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Up-to-date long-term survival of cancer patients: an evaluation of period analysis on Swedish Cancer Registry data

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Abstract

The natural development of cancers as well as the measures to fight the disease are often long processes that require decades of follow up. Available information on long-term survival will thus often appear outdated and irrelevant. A few years ago, period-survival analysis was proposed as a means to obtain more up-to-date information on long-term cancer survival.

This article assesses period and conventional cohort-based survival analyses on their ability to predict future survival. Based on historical data from the nationwide Swedish Cancer Registry 5-, 10- and 15-year relative survival actually observed for patients diagnosed at one particular point in time are compared to the most recent period and cohort-based survival estimates available at that point in time. The study shows that period analysis can, in most cases, be used to provide more up-to-date long-term estimates of cancer survival. Period analysis reduces the time lag of the survival estimates by some 5–10 years for all cancers combined and especially affects the survival estimates for small intestine carcinoids, meningioma and intracranial neurinoma of the brain, non-seminoma testicular cancer, chronic lymphocytic leukaemia and Hodgkin's lymphoma.

Keywords: Cancer registries; Statistical methods; Survival analysis; Period analysis; Prognosis

1. Introduction

Up-to-date information on cancer survival is important as reference material for clinicians, oncologists and scientists involved in clinical work, medical auditing or research. It provides a basis for evaluation of decision-making, and is used in debate on the effects of cancer treatment and prevention. Long-term follow up periods are generally needed to evaluate changes in cancer survival since the natural development of cancers, as well as the measures to fight the disease, often are long processes that sometimes require decades of follow up. However, survival estimates of long-term follow up may often appear irrelevant since the time lag between diagnosis and evaluation is considered too long, and they often pertain to clinical methods no longer in use. This time lag may be reduced with period survival analysis, which was introduced into cancer research some 6 years ago [1,2], since it aims to provide more up-to-date estimates of survival than can be derived from conventional cohort-based analysis.

Empirical evaluation of period survival analysis on large data has so far been mainly performed on material from the Finnish Cancer Registry [3–6]. These analyses show that period analysis in general provides more up-to-date estimates of long-term cancer survival than cohort-based survival estimates. They also suggest that period estimates from a given time period in most cases quite accurately predict the long-term survival for patients diagnosed during that particular period. The period approach has been used to estimate long-term survival for patients diagnosed in recent years (e.g. [7–10]).

The aim of the present study is to provide an empirical evaluation of period survival analysis on Swedish Cancer Registry data. If this proves successful, the

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ultimate goal is to incorporate period survival estimates in the regular statistical publications from the Cancer Registry.

2. Materials and methods

2.1. The Swedish Cancer Registry

Since 1958 every clinician, pathologist and cytologist in Sweden has been required by law to notify the Cancer Registry at the National Board of Health and Welfare of each new cancer diagnosed. The non-reporting rate has been estimated at less than 2% [11]. The Swedish Cancer Registry is population based and today covers 8.9 million people. For the years 1958–1998 the register has accumulated 1.6 million tumours for 1.4 million persons.

2.2. Data material

The study was based on all cancer cases reported between 1960 and 1998. Forty different forms of cancer and all sites combined were analysed. This selection is the same data that have previously been used in a comprehensive overview of the development of cancer survival in Sweden during the past four decades, amended with one additional year of follow up [12]. Excluded from the analyses were multiple tumours at the same anatomical site, autopsy findings, cases with zero survival time, and patients who were 90 years or older at diagnosis. In the definition of a few sites, some histopathological groups were excluded from the analyses due to low incidence and/or due to survival probabilities that differ from the dominating pattern for that particular site. For small intestine, testis and brain and nervous system, different histopathological groups within the same site were analysed separately. Basal cell carcinoma has not been a part of the cancer registration historically, and is not included in the non-melanoma skin cancer group.

A total of 512,133 men and 509,288 women were included in the analysis. The Cancer Register is linked annually by personal identification numbers to the Cause of Death Register at the National Board of Health and Welfare and to the Migration and Population Registries at Statistics Sweden, to obtain dates of death or censoring and to confirm continued residency in Sweden. At the time of analysis the follow up was completed up to and including 31 December 2001. Complete follow up was available for 99.9% of the recorded cases.

2.3. Statistical analysis

The analyses were performed with a publicly available SAS macro that can be used for both period and cohort-based analysis [13]. The Hakulinen method [14] adjusting for potential heterogeneous follow up time is implemented in the macro and was used for the cumulative relative survival rate (RSR) estimates. Prior to analysis, the macro was updated to facilitate the use of annual population survival probabilities. The results were compared to SURV3 developed at the Finnish Cancer Registry [15,16]. Cohort-based RSRs can be estimated directly by SURV3 and the period estimates can be calculated with partial result from SURV3 and an extension of the modified life-table approach described by Brenner and Gefeller [1]. The updated SAS macro and SURV3 yield equivalent results (data not shown). Relative survival is defined as the observed survival among the cancer patients divided by the expected survival for a comparable group from the general population with respect to the main factors affecting survival, in this case sex, age and calendar year.

For all sites combined and for each of the 40 different forms of cancer analysed the 5-, 10-, and 15-year RSRs actually observed for different cohorts of patients were calculated. These observed RSRs were then compared with the most up-to-date survival estimates available at that particular cohort's time of diagnosis, using two conventional cohort-based methods for survival estimates, denoted 'cohort' and 'complete' analysis [2], as well as for period analysis. 'Cohort analysis' evaluates survival for cohorts of patients diagnosed at close proximity in time to each other (e.g. within the same calendar year). Hence, all patients have the potential to be under observation for the entire period of follow up. 'Complete analysis' additionally includes in the cohort patients diagnosed in later years, providing a mixture of patients with short and long potential follow up time. This is illustrated in Fig. 1 for the year 1996, which is the last available period (dashed frame) at the time of analysis for which it is also possible to calculate the actual observed 5-year RSR (solid thick frame). Fig. 1 also depicts the corresponding cohort (solid thin frame) and complete analyses (squares frame) that were available in 1996.

The RSRs were calculated for 1-year intervals, and for 3- and 5-year moving averages. Single-year estimates were used for common cancers. For less common sites, 3- or 5-year moving averages were used, making a necessary trade off between up-to-date information and precision. The analysis was done for males and females separately as well as for both sexes combined and for different age groups. This article reports only results for males and females combined, with the exception for breast, prostate, testis and gynaecological cancers, and for the age group 0–89 years at diagnosis.

In period analysis, follow up is restricted to a narrow calendar time period (e.g. one calendar year). The estimates are obtained by left truncation of the data at the beginning of the period and by right censoring at its end.

