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Timely disclosure of progress in childhood cancer survival by 'period' analysis in the Automated Childhood Cancer Information System

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Background: A few years ago, a new method of survival analysis, denoted 'period' analysis, was introduced to provide more up-to-date survival estimates of cancer patients.

Patients and methods: We evaluated the period survival method using the large database of the Automated Childhood Cancer Information System (ACCIS). Our evaluation is based on data from 35 191 children diagnosed with cancer in 13 European countries between 1975 and 1989 and followed for vital status until around 1999.

Results: Using the follow-up data available in 1989, 10-year survival for all children with cancer calculated by the period method for the 1985–89 period was 58%, while it was 43% when calculated by traditional 'cohort' life-table analysis (based on children diagnosed in 1975–79). The period method provided a better estimate of the true 10-year survival of 62%, observed 10 years later in the cohort of patients diagnosed in 1985–89. Similar results were observed for each of the common groups of childhood cancer.

Conclusion: Period analysis is especially useful for monitoring childhood cancer survival, because at a given point in time it provides more timely estimates of long-term survival expectations than the cohort life-table method. Using the ACCIS database, up-to-date estimates of period survival for childhood cancer are derived in subsequent papers in this journal.

Key words: cancer registries, childhood cancer, population-based, prognosis, survival

introduction

In recent decades, survival of children with cancer has improved dramatically in the populations of the developed world, mainly due to progress in therapy [1–6]. Nevertheless, the full extent of this improvement has only been disclosed with substantial delay to clinicians, the patients, their families and the public, when the calculation was based upon the 'cohort'-based method, as used traditionally for survival analysis of population-based data.

For example, the EUROCARE project reported in 2001 and 2002 [2, 3] 5-year cohort survival for children diagnosed in various European countries in 1978–89 and 1978–92, respectively. The most recent report on childhood cancer survival from the EUROCARE study, dated 2005, included children diagnosed up to 1994 [5]. With the traditional cohort-based type of analysis used in these studies (as in most other studies of survival), reliable 10-year survival estimates for children diagnosed in those years may only become available another 5 years later. In the meantime, however, there have been further improvements in therapy, and it would be highly desirable to disclose the resulting improvement in survival figures in a timely manner.

Changes in survival of cancer patients can be detected earlier if the 'period survival method' is used [7, 8]. This method has been thoroughly evaluated and found useful in the monitoring of long-term survival of adult cancer patients [9–12]. A recent analysis using data from the Surveillance, Epidemiology and End Results (SEER) Program of the United States National Cancer Institute suggested that the method might be particularly appropriate for childhood cancers, where progress in therapy has been generally faster and improvement in prognosis more pronounced than for most cancers of adults [13]. However, due to sample size limitations, the analysis of SEER data was restricted to a few major groups of childhood cancer.

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By application of the period method to the world's largest database of childhood cancer collected within the Automated Childhood Cancer Information System (ACCIS) [4], we are able to provide up-to-date estimates of survival for different types of childhood cancer in a series of four subsequent papers in this journal [14–17]. The aim of this paper is to demonstrate the difference between period and cohort methods and to assess, using historical data, how closely the different methods predict the survival actually experienced by the patients.

patients and methods

database

The ACCIS database contains some 160 000 records of childhood and adolescent cancer cases registered over the past 30 years in 78 European population-based cancer registries, covering 1300 million person-years [4]. The data were verified in collaboration with participating registries, analysed centrally and a dataset from each registry was evaluated for comparability [18]. The tumours were classified according to the International Classification of Childhood Cancer (ICCC) [19].

For the current analysis, all childhood cancer cases diagnosed between 1975 and 1989 in children aged 0–14 years in 15 registries in 13 European countries were extracted from the ACCIS database (Table 1). Only those registries with first incidence year 1977 or earlier, and with follow-up for vital status complete until the end of 1997 or later were included in the analyses. Records of patients notified by death certificate only (0.2%) or with missing information on vital status (1.2%) were excluded from the analysis.

