(16%)
23	Testis	√	√	√	√	√	V	√
24	Kidney	√	√	√	√	↓(17%)	√	√
25	Urinary bladder	√	√	√	√	√	√	√
26	Eye	NI	√	NI	√	√	√	√
27	Brain	NI	NI	NI	NI	NI	√	√
28	Thyroid	√	√	NI	√	√	√	√
29	Hodgkin Disease	√	√	NI	√	√	√	√
30	Non-Hodgkin	√	√	√	√	√	NI	√
31	Multiple myeloma	√	√	√	↓(12%)	↓(17%)	NI	√
32	Leukaemia	√	√	↓(10%)	√	√	↓(11%)	√

Sites for which the 1– (M/I) ratio overestimated or underestimated 5-year relative survival by at least 10% are indicated. NI = not included in the analyses because data on incidence or mortality or relative survival are not publicly available for the same calendar period. Downward arrow indicates underestimated and upward arrow indicates overestimated relative survival
a: The order is based on the ICD-10 codes

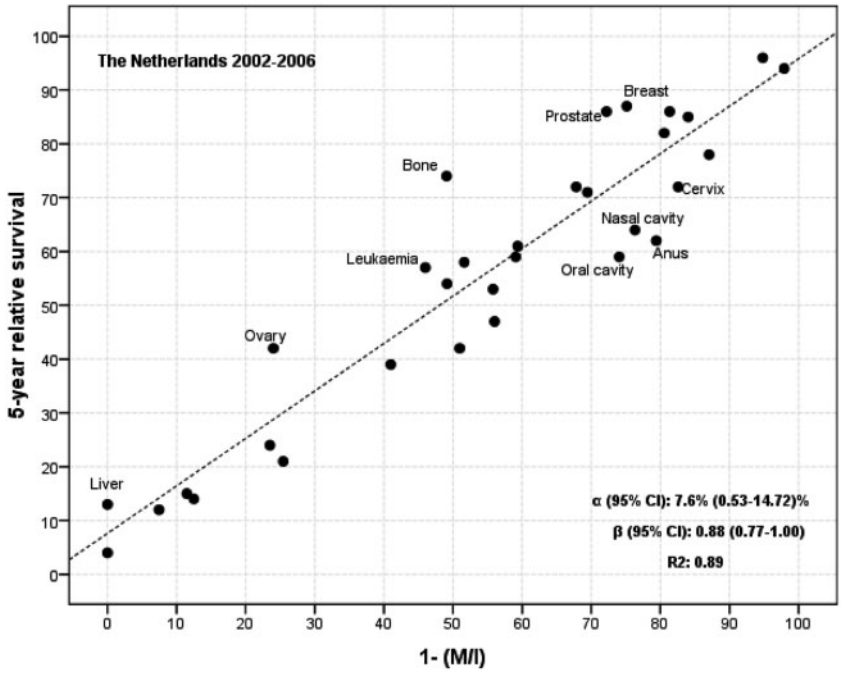

Figure 1 Regression line of 5-year relative survival on 1 – (*M*/*I*) ratio using data from the Netherlands cancer registry, 2002–06

longer (10 years) survival. Subsequently, the $1-(M/I)$ ratio was evaluated as a proxy for the 5-year relative survival in (approximately) the same calendar period for all seven cancer registries. Regression lines were fitted through the observed relative survival estimates on the *Y*-axis and the calculated $1-(M/I)$ on the *X*-axis for all cancer sites. Deviations from the perfect line $Y=X$ were evaluated as an indication of systematic bias, while random bias was quantified by r^2. In addition, for each tumour site reported by each of the seven registries we visually identified poor predictions of survival by the $1-(M/I)$ ratio. We chose an arbitrary minimal value of 10% to define a relevant absolute difference between observed relative survival and estimated survival by $1-(M/I)$.