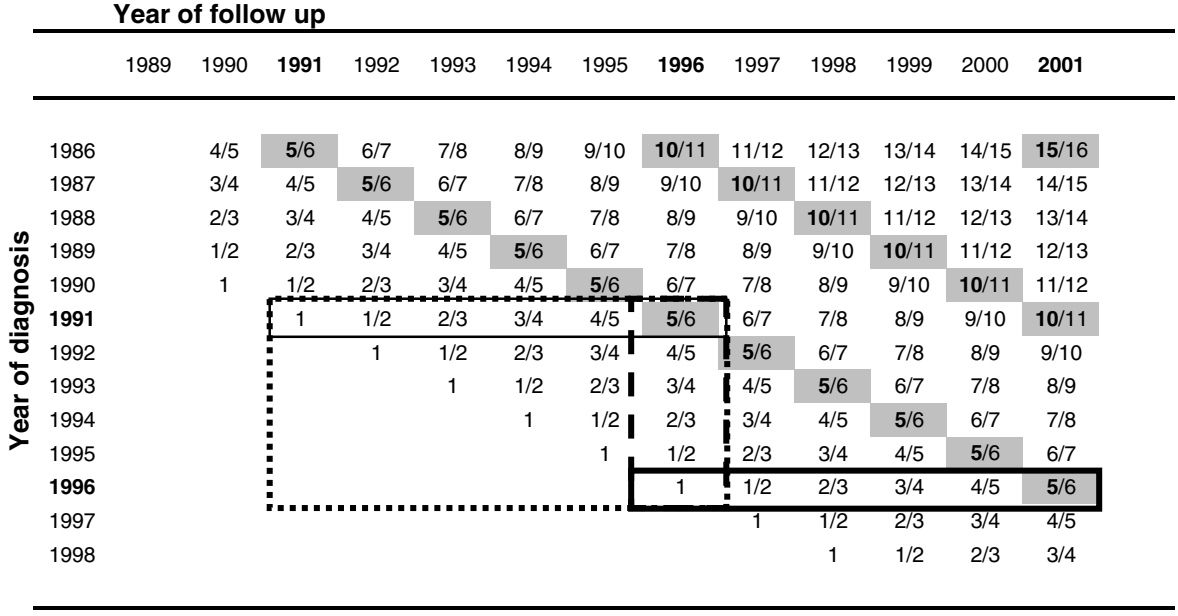

Fig. 1. Data included to calculate *observed* 5-year survival of patients diagnosed 1996 (solid thick frame), and the corresponding most up-to-date estimates that could have been obtained in 1996 by *cohort* (solid thin frame), *complete* (squares frame), and *period* analysis (dashed frame). Numbers within cells indicate years of follow up since diagnosis.

Only those at risk and events (death or censoring) occurring during this particular period are considered, and survival experiences during other years are discarded. Hence, the period estimates reflect only survival experienced during the chosen calendar period. For the example in Fig. 1, the survival probability for the first year of follow up is solely estimated from patients diagnosed in 1995–1996, and conditional probabilities for the second, third, fourth and fifth year of follow up are estimated by patients diagnosed in 1994–1995, 1993–1994, 1992–1993 and 1991–1992, respectively (dashed frame). The interval-specific survival probabilities are then multiplied to obtain cumulative survival probabilities. The alternatives to period analysis would have been to calculate the survival for the last available cohort with 5 years of follow up, patients diagnosed in 1991 (solid thin frame), or to use the complete available information from patients diagnosed in 1991–1996 (squares frame). If the actual 1991 cohort is not the particular focus of the investigation, the complete approach seems to be the best choice since it utilises the available data in a more efficient way and provides more updated information.

Most of the increased mortality experienced by cancer patients occurs during the first few years after diagnosis, on which the cumulative RSRs to a large extent depend. Since the time lag for period analysis for the first years after diagnosis is short, and the later years of follow up have a more limited impact on the shape of the cumulative survival curve, the period analysis will respond more quickly to changes in survival. Fig. 2 illustrates the common shape for interval-specific curves:

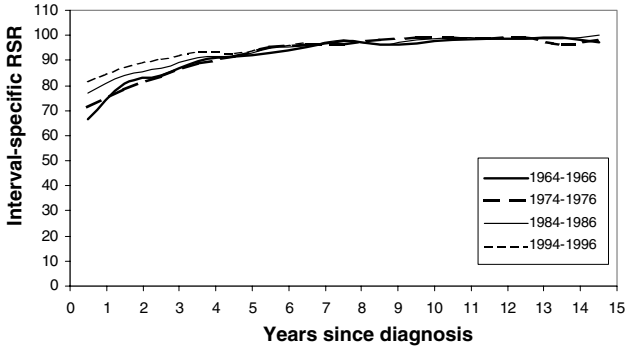

Fig. 2. Graph illustrating the way the interval-specific relative survival rates (RSR) commonly shift upward for more recent years of diagnosis during the first years of follow up, after which the difference between the survival curves decrease. Observed RSR of the rectum. Males and females, 0–89 years of age at diagnosis (site chosen for illustrative purposes).

a shift upward for more recent years of diagnosis during the first years of follow up after which the difference between the survival curves decreases and, in this example, becomes negligible after 5 years.

In order to evaluate the period analysis approach compared to the cohort-based methods the mean difference and the mean squared difference between the observed RSR and the latest cohort, complete and period RSRs available at the time of diagnosis were calculated. The mean difference is a measure of systematic over- or underestimation of the RSRs, and the mean squared difference quantifies the degree of deviation and is determined both by systematic and random variability

in the RSRs. This allows us to address the question of to what extent the relative survival observed for patients diagnosed at one particular point in time could have been predicted by period analysis and by the cohort and complete methods at the time of diagnosis. The mean squared difference is not a formal test statistic and should only be used to compare the relative size of the differences for the same form of cancer.

3. Results

An evaluation of the cohort, complete and period RSRs available at a given point in time compared to the RSRs observed for patients diagnosed at this particular point in time are shown in Tables 1–3 for a follow up of 5, 10 and 15 years, respectively.

The period width at which each form of cancer has been evaluated was chosen by considering the number at risk together with a visual inspection of the stability of the respective 5-, 10-, and 15-year RSR curves. For each individual form of cancer a common width was chosen for all lengths of follow up. All sites combined, as well as breast and prostate cancer, were large and stable enough to be evaluated using single-year periods. A period width of 3 years (3-year moving averages) was chosen for e.g. colon, rectum, lung, cervix uteri, kidney, skin and non-Hodgkin's lymphoma. Less common cancers were evaluated at a period width of 5 years (5-year moving averages), e.g. lip, small intestine, primary liver, testis, eye, bone, and acute lymphocytic and acute myeloid leukaemia. All the RSR curves underlying the results in Table 1–3 appear stable in terms of percentage units. In some cases, e.g. primary liver cancer, this is more due to very low survival probabilities than to the number at risk.

