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Updating long-term childhood cancer survival trend with period and mixed analysis: Good news from population-based estimates in Italy

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ARTICLE INFO

Article history:
Received 15 July 2005
Received in revised form
13 August 2005
Accepted 28 August 2005
Available online 21 April 2006

Keywords:
Childhood neoplasms
Leukaemia
Central nervous system neoplasms
Survival analysis
Cancer registries
Population-based studies
Statistical methods

ABSTRACT

An empirical evaluation of long-term period survival analysis was performed using data from the Childhood Cancer Registry of Piedmont, Italy. The aim was to update survival time trends and provide 25-year projections for children currently diagnosed with cancer. The observed survival experiences up to 15 years after diagnosis of five quinquennial cohorts (cohort analysis) were compared to the corresponding estimates obtained by period analysis. The two methods generally produced very similar findings, although period analysis estimates were slightly lower than those obtained from cohort analysis. We then used mixed analysis to assess time trends in long-term survival. This showed that the probability of surviving 25 years after a cancer in childhood has more than doubled compared to cohort analysis estimates from patients diagnosed more than 25 years ago (73% vs. 32%), providing further evidence of an ongoing improvement in prognosis.

1. Introduction

Since the early 1970s there have been impressive and continuing improvements in prognosis for childhood tumours.[1–7] Both short-term[8,9] and long-term[10–13] mortality appear to have reduced, although the latter is still not negligible for some types of childhood cancer.[12]

Long-term survival remains the most direct measure of outcome for children with cancer. However, long-term survival is usually estimated from the observed experience of cohorts of patients diagnosed many years in the past. For example, 25-year survival has typically been estimated from the survival experience of patients diagnosed 25 years ago and followed-up until the current day. When there are continuing improvements in survival, such historical data will not provide valid predictions of survival of patients diagnosed currently who will experience the benefits of recent improvements in therapy. It is, therefore, important to use more valid

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0959-8049/$ - see front matter
doi:10.1016/j.ejca.2005.08.046

estimates of the likely survival of currently diagnosed cancer patients. This may be particularly important for childhood cancer since children have long-term life expectations, and it is crucial to avoid overly pessimistic projections and to detect any improvement in long-term survival rates.

Brenner and Gefeller[14] have suggested a new method, termed 'period analysis', to provide up-to-date estimates of long-term survival by considering the most recent data available for each survival period (0–5 years, 5–10 years, etc.), e.g., by considering the 5-year survival for patients diagnosed five years ago, and considering the 5–10-year survival for patients diagnosed 10 years ago. The term 'period analysis' refers to the fact that all of the data employed comes from the most recent time period with different 'cohorts' providing the survival estimates for each survival period. This approach differs from 'cohort analysis' in which long-term survival is estimated from data from a single cohort of patients followed over a long period of time. Recently, Brenner and Spix[15] have proposed combining the advantages of period analysis with those of the more traditional cohort analysis in a 'mixed analysis'. Although this approach has undergone extensive empirical evaluation on adult cancer data sets [16,17], with regards to childhood cancer its application has been limited to data from the German Childhood Cancer Registry[18–20] and from the SEER,[21] using period[19,21] and mixed methods.[18,20]

In the present paper we used data from the Childhood Cancer Registry of Piedmont, Italy[22] to: (i) perform an empirical evaluation of long-term estimates of childhood cancer survival, comparing period analysis with the actual experience of observed cohorts; (ii) use the period method to estimate 25-year survival for currently diagnosed cases of childhood cancer in North-West Italy; (iii) update long-term survival time trends using estimates from the mixed method for cases diagnosed during 1972–2001.

2. Patients and methods

2.1. Data

The Childhood Cancer Registry of Piedmont, Italy, is a population-based registry which, since 1967, has recorded incident cases of cancer in children (aged less than 15 years) resident in the region. Procedures for data collection, follow-up and classification as well as criteria for inclusion in the CCRP database have been reported elsewhere.[22] Cancer site, morphology and behaviour were coded according to the International Classification of Disease for Oncology (ICD-O-2)[23] and tumour types were grouped according to the International Childhood Cancer Classification (ICCC).[24] Intracranial neoplasms of benign and unspecified histology were included; angiomas (even if intracranial) and hystiocytosis X were excluded.