The registries included in the analysis cover different parts of Europe; eight of them are national. Almost half of all cases were contributed by the childhood cancer registry of England and Wales, UK. Most registries provided records for children diagnosed within the entire time window 1975–89, and had complete follow-up until the end of 1999 (Table 1). Due to non-comparable coding of childhood cancer types of interest in this paper, two registries (national registries from the Czech Republic and Sweden) contributed to the analyses only for all forms of cancer combined. These two datasets represented about 19% of the total dataset.

Statistical methods

Focusing on 10-year survival, we compared three methods of analysis: two traditionally used methods [20], the 'cohort' analysis (restricted to cohorts of patients with complete 10-year follow-up), the 'complete' analysis (including all patients with complete 10-year follow-up as well as those with censored survival time) and the 'period' analysis [7, 8]. The group of patients and the years of follow-up included in each analysis are illustrated in Figure 1. The cohort analysis was applied to the cohort of patients diagnosed between 1975 and 1979 who had a complete 10-year follow-up by the end of 1989. In Figure 1, this corresponds to the upper horizontal black rectangle. The grey trapezium in Figure 1 represents the patients diagnosed in 1975–89, followed for between 0 and 10 years by the end of 1989, who were included in the complete analysis. The third method, period analysis, is represented in Figure 1 by the vertical rectangle with dashed borders, and reflects the survival experience observed in 1985–89 for the patients diagnosed between 1975 and 1989.

In all three methods, life-table estimates of cumulative survival are obtained by multiplication of the conditional probabilities of survival of the first 10 yearly follow-up intervals. In contrast to the traditional methods, the period analysis reflects conditional survival probabilities of the children with cancer prevalent in 1985–89 only. Survival probability for the first year after diagnosis is obtained from patients diagnosed between 1984 and 1989, conditional survival probability for the second year is obtained from children diagnosed in 1983–88, and so on, until the survival probability in the tenth year following diagnosis, which is obtained from experience of the children diagnosed in 1975–80. For a detailed description of the period analysis methodology please refer to a recent review article [21].

Although the three methods use different segments of the database, they have a common closing date for survival analysis, the end of 1989. Using the data that were available at this date, we calculated three sets of survival statistics and drew a survival curve for each. Working with historical data permitted us to compare the results of the three methods available at the end of 1989 with the 10-year survival actually observed 10 years later for children diagnosed in 1985–89 (lower horizontal black rectangle in Figure 1). This comparative measure was calculated using the cohort method with the closing date 'end of 1999'.

Table 1. Registries, years of diagnosis, years of follow-up and number of cases included in the analyses

Country	Registry[a]	Years of diagnosis	Years of follow-up	Number of cases
Czech Republic	National (G)	1977–89	1977–98	3481
Estonia	National (G)	1975–89	1975–98	552
Finland	National (G)	1975–89	1975–98	2029
France	Bas-Rhin (G)	1975–89	1975–97	376
Hungary	National (P)	1977–89	1977–99	2750
Iceland	National (G)	1975–89	1975–99	112
Italy	Piedmont (P)	1976–89	1976–99	1370
Italy	Lombardy (G)	1976–89	1976–99	322
Norway	National (G)	1975–89	1975–99	1724
Slovenia	National (G)	1975–89	1975–99	700
Spain	Navarra (G)	1975–89	1975–97	225
Sweden	National (G)	1975–89	1975–99	3114
Switzerland	Geneva (G)	1975–89	1975–99	98
United Kingdom	England and Wales (P)	1975–89	1975–99	16 533
United Kingdom	Scotland (G)	1975–89	1975–99	1805
Total		1975–89	1975–99	35 191

[a]Type of registry: (P), paediatric cancer registry; (G), general cancer registry.