The highest mean annual increases in 5-year RSR during the past decades were for acute myeloid and lymphocytic leukaemia, 7.2% and 4.3%, respectively, primary liver (4.7%), chronic myeloid leukaemia (3.5%), gallbladder with biliary tract (3.3%) and non-seminoma testicular cancer (3.0%). The same cancers were also amongst those with the highest mean annual increase in 10- and 15-year RSR, and amongst those with the largest percent unit increase over the decades: non-seminoma testicular cancer (48.5, 36.4 and 24.6), Hodgkin's lymphoma (45.1, 30.9 and 21.9), acute lymphocytic leukaemia (43.2, 37.4 and 17.0), meningioma of the brain (36.3, 23.2 and 10.8), and chronic lymphocytic leukaemia (35.0, 18.6 and 11.3), for 5-, 10-, and 15-year RSRs (Tables 1–3).

In general, the period RSR is a better estimate of the ultimately observed RSR than the cohort and complete estimates. The variability between the period and observed RSRs is in most cases much smaller than for the corresponding cohort and complete estimates. The difference between the estimated and observed RSRs increases with increasing length of follow up and the estimated RSRs are in most cases an underestimation of the future observed RSR. The latter indicates that for many forms of cancer there have been continuing improvements in survival during the past four decades.

For the 5-year RSRs (Table 1) the advantage of the period approach compared to the cohort and complete analyses in early detection of the future survival, expressed as the mean difference in percent units to the observed RSR, is most noticeable for small intestine carcinoids (−4.5, −3.0, −0.2), meningioma and intracranial nerve neurinoma of the brain (−6.2, −4.1, −0.3 and −4.4, −2.7, −0.5, respectively), non-seminoma testicular cancer (−8.4, −5.1, −1.8), chronic lymphocytic leukaemia (−5.7, −4.0, −1.9), and Hodgkin's lymphoma (−8.0, −5.6, −2.1), for the cohort, complete and period RSRs, respectively. The deviation between the period and observed RSRs, as measured by the mean squared difference, are for these same cancers only some 6–30% and 20–65% of the deviation for the cohort and complete RSRs, respectively. This indicates a considerably closer relation between the observed and period RSRs than was achieved by conventional cohort-based survival analysis. The same pattern holds also over 10 and 15 years of follow up for the cancer sites exhibiting survival good enough to have stable estimates for that length of time (Tables 2 and 3).

According to the cohort, complete and period RSRs that are comparable in time to the last available observed RSRs (Tables 1–3), some forms of cancer had a continuing improvement in survival, whereas others appear to have levelled off. Others still, such as oesophagus, primary liver, gallbladder, pancreas and lung, ought to be evaluated at a shorter follow up interval since only a small fraction of the patients survive for 5 years. For the same reason these cancers also exhibit the smallest mean and mean squared difference between the estimated and observed RSRs.

A good example of a cancer site where period analysis would have detected early the exceptional improvement in long-term survival during the recent decades is non-seminoma testicular cancer. The variability, mean squared difference, between the period and observed RSRs is only some 4–8% of the variability between the observed and cohort curves, indicating a considerably closer relation between the observed and period RSRs. Despite this close relation the period analysis underestimates the observed RSR by on average some 2%, 3%, and 6% units for a follow up of 5, 10 and 15 years, respectively. The last available estimate shows that the 5-year RSR had levelled of at about 94% in the late 1980s (Table 1). For 10-, and 15-year RSR the equal period and observed RSRs of 94% and 89%, respectively, are considerably higher than the cohort and complete RSRs of 73% and 86%, and 47% and 68%, respectively (Tables 2 and 3).

Table 1
Five-year relative survival rate (RSR) for patients diagnosed between 1965–1996 at 0–89 years of age

Site	Sex	Period width in years	Mean number at risk	First available RSR	Mean annual change	Mean difference			Mean squared difference			Last available comparable RSRs			
						Cohort	Complete	Period	Cohort	Complete	Period	Cohort	Complete	Period	Observed
All sites combined	M & F	1	13415	40.3	1.4	−3.1	−2.6	−0.7	11.0	7.1	0.8	57.6	58.2	59.6	61.0
Lip	M & F	5	711	95.5	−0.2	0.6	0.5	0.7	5.8	3.6	4.1	94.2	93.1	92.8	88.9
Oral cavity and mesopharynx	M & F	5	613	46.7	0.0	−0.5	−0.5	−0.3	10.0	5.5	3.8	45.4	47.5	49.8	52.1
Oesophagus	M & F	5	89	4.4	2.4	−0.6	−0.2	−0.2	1.8	0.6	0.3	8.5	9.8	10.3	10.5
Stomach	M & F	3	652	12.4	2.0	−1.1	−0.7	−0.2	2.7	1.2	0.5	19.2	19.2	19.1	20.4
Small intestine, adenocarcinoma	M & F	5	50	22.3	1.3	−1.1	−0.5	0.3	23.9	11.8	11.9	30.3	27.6	26.6	22.2
Small intestine, carcinoids	M & F	5	192	43.9	1.8	−4.5	−3.0	−0.2	48.4	21.4	14.0	63.4	66.1	68.7	71.6
Colon, adenocarcinoma	M & F	3	2826	40.6	1.3	−2.6	−2.0	−0.5	11.2	5.2	0.7	53.6	54.9	56.6	56.8
Rectum, adenocarcinoma	M & F	3	1644	38.9	1.5	−3.1	−2.4	−1.0	13.0	7.8	2.8	50.6	52.6	55.1	56.7
Liver, primary	M & F	5	38	1.5	4.7	−0.7	−0.3	−0.1	1.0	0.3	0.2	4.4	5.3	6.1	6.2
Gall bladder, biliary tract	M & F	5	142	4.0	3.3	−0.9	−0.4	−0.1	1.7	0.6	0.4	8.7	8.8	9.6	9.1
Pancreas	M & F	5	86	2.6	−1.2	0.3	0.3	0.2	0.3	0.2	0.1	2.3	2.2	2.0	1.7
Nose and nasal sinuses	M & F	5	142	45.5	1.2	−1.8	−1.1	−0.1	34.0	15.3	11.5	57.3	58.1	57.8	55.9
Larynx	M & F	5	596	71.5	−0.3	0.1	−0.1	0.1	9.3	5.2	4.7	68.8	68.3	69.4	68.3
Lung	M & F	3	565	8.1	1.3	−0.5	−0.2	−0.0	1.2	0.4	0.3	9.7	11.0	11.9	12.9
Breast	Females	1	2890	63.1	0.9	−3.2	−2.5	−1.2	16.4	9.8	4.2	83.3	83.1	83.6	84.7
Cervix uteri	Females	3	1176	67.8	0.2	−0.8	−0.8	−0.3	4.9	2.4	1.7	70.6	69.6	70.3	70.9
Corpus uteri	Females	3	1994	74.8	0.3	−1.0	−0.9	−0.2	3.0	2.1	1.7	79.2	80.4	82.3	83.4
Ovary	Females	3	1088	34.5	0.9	−1.3	−0.8	0.3	6.4	2.8	1.4	41.5	42.9	45.6	45.4
Prostate	Males	1	1877	42.3	1.6	−4.7	−3.5	−1.5	29.5	15.9	6.0	67.9	69.2	70.2	72.4
Testis, seminoma	Males	5	366	88.4	0.7	−2.3	−1.4	−0.4	15.8	7.1	3.8	96.4	97.1	97.3	97.3
Testis, non-seminoma	Males	5	298	45.1	3.0	−8.4	−5.1	−1.8	121.8	44.4	9.9	94.5	93.7	93.5	93.6
Kidney excluding renal pelvis	M & F	3	1026	33.7	1.6	−3.1	−2.2	−0.3	13.7	5.9	1.1	48.8	50.0	51.7	54.1
Urinary bladder and urethra	M & F	3	2529	57.7	0.8	−2.6	−2.0	−0.6	11.1	6.3	2.4	70.5	71.0	71.9	72.0
Malignant melanoma of skin	M & F	3	2106	71.5	0.8	−4.2	−2.8	−1.4	26.2	12.1	4.5	87.4	87.3	87.3	87.9
Malignant skin cancer, excl. melanoma	M & F	3	2095	87.8	0.1	−0.3	−0.3	0.1	3.2	2.4	3.3	87.6	87.8	88.8	88.4