The CCRP database includes 3366 cases diagnosed during the period 1st January 1967–31st December 2001. Cases documented only by a death certificate (59) were excluded from the analysis. Survival of patients who developed a second malignant tumour in childhood (10) was computed starting from the diagnosis of the first tumour. Microscopic verification (MV) of diagnosis was available for 92% of cases, ranging from 75% for retinoblastoma to 99% for acute non-lymphoblastic leukaemia and Hodgkin disease. Vital status of registered cases was updated in 2004 but, in order to eliminate bias due to delays in recording of incident cases,[25] follow-up for the present study was terminated on 31st December 2001, when 1831 (56%) cases were reported to be alive, 1439 (44%) dead, and 27 cases (uniformly distributed over the study period) were lost to follow-up (0.8%).

2.2. Statistical analysis

Survival was estimated through the Kaplan–Meier method[26] applied to the CCRP database using both 'cohort' analysis and 'period' analysis.[14,17] Cohort and period information were also used for analyses using the 'mixed' method.[15] Ninety-five percent Confidence Intervals (95% CI) were computed for cumulative survival using the Greenwood formula for the variance.[27] Relative survival was not computed as all-cause mortality is negligible in the general population for the age classes under consideration.

2.2.1. Validation

In order to verify the ability of period analysis to provide valid long-term survival estimates, an empirical validation study was performed using the CCRP records. Five quinquennial cohorts of diagnosis (1972–1976 to 1992–1996) were identified and their full survival experiences observed up to 15 years after diagnosis. These estimates, considered as the 'gold standard', were then compared to the corresponding long-term (5, 10 and 15-year) cumulative survival estimates that could have been obtained by period analysis in the most recent year of the cohort's recruitment period, e.g., we have computed survival projections (up to 15-years since diagnosis) as they would have been computed in a period analysis conducted in 1986, and compared them to the actual observed survival experience of the 1982–1986 cohort, which completed 15 years of follow-up only in 2001. Similarly, comparisons were made between the survival estimates for other cohorts (the 1972–1976, 1977–1981, 1982–1986, 1987–1991, 1992–1997 cohorts) and the corresponding period analysis projections (for the 1976, 1981, 1986, 1991, 1997 calendar year periods).

In order to stabilise our estimates, period survival analyses were then repeated extending the time windows of survival experience observation to three and five years.

A two-tailed test for the difference between period and cohort estimates was computed assuming a normal distribution for cumulative survival[28] and the level of statistical significance was set at 5%.

2.2.2. Mixed analysis of trends in long-term survival

A combination of the cohort and period methods in a 'mixed analysis' was used for analyses of trends in long-term survival.[15,20] For example, in 2001, patients diagnosed in 1991 had completed only 10 years of follow-up yet. Fifteen-year survival for those patients was estimated by combining their survival experience during the first 10 years following diagnosis (cohort analysis), with the most recent (2001) period estimates of conditional survivals for years 11th–15th following diagnosis (period analysis). Similarly, 10-year survival for patients diagnosed in 1996 was estimated by combining their survival experience during the first 5 years following diagno-

sis (cohort analysis), with the most recent (2001) period estimates of conditional survivals for years 6th–10th after diagnosis (period analysis).[15] Thus, for more recent cohorts, an increasing proportion of the survival function was obtained by period analysis, and the estimate for the 2001 cohort was exclusively obtained through period analysis.

In order to obtain more stable survival figures we have considered 5-year cohorts for cohort and mixed analysis, and 5-year time windows for period and mixed analysis.

Diagnostic groups considered were all cancer types, leukaemias (and acute lymphoblastic leukaemia [ALL]), central nervous system (CNS) tumours and other solid tumours.