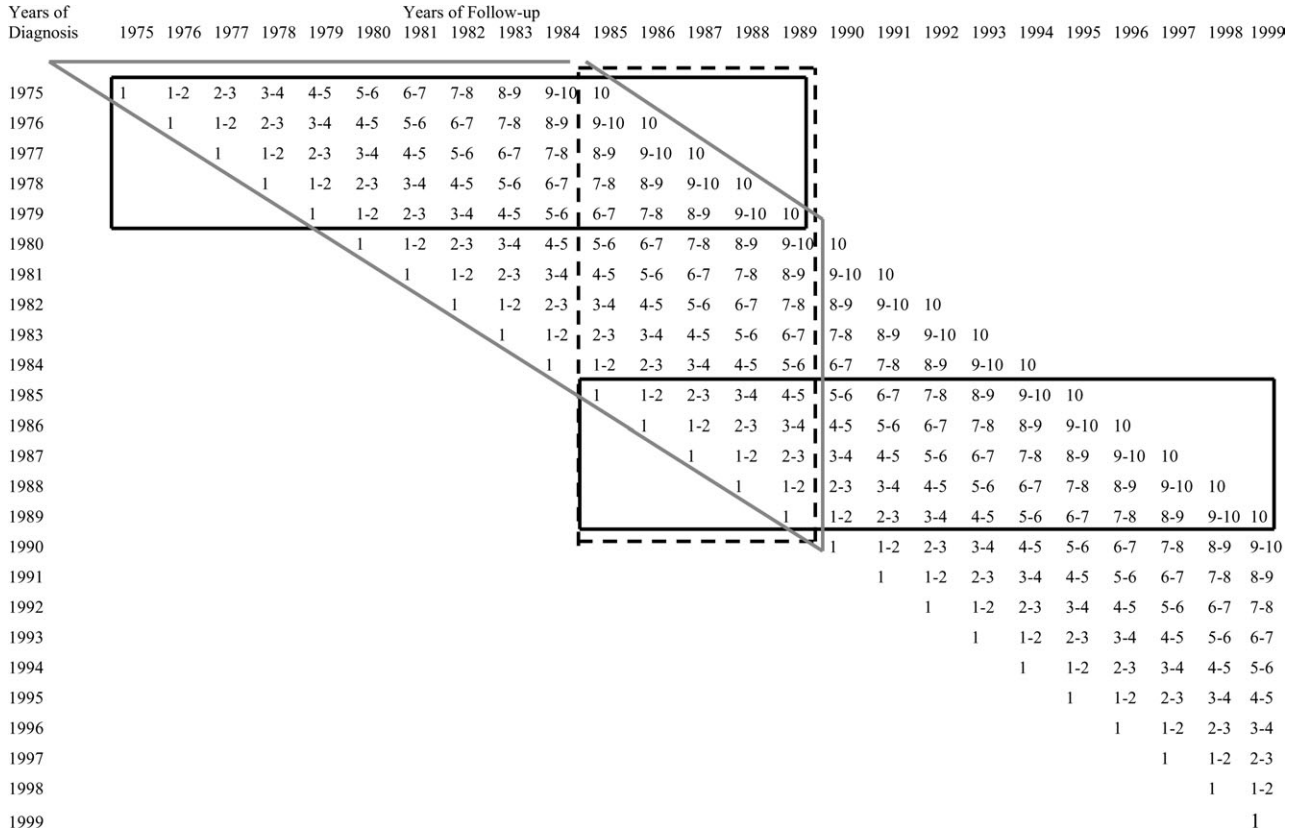

Figure 1. Years of diagnosis and years of follow-up included in derivation of survival estimates by various methods: observed 10-year survival of children diagnosed in 1985–89 (lower black solid frame), 10-year cohort survival (upper black solid frame), 10-year complete survival (grey solid frame) and 10-year period survival (black dashed frame) available in 1985–89. The numbers within the cells indicate the years since diagnosis.

For comparison purposes we also report 5-year survival for selected groups of patients. These were obtained using the same methodology and same sets of data.

All analyses were carried out with a recently published SAS macro, which can be used for both traditional survival analysis and for period analysis [22].

results

Overall, 35 191 childhood cancer cases were extracted from the ACCIS database and included in the analyses. The numbers and proportions of patients included in tumour-specific analyses are shown in Table 2. Lymphoid leukaemia was by far the most common diagnosis, accounting for more than one in four childhood cancers. The other 11 forms of cancer assessed in this analysis accounted for between 2.1 and 8.2% of all childhood cancers. The minimum number of cancers per diagnostic group was 597. Almost 80% of all childhood cancers were included in the cancer-specific analyses for 12 selected tumour types.