Tabel 1 (*Continued*)

Site	Sex	Period width in years	Mean number at risk	First available RSR	Mean annual change	Mean difference			Mean squared difference			Last available comparable RSRs			
						Cohort	Complete	Period	Cohort	Complete	Period	Cohort	Complete	Period	Observed
Eye	M & F	5	332	70.0	0.3	−1.2	−1.0	−0.6	16.5	9.4	6.4	74.0	74.1	75.0	75.2
Brain, excl. cranial nerves, meningioma	M & F	3	484	21.5	1.9	−2.3	−1.5	−0.6	10.1	4.1	1.4	30.7	32.0	33.1	34.3
Brain, meningioma	M & F	3	454	56.9	2.0	−6.2	−4.1	−0.3	65.9	22.4	6.3	90.4	92.0	93.1	93.2
Brain, intracranial nerves neurinoma	M & F	5	242	72.5	1.6	−4.4	−2.7	−0.5	65.1	20.0	4.0	99.1	99.3	99.3	99.0
Thyroid gland	M & F	3	623	64.9	0.9	−3.4	−2.6	−0.9	15.8	8.7	2.7	83.6	83.3	83.8	85.2
Endocrine glands	M & F	3	1337	75.3	0.8	−3.9	−2.4	−0.4	20.9	7.9	1.2	93.2	93.7	94.5	95.1
Bone	M & F	5	207	37.5	1.8	−4.8	−3.2	−1.4	43.9	21.0	14.5	63.2	64.0	65.0	65.8
Connective tissue, muscle	M & F	5	549	41.8	0.7	−2.0	−1.4	−0.4	14.8	7.2	4.8	55.2	54.6	54.7	55.6
Non-Hodgkin's lymphoma	M & F	3	1142	29.0	2.2	−3.7	−2.6	−1.0	24.3	10.8	3.1	52.3	53.0	54.6	54.8
Hodgkin's lymphoma	M & F	3	343	35.9	2.9	−8.0	−5.6	−2.1	74.4	36.4	10.1	76.9	78.8	80.8	81.0
Multiple myeloma	M & F	3	422	22.0	1.2	−1.9	−1.0	−0.0	8.3	3.8	2.9	30.8	31.7	32.9	33.6
Acute lymphocytic leukaemia	M & F	5	221	20.2	4.3	−6.8	−5.0	−2.8	85.1	44.6	18.9	59.0	59.4	60.3	63.4
Chronic lymphocytic leukaemia	M & F	3	450	33.4	2.5	−5.7	−4.0	−1.9	43.6	21.0	7.6	63.6	65.2	68.3	68.4
Acute myeloid leukaemia	M & F	5	92	2.4	7.2	−2.6	−1.6	−0.9	9.7	4.3	1.7	14.1	14.9	15.5	18.2
Chronic myeloid leukaemia	M & F	5	144	17.3	3.5	−4.9	−3.6	−2.1	47.8	27.8	17.6	36.1	40.2	43.5	50.7

Period width in years: 1 = 32 one-year intervals between 1965 and 1996; 3 = 3-year moving averages, 30 intervals between 1966 and 1995; 5 = 5-year moving averages, 28 intervals between 1967 and 1994. Mean number at risk: Mean number at risk at the beginning of the fifth year after diagnosis for the 1-, 3- and 5-year periods, respectively. First available RSR: First available cohort/observed RSR. Period width = 1, diagnostic year 1960; period width = 3, diagnostic year 1960–1962; period width = 5, diagnostic year 1960–1964. Mean annual change: Mean annual change of cohort/observed RSR in percent. Mean difference: Cohort = mean of all (cohort − observed); complete = mean of all (complete − observed); period = mean of all (period − observed). Mean squared difference: Cohort = mean of all ((cohort − observed)^2); complete = mean of all ((complete − observed)^2); period = mean of all ((period − observed)^2). Last available comparable RSRs: Period width = 1, Cohort (diagnostic year) = 1991, Complete (diagnostic year) = 1991–1996, Period (Period) = 1996 and Observed (diagnostic year) = 1996. Period width = 3, Cohort = 1989–1991, Complete = 1989–1996, Period = 1994–1996 and Observed = 1994–1996. Period width = 5, Cohort = 1987–1991, Complete = 1987–1996, Period = 1992–1996 and Observed = 1992–1996.

First and last available cohort/observed RSR with its mean annual change in percent. Mean difference and mean squared difference between the cohort, complete and period RSRs available at a given time and the RSR later observed for patients diagnosed in this interval. Last available cohort, complete, period and observed RSRs that are comparable in time.