Results

The regression of the 3-, 5- and 10-year relative survival rates on the $1-(M/I)$ ratio using the SEER cancer registries from the USA showed that the proxy clearly performs best for the 5-year survival. The findings are less clear for The Netherlands (See Supplementary table 1). In the remaining of this article, we focused on 5-year relative survival.

In figure 1 the 5-year relative survival rates are regressed on the $1-(M/I)$ ratio for 32 cancer types as reported by the Netherlands Cancer Registry (similar figures for SEER and the Scandinavian registries are shown in Supplementary figures 1B–G). For Denmark, Finland, Iceland, Norway and the USA, the regression lines of the 5-year relative survival on the complement of the *M*/*I* ratio yield intercepts and regression coefficients (slopes) which are very close to 0 and 1%, respectively (see table 2). In other words, the regression lines do not deviate from the perfect line $Y=X$, indicating no systematic bias in using the $1-(M/I)$ ratio as a proxy for 5-year relative survival. In Sweden and the Netherlands, however, the regression lines deviate somewhat from the $Y=X$ line and are tilted in a clockwise direction. In Sweden the intercept is 11.0% [95% confidence interval (CI) 6.02–18.00%] and the regression coefficient is 0.86 (95% CI 0.78–0.95). In the Netherlands these parameters are estimated at 7.6% (95% CI 0.53–14.72%) and 0.88 (95% CI 0.77–1.00), respectively.

In addition to this small systematic bias in two of the seven countries, there appears to be a fairly substantial 'random variation' with survival from some tumour sites that are underestimated or overestimated. The estimated r^2 is lowest in Iceland (73%) and highest in Finland (97%). If survival from the same cancer site is underestimated or overestimated in more than one country, this may be an indication for a second type of systematic bias instead of random bias. Using an arbitrary criterion of 10% survival overestimation or 10% underestimation to indicate a poorly performing proxy [e.g. $1-(M/I)$ is $\leq$50% or $\geq$70 while relative survival = 60%], then it appears that survival rates from some tumour sites cannot be accurately predicted. In table 1, tumour sites are listed for which survival is underestimated or overestimated by more than an absolute value of 10%. Survival from oral cavity (six countries) and liver cancer (two countries) is overestimated with $\geq$10% in at least two countries. Survival from bone (four countries), breast (five), prostate (four), oesophageal cancer (two), soft tissue (three), leukaemia (two) and multiple myeloma (two) is underestimated with $\geq$10% in at least two registries.

We were not able to conduct gender-specific analyses for all countries but such analyses using the SEER data set (see Supplementary figure 2A and B) show strikingly similar results for men and women.

Discussion

The mortality to incidence ratio has been used in some studies as a proxy for 5-year survival rates, as a qualitative indicator for cancer registry completeness, and as an indicator for racial and sex disparities in cancer survival.[3,8] It has been stated by Parkin *et al.* that this ratio equals the probability of 5-year survival in a steady state of constant incidence and survival provided that the reporting of causes of death were completely accurate.[2] However, as far as we know, this statement has never really been validated using more than one data set. The results from our analyses indicate that the measure is a valid proxy for the 5-year survival rate for most tumour sites. There appears to be no (most countries) or only a small (two countries) systematic bias as indicated by the closeness of the regression lines

Table 2 Regression coefficients (and 95% CI) of the linear regression analysis of 5-year relative survival on the 1 – (*M*/*I*) ratio using data from seven countries

Registry	Intercept (95% CI)	Slope (95% CI)	Adjusted R^2
Denmark	5.20% (−0.14 to 10.73)	0.94 (0.83 to 1.04)	0.94
Finland	−0.48% (−5.01 to 4.06)	1.00 (0.93 to 1.10)	0.97
Iceland	5.60% (−8.60 to 19.70)	0.89 (0.63 to 1.15)	0.73
Norway	−2.62% (−8.74 to 3.49)	1.00 (0.94 to 1.14)	0.94
Sweden	11.00% (6.02 to 18.00)	0.86 (0.78 to 0.95)	0.95
The Netherlands	7.6% (0.53 to 14.72)	0.88 (0.77 to 1.00)	0.89
USA	3.00% (−7.56 to 13.58)	0.98 (0.81 to 1.15)	0.85

between the $1-(M/I)$ ratio and 5-year survival to the reference line $Y=X$.