Among children diagnosed with any form of cancer in 1985–89, 65% were still alive after 5 years and 62% after 10 years of follow-up (Table 2, observed survival). However, using the cohort method, the survival estimate available in 1989 was only 47% at 5 years and 43% at 10 years of follow-up. An estimate of survival available at the end of 1989 from complete analysis (pertaining to all children diagnosed in 1975–89) was somewhat higher (55% at 5 years and 50% at 10 years), but still substantially lower than the survival actually experienced by the patients diagnosed in 1985–89. By contrast, 5-year survival estimated by period analysis at the end of 1989 was 63% and 10-year survival 58%, i.e. much closer to the survival estimates eventually observed for children diagnosed in 1985–89.

The results of the three methods are compared for the selected diagnostic groups of childhood cancer in Table 2 and Figure 2. Despite major variation of survival between different types of childhood cancer, the survival curves obtained by the period method for 1985–89 (dashed curves in Figure 2) were very close to the true survival curves of patients diagnosed in 1985–89, observed at the end of 1999 (upper black solid curve in Figure 2), for most diagnostic groups. Period analysis almost perfectly predicted survival curves of children with lymphoid leukaemia, Hodgkin lymphoma, primitive neuroectodermal tumours, neuroblastoma, retinoblastoma, osteosarcoma and rhabdomyosarcoma. For the other diagnostic groups, the period estimates were somewhat lower, but much less so than the traditional cohort and complete estimates. The differences between the estimates obtained by the

Table 2. Numbers and proportions of patients included in the analyses by diagnostic group, and 10-year survival (with standard error, SE) actually observed for patients diagnosed in 1985–89 compared to the most up-to-date 10-year survival estimates available in 1985–89 by cohort analysis, complete analysis and period analysis

Diagnostic group	ICCC[a]	Number of cases (%) in 1985–89	10-year survival (SE) in %			
			Observed	Available estimates in 1985–89		
				Cohort	Complete	Period
Lymphoid leukaemia	Ia	7632 (26.7)	66.9 (0.9)	43.3 (1.0)	53.0 (0.7)	63.8 (1.0)
Acute non-lymphocytic leukaemia	Ib	1536 (5.4)	36.5 (2.1)	12.9 (1.4)	19.7 (1.2)	29.4 (2.2)
Hodgkin lymphoma	IIa	1320 (4.6)	88.4 (1.6)	81.1 (1.9)	83.6 (1.2)	86.0 (1.6)
Non-Hodgkin lymphoma	IIb	1510 (5.3)	68.3 (2.1)	31.3 (2.0)	47.5 (1.4)	64.6 (2.3)
Astrocytoma	IIIb	2330 (8.2)	68.3 (1.6)	55.6 (1.8)	59.6 (1.2)	64.2 (1.7)
Primitive neuroectodermal tumours	IIIc	1330 (4.7)	35.1 (2.2)	28.1 (2.2)	31.2 (1.5)	34.3 (2.3)
Neuroblastoma and ganglioneuroblastoma	IVa	1910 (6.7)	41.9 (1.9)	28.6 (1.9)	36.6 (1.2)	41.9 (1.9)
Retinoblastoma	V	771 (2.7)	91.2 (1.7)	86.9 (2.1)	87.4 (1.4)	89.7 (1.9)
Wilms' tumour, rhabdoid and clear-cell sarcoma	VIa	1649 (5.8)	83.0 (1.6)	67.0 (2.0)	72.1 (1.2)	78.8 (1.8)
Osteosarcoma	VIIIa	771 (2.7)	51.3 (3.2)	23.4 (2.6)	35.3 (2.0)	50.8 (3.4)
Ewing sarcoma	VIIIc	597 (2.1)	46.4 (3.7)	27.5 (3.2)	31.8 (2.3)	37.3 (3.6)
Rhabdomyosarcoma and embryonal sarcoma	IXa	1096 (3.8)	56.5 (2.5)	42.4 (2.7)	48.4 (1.7)	57.1 (2.6)
Total		35 191 (100)[b]	61.9 (0.4)	43.2 (0.5)	50.4 (0.3)	58.4 (0.5)

[a]International Classification of Childhood Cancer.
[b]28 596 patients included in site-specific analyses.

traditional methods and by period analysis were largest for those cancers with the strongest improvement in prognosis over time, i.e. lymphoid leukaemia, acute non-lymphocytic leukaemia, non-Hodgkin lymphoma and osteosarcoma.