Table 2
Ten-year relative survival rate (RSR) for patients diagnosed between 1970–1991 at 0–89 years of age

Site	Sex	Period width in years	Mean number at risk	First available RSR	Mean annual change	Mean difference			Mean squared difference			Last available comparable RSRs			
						Cohort	Complete	Period	Cohort	Complete	Period	Cohort	Complete	Period	Observed
All sites combined	M & F	1	9053	38.2	1.4	−5.4	−3.4	−0.5	30.4	12.3	0.9	44.8	46.6	49.6	51.0
Lip	M & F	5	503	90.7	−0.3	3.2	2.3	1.3	14.5	9.3	8.1	88.0	86.7	86.3	88.8
Oral cavity and mesopharynx	M & F	5	377	40.4	−0.3	3.1	1.9	1.6	24.3	12.0	10.1	34.3	35.4	37.3	37.6
Oesophagus	M & F	5	42	4.6	1.6	−0.5	−0.3	−0.2	0.8	0.6	0.8	4.1	4.7	4.6	6.5
Stomach	M & F	3	398	10.6	2.6	−2.7	−1.7	−0.4	9.9	4.0	0.9	13.2	15.3	16.2	17.1
Small intestine, adenocarcinoma	M & F	5	36	16.9	1.4	−5.9	−4.1	−2.5	80.1	48.9	36.3	30.6	26.8	27.4	25.0
Small intestine, carcinoids	M & F	5	122	36.6	1.8	−6.8	−2.5	2.3	71.6	17.9	24.0	49.1	51.7	54.1	52.5
Colon, adenocarcinoma	M & F	3	1834	37.6	1.4	−4.7	−2.6	0.1	31.1	10.1	1.0	45.6	46.7	48.7	47.7
Rectum, adenocarcinoma	M & F	3	999	34.8	1.3	−4.3	−2.5	−0.2	21.4	7.1	1.2	37.4	40.5	42.9	43.7
Liver, primary	M & F	5	15	1.4	5.4	−0.3	0.0	0.3	1.0	0.8	0.7	1.1	1.6	2.0	3.6
Gall bladder, biliary tract	M & F	5	82	4.4	2.5	−0.7	−0.1	0.3	1.1	0.5	0.7	4.7	5.5	6.2	7.3
Pancreas	M & F	5	43	1.8	0.2	0.5	0.3	0.1	0.6	0.2	0.0	1.3	1.6	1.6	1.4
Nose and nasal sinuses	M & F	5	86	34.7	2.7	−5.1	−3.0	−0.9	77.6	34.7	18.5	36.0	39.3	40.8	52.2
Larynx	M & F	5	422	64.8	−0.8	3.9	2.8	2.1	20.2	9.7	9.1	60.5	58.5	57.4	56.2
Lung	M & F	3	322	7.1	0.1	−0.3	0.1	0.4	0.6	0.2	0.6	7.6	7.7	7.6	7.2
Breast	Females	1	2042	54.1	1.5	−7.1	−5.1	−2.5	59.4	32.6	12.7	65.8	65.8	68.5	74.6
Cervix uteri	Females	3	927	62.2	0.4	−1.2	−1.0	−0.5	9.7	4.8	2.5	60.0	62.7	66.2	67.4
Corpus uteri	Females	3	1650	75.9	0.2	−2.6	−1.7	−0.4	11.5	6.1	2.7	79.4	78.8	79.1	75.9
Ovary	Females	3	856	33.4	0.7	−2.9	−1.3	0.9	11.6	4.7	3.4	37.3	38.7	39.1	35.0
Prostate	Males	1	815	30.1	1.5	−7.2	−4.4	−1.3	64.7	30.2	13.0	39.2	41.7	44.7	47.6
Testis, seminoma	Males	5	327	84.2	0.8	−5.2	−3.0	−1.0	36.8	11.4	6.6	86.7	91.9	93.6	94.9
Testis, non-seminoma	Males	5	286	57.3	3.4	−23.1	−12.1	−2.6	571.8	166.7	22.2	73.2	86.2	93.6	93.7
Kidney excluding renal pelvis	M & F	3	699	32.0	1.2	−4.6	−2.4	0.3	22.7	7.0	1.7	36.7	38.8	40.5	42.0
Urinary bladder and urethra	M & F	3	1720	57.9	0.5	−5.9	−3.3	−0.7	44.7	15.9	3.8	62.4	62.5	63.8	64.4
Malignant melanoma of skin	M & F	3	1688	68.7	1.1	−8.8	−4.9	−2.1	92.5	29.0	8.5	74.9	76.9	79.4	84.1
Malignant skin cancer, excl. melanoma	M & F	3	1238	82.5	−0.2	−0.4	−0.0	0.2	8.3	8.6	13.5	78.8	80.0	80.9	80.8

Table 2 (*Continued*)

Site	Sex	Period width in years	Mean number at risk	First available RSR	Mean annual change	Mean difference			Mean squared difference			Last available comparable RSRs			
						Cohort	Complete	Period	Cohort	Complete	Period	Cohort	Complete	Period	Observed
Eye	M & F	5	236	60.2	0.2	−1.7	−1.1	−0.4	11.7	8.2	7.8	65.5	63.4	60.6	64.6
Brain, excl. cranial nerves, meningioma	M & F	3	352	18.2	3.2	−4.3	−2.4	−0.8	31.5	12.2	3.4	23.4	25.3	26.9	28.2
Brain, meningioma	M & F	3	376	64.3	1.7	−12.4	−5.8	2.5	167.0	36.8	49.2	78.6	79.6	82.2	87.5
Brain, intracranial nerves neurinoma	M & F	5	220	70.7	2.0	−11.4	−4.9	0.9	256.3	70.1	22.3	94.1	97.2	98.7	100.4
Thyroid gland	M & F	3	561	69.3	1.0	−7.5	−4.1	−0.2	61.1	19.3	5.5	78.1	78.9	81.7	84.4
Endocrine glands	M & F	3	1142	76.7	0.6	−8.2	−3.7	−0.1	83.2	17.7	2.9	84.2	85.2	86.5	87.4
Bone	M & F	5	169	41.9	2.4	−10.2	−6.4	−2.4	112.9	44.2	11.8	47.9	51.3	54.2	59.3
Connective tissue, muscle	M & F	5	413	45.4	0.3	−4.8	−2.4	−0.1	46.2	15.6	6.5	48.3	49.5	50.0	49.5
Non-Hodgkin's lymphoma	M & F	3	679	30.1	2.1	−6.9	−3.9	−0.8	56.8	19.9	7.3	31.9	37.3	40.5	42.0
Hodgkin's lymphoma	M & F	3	282	42.4	3.0	−18.1	−11.7	−3.3	333.5	140.1	19.1	55.6	62.7	72.7	73.3
Multiple myeloma	M & F	3	128	12.8	0.9	−1.0	−0.3	0.3	4.0	3.4	5.5	11.6	11.7	12.7	13.4
Acute lymphocytic leukaemia	M & F	5	186	19.5	5.9	−23.4	−17.3	−10.7	588.3	327.7	161.1	40.9	49.0	55.3	56. 9
Chronic lymphocytic leukaemia	M & F	3	206	22.9	3.5	−11.0	−7.3	−3.6	133.1	60.4	22.0	34.6	36.9	41.6	41.5
Acute myeloid leukaemia	M & F	5	52	3.3	9.6	−3.6	−2.2	−1.0	17.7	7.7	3.3	5.5	8.3	11.5	12.8
Chronic myeloid leukaemia	M & F	5	41	7.7	5.6	−3.3	−2.6	−1.6	29.0	22.2	15.8	6.4	8.4	10.9	21.9