The predictions for some tumour sites do deviate, however, from the observed survival by more than an absolute value of 10%. This seemingly random bias (when considering the results for each country separately) may be systematic bias after all if survival from specific tumour sites is underestimated or overestimated in more countries. Indeed, survival from oral cavity and liver cancer was overestimated with >10% by the proxy in at least two of the seven countries. Survival from bone, soft tissue, breast, prostate, oesophageal cancer, leukaemia and multiple myeloma was underestimated in at least two countries. Although this may still be coincidence, it may also indicate systematic bias for these tumour sites. One may argue that the criterion for a relevant difference between relative survival and $1-(M/I)$ ratio should not be fixed at, e.g. 10% but based on the width of the 95% CI of the $1-(M/I)$ ratio which is different for the rarer and the more prevalent tumours. To illustrate this point, we undertook a reanalysis using crude numbers for mortality and incidence from The Netherlands and calculated 95% CIs of the $1-(M/I)$ ratio (see Supplementary table 2). It appears that for all tumour sites for which we found large differences between relative survival and $1-(M/I)$ ratio in the original analysis (see table 1), the relative survival lies outside the 95% CI of the $1-(M/I)$ ratio (Supplementary table 2). On the other hand, the relative survival of some tumour sites (lung, soft tissue, uterus, eye) lie outside the 95% CI of the $1-(M/I)$ ratio while we did not conclude that the two parameters were 'different' by >10%. We believe, however, that it is the point estimate of survival that is of most interest. If survival from a tumour is estimated by a proxy with an error of more than, e.g. 10% then this proxy cannot be considered valid, whether or not the 95% CI of the $1-(M/I)$ overlaps the relative survival.

Naturally, the $1-(M/I)$ ratio can only validly be used in situations of population-based incidence and mortality registries. Furthermore, the proxy is expected to perform best for tumour sites for which three requirements are met: (i) there is not a strongly increasing or decreasing trend in time for incidence, mortality or survival; (ii) the hazard rate of mortality is not increasing after 5 years survival[9] (i.e. conditional survival is not decreasing during follow-up); and (iii) the registration of new occurrences, causes of death and vital status is accurate. These requirements may hold for most but not all tumour sites. For example, the $1-(M/I)$ ratio appears to underestimate survival from prostate cancer. This may be due to the fact that prostate cancer related death may occur long after 5 years of survival in patients who are diagnosed with localized disease or even in patients who are diagnosed with an androgen dependent non-localized tumour. There may also be some misclassification in the registration of prostate cancer as cause of death.[10] Most men who are diagnosed with prostate cancer do not die from the disease. Nevertheless, in case of death the cause of death may still be considered to be related to the prostate cancer diagnosis. This may lead to overestimated mortality rates and consequently underestimated survival rates.

Late deaths from breast cancer, long after 5 years of follow-up, may also be the reason why 5-year survival from breast cancer is underestimated in some registries.[11] Availability of screening tests for both breast and prostate cancer has increased the incidence of (mainly early stage) cancer, whereas mortality in recent years mainly occurs among the smaller number of patients diagnosed a long time ago. There may be different reasons for an underestimated survival from bone cancer such as misclassification of bone metastases as bone cancer in mortality statistics. The small numbers of these tumours may also give rise to random variations in survival, incidence and mortality estimates. Obviously, some of these estimates are based on larger numbers (e.g. breast and prostate cancer) than others (e.g. bone cancer, multiple myeloma). It is possible that just by chance the $1-(M/I)$ ratio is underestimating (or overestimating) survival from one tumour site in more than one registry. We also observed some cancer sites for which 5-year survival was overestimated at least twice. One of these is oral cavity cancer. In theory, this may be due to the registration of new occurrences or recurrences as second primary tumours. This will increase the incidence rate and the $1-(M/I)$ ratio while the prognosis of patients with such 'second' primaries is known to be worse. Survival from liver cancer was also overestimated in two countries. Except for chance findings due to small numbers, the reason for this is not obvious to us. In theory, it may be caused by an inaccurate registration of liver metastases as liver cancer in cancer incidence but not mortality registries.