Standard errors of 10-year survival estimates were similar for cohort and period analysis (ranging from 1.0 to 3.2 % and from 1.0 to 3.6%, respectively, for the different types of cancer) and somewhat lower for complete analysis (range: 0.7 to 2.3%) (Table 2).

discussion

In this article we demonstrate how well the period survival method estimates predicted survival for recently diagnosed patients, using childhood cancer cases from the ACCIS database [4]. In particular, using historical data we showed that the period survival method provides much more up-to-date estimates of eventually observed long-term survival of children with cancer than the traditional cohort and complete life-table analysis. This pattern was consistent for all common forms of childhood cancer included in this analysis. These results are in agreement with and extend the previous findings obtained for cancers of adults and for selected forms of childhood cancer in relatively small samples of children [9, 10, 13, 23].

We have deliberately chosen to report 10-year survival to emphasize the increased mortality affecting 5-year survivors, which may sometimes be forgotten when survival is reported for 5-year follow-up periods.

With very few exceptions [19–25], childhood cancer survival figures available in the literature have been derived using cohort analysis, complete analysis or a mixture of both [1–6, 26]. Although these survival statistics are useful for evaluation of survival of defined cohorts of patients, they are less so when interest lies in obtaining information on survival expectations of recently diagnosed cancer patients. The period survival method is of particular value in this context, and this increases with the length of the follow-up, and with the speed of change in prognosis. In the evaluations presented in this paper, the advantage of period analysis was largest for lymphoid leukaemia, acute non-lymphocytic leukaemia, non-Hodgkin lymphoma and osteosarcoma, the cancers for which prognosis has improved most dramatically in recent decades.

For some diagnostic groups (e.g. acute non-lymphocytic leukaemia) the survival curves obtained by the period survival method tended to be still somewhat pessimistic (albeit much less so than the traditional cohort and complete estimates). This phenomenon is indicative of ongoing further strong improvement of survival of patients diagnosed in 1985–89 during later years of follow-up, i.e. after 1989, which was not reflected in the conditional survival probabilities available at the end of 1989.

In theory, period estimates may also become (transiently) too optimistic, if changes in early detection only increase lead time. A pertinent impact of early detection might be recognized for neuroblastoma, where screening practices or increased awareness have increased early diagnosis or led to overdiagnosis, which artificially prolonged survival time without reducing mortality [27]. However, even for neuroblastoma, the period estimate of 10-year survival for the 1985–89 period was almost identical with the 10-year survival later observed for patients diagnosed in 1985–89. In general, advances in childhood cancer therapy appear to have reduced both early and late cancer deaths [28–30]. This is in agreement with our finding that some underestimation rather than overestimation of long-term survival is the issue to be concerned about in practice, even with period analysis, as