Period width in years: 1 = 22 one-year intervals between 1970 and 1991; 3 = 3-year moving averages, 20 intervals between 1971 and 1990; 5 = 5-year moving averages, 18 intervals between 1972 and 1989. Mean number at risk: Mean number at risk at the beginning of the tenth year after diagnosis respectively for 1-, 3- and 5-year periods. First available RSR: First available cohort/observed RSR. Period width = 1, diagnostic year 1960; period width = 3, diagnostic year 1960–1962; period width = 5, diagnostic year 1960–1964. Mean annual change: Mean annual change of cohort/observed RSR in percent. Mean difference: Cohort = mean of all (cohort − observed), Complete = mean of all (complete − observed), Period = mean of all (period − observed). Mean squared difference: Cohort = mean of all ((cohort − observed)^2); complete = mean of all ((complete − observed)^2); period = mean of all ((period − observed)^2). Last available comparable RSRs: Period width = 1, Cohort (diagnostic year) = 1981, Complete (diagnostic year) = 1981–1991, Period (Period) = 1991 and Observed (diagnostic year) = 1991. Period width = 3, Cohort = 1979–1981, Complete = 1979–1991, Period = 1989–1991 and Observed = 1989–1991. Period width = 5, Cohort = 1977–1981, Complete = 1977–1991, Period = 1987–1991 and Observed = 1987–1991.

First and last available cohort/observed RSR with its mean annual change in percent. Mean difference and mean squared difference between the cohort, complete and period RSRs available at a given time and the RSR later observed for patients diagnosed in this interval. Last available cohort, complete, period and observed RSRs that are comparable in time.

Table 3
Fifteen-year relative survival rate (RSR) for patients diagnosed between 1975 and 1986 at 0–89 years of age

Site	Sex	Period width in years	Mean number at risk	First available RSR	Mean annual change	Mean difference			Mean squared difference			Last available comparable RSRs			
						Cohort	Complete	Period	Cohort	Complete	Period	Cohort	Complete	Period	Observed
All sites combined	M & F	1	6459	38.7	1.2	−7.0	−3.8	0.6	50.5	14.9	0.5	37.3	41.4	45.5	44.9
Lip	M & F	5	334	82.3	−1.3	10.8	8.9	6.6	120.6	84.9	59.4	87.8	88.1	89.4	76.3
Oral cavity and mesopharynx	M & F	5	238	29.8	0.8	5.3	3.6	0.9	29.4	15.2	7.5	37.4	33.6	30.5	31.9
Oesophagus	M & F	5	24	3.8	1.2	−0.1	0.3	0.5	0.3	0.1	0.3	3.7	4.2	4.4	4.4
Stomach	M & F	3	271	11.8	4.0	−3.7	−2.9	−0.9	17.8	10.7	2.3	10.3	11.9	15.1	16.1
Small intestine, adenocarcinoma	M & F	5	28	17.2	2.2	−9.5	−7.7	−6.1	109.2	71.0	46.9	12.3	18.4	21.1	23.2
Small intestine, carcinoids	M & F	5	80	36.1	1.8	−5.0	−2.1	1.1	74.6	32.1	84.2	26.5	34.7	36.6	40.8
Colon, adenocarcinoma	M & F	3	1274	39.3	1.4	−6.1	−3.6	1.3	39.7	13.2	2.3	37.6	41.9	47.1	44.5
Rectum, adenocarcinoma	M & F	3	692	36.0	1.3	−5.7	−3.5	−0.6	35.2	15.0	2.8	33.6	35.9	40.0	39.9
Liver, primary	M & F	5	8	1.9	−2.4	−0.2	0.0	−0.1	0.2	0.3	0.3	1.8	1.6	1.2	2.2
Gall bladder, biliary tract	M & F	5	55	4.2	2.5	−0.5	−0.2	0.1	0.9	0.4	0.4	3.1	3.9	4.3	5.0
Pancreas	M & F	5	27	1.2	3.3	0.7	0.3	−0.0	0.7	0.1	0.0	2.0	1.5	1.3	1.5
Nose and nasal sinuses	M & F	5	47	33.0	3.5	−0.5	−0.6	0.5	16.2	14.5	10.3	32.9	34.1	37.6	39.6
Larynx	M & F	5	274	50.4	−0.3	5.0	3.6	1.3	27.6	13.1	3.4	56.6	52.6	49.1	48.1
Lung	M & F	3	212	6.3	0.1	−0.4	0.2	0.9	0.5	0.2	1.4	5.9	6.9	6.9	6.7
Breast	Females	1	1457	50.8	1.3	−9.7	−6.5	−2.2	98.5	44.1	7.1	47.2	53.4	58.6	60.0
Cervix uteri	Females	3	796	59.6	1.0	−1.7	−1.6	−1.3	8.7	6.9	4.6	60.2	60.7	63.6	63.1
Corpus uteri	Females	3	1419	76.6	0.1	−5.9	−3.9	−1.3	43.1	18.6	6.6	75.2	76.2	77.0	77.7
Ovary	Females	3	736	36.8	1.0	−5.1	−2.8	0.3	26.4	8.3	1.2	33.9	36.3	39.7	39.9
Prostate	Males	1	332	27.9	0.5	−8.7	−3.3	1.6	89.4	26.0	19.9	23.3	31.7	32.4	32.9
Testis, seminoma	Males	5	293	84.7	1.0	−2.5	−0.9	2.8	12.6	3.6	9.7	84.6	88.0	92.2	91.9
Testis, non-seminoma	Males	5	260	64.3	4.8	−35.4	−20.6	−6.4	1325.6	441.1	52.5	46.8	67.6	88.5	88.9
Kidney excluding renal pelvis	M & F	3	492	29.5	1.3	−5.9	−2.6	1.6	40.9	9.9	5.5	31.5	33.8	36.0	32.5
Urinary bladder and urethra	M & F	3	1153	57.3	0.7	−11.8	−5.9	−1.0	145.1	36.4	2.2	53.5	57.5	60.7	60.8
Malignant melanoma of skin	M & F	3	1413	69.2	0.8	−14.6	−7.1	−2.5	231.6	53.6	9.6	66.1	71.3	74.9	76.9
Malignant skin cancer, excl. melanoma	M & F	3	690	77.2	0.4	−1.5	−0.3	0.1	5.6	2.2	14.5	79.1	78.1	77.1	77.3