In Sweden and the Netherlands, a fairly high intercept of the regression line was found. This suggests that in these countries there is a small, though statistically significant, systematic bias towards underestimation of survival of cancer sites with a poor prognosis. One may wonder whether this can be related to the fact that in these countries death certificate only (DCO) cases are not registered in the cancer registry. Indeed, by missing DCO cases, the $1-(M/I)$ will be artificially small because DCO cases are registered in the mortality registry but not in the incidence registry. Although this bias exists for all tumour sites it may be larger for the prognostically poor tumours. To illustrate this, we assumed that the cancer-specific mortality statistics would be 10% higher than observed. Indeed, this assumption tilts the regression line further clockwise (see Supplementary figure 3). However, if DCO cases are not registered, the 'gold standard' relative survival will be biased as well, because there is a relative lack of cases with a poor prognosis in the cohort that is used for the calculation of survival. An alternative explanation for the observation in Sweden and The Netherlands is that not the $1-(M/I)$

ratio but relative survival is biased so that the 'proxy' is a better measure than the gold standard itself.[12–14] If follow-up for vital status is imperfect, e.g. because of imperfect linkage of the cancer registry with the vital statistics registry, then relative survival will be overestimated. This may lead to the phenomenon that is observed in Sweden and the Netherlands. Let's imagine a simplified situation in which a linkage protocol misses 10% of all deceased cases. For a prognostically poor tumour site with 100 new cases and 90 deaths, the $1-(M/I)$ ratio will be correctly estimated at 10% but survival will be overestimated at 10 survivors + 9 misclassified/100 = 19%. For a prognostically favourable tumour site with 100 new cases and 10 deaths, the $1-(M/I)$ ratio will be 90% (correct) while survival will be overestimated at 90 survivors + 1 misclassified/100 = 91%. Because the bias is bigger for tumours with a poor prognosis, this will tilt the regression line in a clockwise manner, as was observed for the two countries.

An important limitation of our study is the lack of corresponding incidence, mortality and survival data from more populations, especially from low and medium resource countries. Therefore, the validity of the proxy in countries where it may be needed the most remains unclear. Nevertheless, in situations where active follow-up is known to be difficult and linkage with vital statistics registries is impossible, the $1-(M/I)$ may be a parameter that can easily (and quicker) be estimated and may even be more valid than survival. An important requirement, of course, is the availability of a cancer registry and causes of death registry covering the same catchment population. Particularly in low- and medium-resource countries, this may be equally problematic as the collection of follow-up data for direct survival estimates.

In summary, despite small differences between predicted and observed relative survival (a proxy of cancer-specific survival) the $1-(M/I)$ ratio appears to be a fairly accurate simple predictor of 5-year survival rates. The proxy may be less valid for tumours from which relatively many patients may die long after 5 years of follow-up, for tumours that suffer from mortality or incidence coding difficulties and for tumours that show strong changes in incidence, mortality and/or survival.

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Supplementary data

Supplementary data are available at *EURPUB* online.

Conflicts of interest: None declared.

Key points

- This study is the first to examine the validity of $1-(M/I)$ ratio as a proxy for site-specific cancer survival using several different data sets.
- The ratio $1-(M/I)$ is a good approximation of the 5-year relative survival for most but not all tumour sites.
- Countries that do not have the opportunity to actively collect valid survival data may use $1-(M/I)$ ratio to support quality of care studies and policy decisions but should be aware of the fact that the proxy is invalid for some cancer sites

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