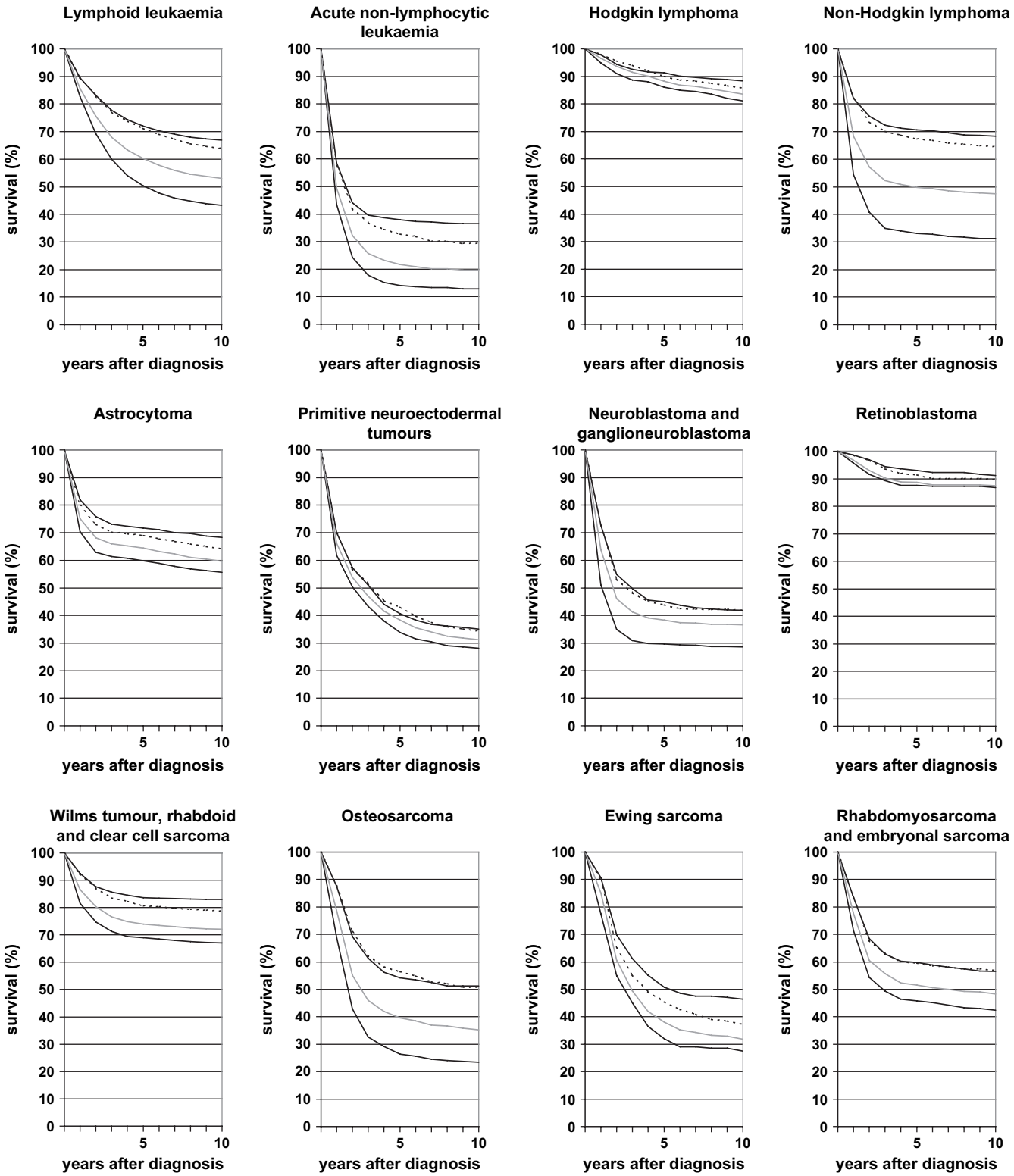

Figure 2. Survival curves eventually observed for children diagnosed with common forms of childhood cancers in 1985–89 (upper black solid curves) compared to the most up-to-date 10-year survival curves available in 1985–89 by cohort analysis (lower black solid curves), complete analysis (grey solid curves) and period analysis (black dashed curves).

long as survival continues to improve. However, such underestimation manifests much less with period analysis than with traditional cohort-based analyses.

When survival remains stable over time, cohort, complete and period estimates are generally very similar. In our analyses, such patterns were seen, for example, for Hodgkin lymphoma

and retinoblastoma. However, period estimates provide some additional information even in that situation, by indicating the absence of major recent progress in survival, which could have been missed by the other methods of survival analysis due to their delayed responsiveness. In the case of a deterioration of survival over time, such an alarming development would also be detected more timely by period analysis.

A potential disadvantage of period estimates compared with complete estimates is their somewhat higher standard error. However, in our analyses the differences between the point estimates were typically much greater than the standard errors of either estimate. An increase in precision is of much less consequence than the greater delay by which progress in prognosis is captured. The issue of precision could become more important, however, in analyses of smaller datasets, or when improvement in survival has levelled off.

Fortunately, improvement in survival seems to be ongoing, and for most childhood cancers the pace of change is dramatic; long-term period survival estimates at a given time are much closer to long-term survival experienced by concurrently diagnosed patients than traditional survival estimates in this very situation. We therefore recommend that period analysis be more widely used for timely monitoring of changes in prognosis of the cancers of childhood at the population level.

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