Table 3 (*Continued*)

Site	Sex	Period width in years	Mean number at risk	First available RSR	Mean annual change	Mean difference			Mean squared difference			Last available comparable RSRs			
						Cohort	Complete	Period	Cohort	Complete	Period	Cohort	Complete	Period	Observed
Eye	M & F	5	185	60.3	0.4	−5.7	−5.3	−3.1	35.1	30.2	16.0	56.6	59.1	62.7	62.4
Brain, excl. cranial nerves, meningioma	M & F	3	287	17.5	4.4	−4.3	−2.9	−0.5	21.5	12.1	1.9	18.2	20.4	25.0	25.9
Brain, meningioma	M & F	3	307	69.0	1.4	−17.5	−6.4	7.9	319.0	46.1	99.3	68.4	77.3	85.2	79.8
Brain, intracranial nerves neurinoma	M & F	5	192	87.2	1.3	−12.6	−6.7	5.1	171.3	50.3	52.3	77.3	93.0	107.8	94.9
Thyroid gland	M & F	3	514	75.9	0.8	−10.4	−4.2	2.4	113.4	19.9	8.2	70.6	78.3	85.1	81.7
Endocrine glands	M & F	3	904	79.6	0.1	−13.5	−3.8	1.5	200.4	23.3	6.2	70.7	79.0	81.3	82.1
Bone	M & F	5	156	47.6	1.4	−15.9	−9.9	−4.2	263.5	99.2	29.7	40.1	44.4	52.1	51.7
Connective tissue, muscle	M & F	5	322	51.9	−1.1	−8.7	−3.4	1.3	76.2	19.1	2.6	40.9	46.9	50.3	49.2
Non-Hodgkin's lymphoma	M & F	3	413	26.3	3.1	−6.2	−2.3	1.7	60.6	9.2	7.9	25.7	29.4	32.5	33.5
Hodgkin's lymphoma	M & F	3	227	45.1	4.5	−27.2	−15.9	−3.9	749.8	259.7	26.4	34.3	46.3	56.3	67.0
Multiple myeloma	M & F	3	43	8.5	−2.5	1.9	2.8	3.3	5.0	8.7	13.3	9.5	8.8	8.5	7.2
Acute lymphocytic leukaemia	M & F	5	175	37.4	4.8	−39.3	−31.5	−22.3	1573.8	994.8	502.6	6.0	19.6	34.1	54.4
Chronic lymphocytic leukaemia	M & F	3	112	19.3	5.3	−13.1	−8.7	−4.0	184.3	81.7	25.4	15.0	20.2	23.5	30.6
Acute myeloid leukaemia	M & F	5	38	4.1	8.5	−4.8	−3.4	−2.6	24.6	12.9	8.0	2.6	3.9	4.7	7.8
Chronic myeloid leukaemia	M & F	5	14	2.8	10.3	−2.0	−1.6	−1.0	5.0	3.1	3.1	3.0	3.0	2.9	5.9

Period width in years: 1 = 12 one-year intervals between 1975 and 1986; 3 = 3-year moving averages, 10 intervals between 1976 and 1985; 5 = 5-year moving averages, 8 intervals between 1977 and 1984. Mean number at risk: Mean number at risk at the beginning of the 15th year after diagnosis respectively for 1-, 3- and 5-year periods. First available RSR: First available cohort/observed RSR. Period width = 1, diagnostic year 1960; period width = 3, diagnostic year 1960–1962; period width = 5, diagnostic year 1960–1964. Mean annual change: Mean annual change of cohort/observed RSR in percent. Mean difference: Cohort = mean of all (cohort − observed); complete = mean of all (complete − observed); period = mean of all (period − observed). Mean squared difference: Cohort = mean of all ((cohort − observed)^2); complete = mean of all ((complete − observed)^2); period = mean of all ((period − observed)^2). Last available comparable RSRs: Period width = 1, Cohort (diagnostic year) = 1971, Complete (diagnostic year) = 1971–1986, Period (Period) = 1986 and Observed (diagnostic year) = 1986. Period width = 3, Cohort = 1969–1971, Complete = 1969–1986, Period = 1984–1986 and Observed = 1984–1986. Period width = 5, Cohort = 1967–1971, Complete = 1967–1986, Period = 1982–1986 and Observed = 1982–1986.

First and last available cohort/observed RSR with its mean annual change in percent. Mean difference and mean squared difference between the cohort, complete and period RSRs available at a given time and the RSR later observed for patients diagnosed in this interval. Last available cohort, complete, period and observed RSRs that are comparable in time.

4. Discussion

To the best of our knowledge this is the largest evaluation of the period approach to survival analysis so far, both in terms of the number of cases included and the number of cancer sites analysed. Evaluations on large data have previously been performed mainly on material from the Finnish Cancer Registry [3–6].

Improvements in survival may reflect a variety of different factors such as increased and/or earlier diagnosis, a shift towards more favourable histological subtypes or sites (for all sites combined), or advances in treatment. But regardless of the origin, period analysis allows for more up-to-date estimates, and if additional knowledge of the possible reasons behind the improvements is available this will lead to more accurate interpretation of the results. There have been substantial improvements in long-term cancer survival in Sweden during the past four decades. The possible reasons for the improvements have recently been reported elsewhere [12]. For all sites combined, cancers with poor survival have decreased and cancers with better survival have increased their relative shares of the total cancer incidence across the decades, and cancers have become relatively more common in older than younger groups.

The individual forms of cancer discussed in Section 3 above have had a variety of different reasons for their improvements in survival. The increase in survival for patients diagnosed with small intestine carcinoids can, at least during the first decade, be attributed to improved diagnostics and staging, centralisation of treatment for this rare disease, increased surgical aggressiveness, and better antitumour drugs, particularly interferon and somatostatin. The improved survival for patients diagnosed with gallbladder and biliary tract cancers is mainly due to better imaging techniques, surgical aggressiveness and postoperative care. For primary liver cancer, better imaging and earlier diagnosis have contributed to the improvements, together with better opportunities to evaluate the extent of liver disease and liver function, and improved surgical techniques and postoperative care. For non-seminoma testicular cancer, better staging procedures and, above all, more effective treatments have caused the marked improvement. The introduction of cisplatin in 1978 has made the greatest contribution. Improved opportunities to diagnose and operate safely on patients are likely causes of the survival improvements for patients diagnosed with meningioma of the brain. Misclassification may also have been prevalent in the early years, which partly explains poor survival for a predominantly benign tumour. In recent years the increased use of radiotherapy may also have contributed to improved survival. The major reason for the improved survival for patients diagnosed with Hodgkin's lymphoma is better treatment. A major step was taken when combination chemotherapy was introduced in the late 1960s. But the improvement is also likely to be partly explained by elimination of previous misclassification. Fewer cases of non-Hodgkin lymphoma (NHL) have been diagnosed as Hodgkin's lymphoma during the past two decades. NHL has poorer survival than Hodgkin's lymphoma. For patients diagnosed with acute lymphocytic leukaemia, better cytostatic treatments are responsible for the improved survival. For chronic lymphocytic leukaemia, the improvements are likely to be a result of better cytostatic drug treatment, but long-term cure is still not possible for this disease with the regimens that have been available so far. For acute myeloid leukaemia, more effective chemotherapy regimens, together with improved supportive care allowing for safer administration of intensive treatment, are responsible for the improved survival. These treatments were introduced in the late 1960s, but continuous improvements have taken place. The survival improvements for chronic myeloid leukaemia can be attributed to improved treatments, chemotherapy, interferon and, more recently, high-dose therapy followed by stem-cell transplantation [12].

As shown with the historical data evaluated in this study, period survival estimates are generally more accurate for describing the current situation than the corresponding complete and cohort estimates. There are only a few exceptions to this general rule. The cohort, complete and period RSRs all tended to underestimate future observed RSR, but the underestimation was considerably smaller for the period approach. If the purpose of the analysis is to estimate/predict survival for a recently diagnosed group of patients, and not to evaluate some particular cohort that has already completed its follow up time of interest, then the period estimates seems to be the best available choice.

When survival improves over time the period estimates will be higher than the corresponding cohort and complete estimates, as is often the case in this study. The opposite is expected if the survival is declining. No systematic difference would be seen if the survival was constant over time. Period analysis will lead to an overestimation of the long-term survival compared to earlier years if improvements in early diagnosis or treatment merely identify cancer at an earlier point in time without prolonging life, i.e. lead-time bias. This is exemplified with an hypothetical example in Fig. 3, which depicts cumulative observed and period RSRs, and period RSRs that have an arbitrary lead-time of 6 and 12 months, respectively, introduced for 50% of the cases for the last five diagnostic years included in the period analysis. In the presence of lead-time the period RSRs will shift upward and thus overestimate the actual survival. The same phenomenon is not seen for the complete estimates if the same lead-time is introduced (Fig. 4). The complete estimates would in this case be the best alternative.

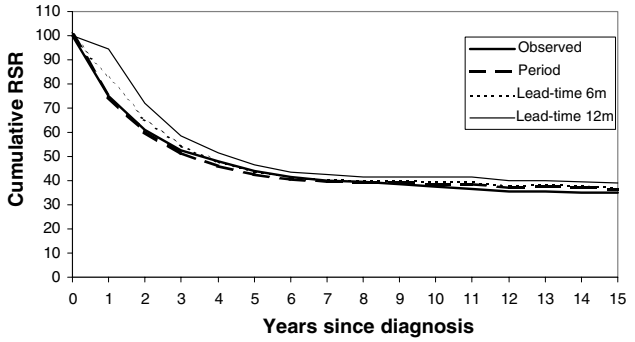

Fig. 3. The effect of lead-time bias in period analysis (an hypothetical example). Cumulative observed and period relative survival rates (RSR), and period RSRs that have an arbitrary lead-time of 6 and 12 months introduced for 50% of the cases for the last 5 years of diagnosis. Cancer of the rectum. Males and females, 0–89 years of age at diagnosis (site chosen for illustrative purposes).

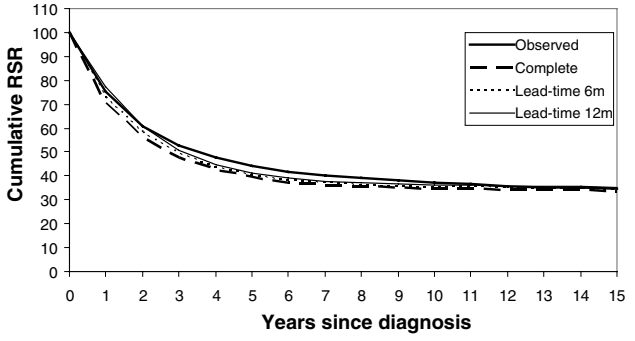

Fig. 4. The effect of lead-time bias in complete analysis (an hypothetical example). Cumulative observed and complete relative survival rates (RSR), and complete RSRs that have an arbitrary lead-time of 6 and 12 months introduced for 50% of the cases for the last 5 years of diagnosis. Cancer of the rectum. Males and females, 0–89 years of age at diagnosis (site chosen for illustrative purposes).

It is the stability of the RSR estimates over time, and not primarily the number at risk, that determines if period analysis will be successful for a given form of cancer. There is, of course, a relation between the number at risk and stable estimates, but there is nothing per se that indicates that cancers with relatively few cases cannot be analysed with the period approach. One disadvantage with period analysis compared to the complete approach is its increase in random variation due to the reduction in the number of patients at risk, as the analysis is restricted to events during one particular time period, commonly 1–5 years. This disadvantage seems in reality to be outweighed by the reduced variability between the observed and period RSRs, and if, as in this case, applied to population-based registry data this problem will probably be limited to rare cancer sites.

To conclude, our evaluation confirms earlier studies [3–6] and shows that period survival analysis can be used as a means to provide more up-to-date estimates of long-term survival for cancer patients. It is, however, important to recognise that both short- and long-term survival should be considered. Otherwise, there is a risk that short-term improvements will be missed, since the focus so often is directed at 5- and 10-year survival.

5. Conflict of interest statement

The authors have no financial or personal relationships or obligation to any person or organisation that have influenced our work with this article.

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