3. Results

3.1. *Validation*

Table 1 shows estimates of 5, 10 and 15-year cumulative survival for all cancer types estimated by cohort analysis (for 5-year cohorts of diagnosis) and period analysis (for time windows of 1, 3 and 5-years). The cohort analysis corresponds to the classical presentation of survival results. Both cohort and period survival estimates were available for up to 15 years for the years in the central part of the table (1982–1986 cohort and 1986, 1984–1986, 1982–1986 periods). For the years preceding 1982, period survival computations were limited to shorter follow-up length (5- and 10-years) since registration started in 1967 and no CCRP cases could have contributed longer follow-up. For the years following 1986, on the other hand, no 5-year diagnosis cohorts could have been entirely followed for 15 years. Hence, validation is limited to periods when both estimation methods could be used.

The period survival projections with a 5-year time window slightly underestimated the observed cohort survival, for all periods of diagnosis but one. The largest discrepancy was observed between the 1982–1986 cohort and the corresponding 5-year period analysis, e.g., the former estimate of 5-year survival was 64% whereas the latter estimate was 58%. On the other hand, for the 1987–1991 cohort, all four methods produced very similar findings. Period analysis based on the narrowest time windows (1 year) produced less precise (larger CIs) survival estimates and overestimated cohort survival in two instances (1996 vs. 1992–1996 cohort and 1981 vs. 1977–1981 cohort). In general, using a 3-year time window for the period analysis yielded findings which were very close to the cohort analysis, with similar precision (i.e. similar CIs). Fig. 1 shows that there was a close agreement in the cumulative survival probabilities up to 10 years after diagnosis (5 years for the most recent cohort) from cohort and period analysis (using the 3 years time window). The largest difference was approximately 5% (cohort 1977–1981 vs. period 1979–81).

Table 1 – Childhood Cancer Registry of Piedmont 1972–2001

	5			10			15		
	CS%	95% CI	P*	CS%	95% CI	P*	CS%	95% CI	P*
Period analysis (1972–1976)[a]	34	29–39	0.16	–	–		–	–	
Period analysis (1974–1976)[a]	34	27–41	0.20	–	–		–	–	
Period analysis (1976)[a]	39	27–50	0.42	–	–		–	–	
Cohort analysis (1972–1976)[b]	37	32–42		–	–		–	–	
Period analysis (1977–1981)[a]	48	44–53	0.21	44	40–49	0.13	–	–	
Period analysis (1979–1981)[a]	56	50–61	0.09	52	46–58	0.14	–	–	
Period analysis (1981)[a]	58	49–68	0.07	57	47–66	0.04	–	–	
Cohort analysis (1977–1981)[b]	51	47–55		48	44–52		–	–	
Period analysis (1982–1986)[a]	58	54–63	0.04	55	50–59	0.03	53	49–58	0.05
Period analysis (1984–1986)[a]	63	57–69	0.40	60	54–65	0.37	57	50–63	0.28
Period analysis (1986)[a]	62	52–72	0.39	60	50–70	0.45	56	45–68	0.35
Cohort analysis (1982–1986)[b]	64	59–68		61	56–65		59	54–63	
Period analysis (1987–1991)[a]	69	65–73	0.47	65	61–70	0.39	–	–	
Period analysis (1989–1991)[a]	70	65–75	0.39	67	61–72	0.45	–	–	
Period analysis (1991)[a]	66	56–76	0.28	66	56–76	0.47	–	–	
Cohort analysis (1987–1991)[b]	69	65–73		66	62–71		–	–	
Period analysis (1992–1996)[a]	75	71–79	0.28	–	–		–	–	
Period analysis (1994–1996)[a]	78	72–83	0.37	–	–		–	–	
Period analysis (1996)[a]	84	77–92	0.03	–	–		–	–	
Cohort analysis (1992–1996)[b]	76	73–80		–	–		–	–	

Comparison of 5, 10 and 15-year cumulative survival (CS%) and 95% confidence interval (95% CI) for all cancer types estimated by cohort and period analysis (for varying time windows).

a 5-, 10-, 15-year cumulative survival as estimated by period analysis for the specified time window.

b 5-, 10-, 15-year cumulative survival as estimated using complete follow-up information available on 31st December 2003 for the specified cohort of diagnosis.

* P-value for the difference between period and cohort estimates.

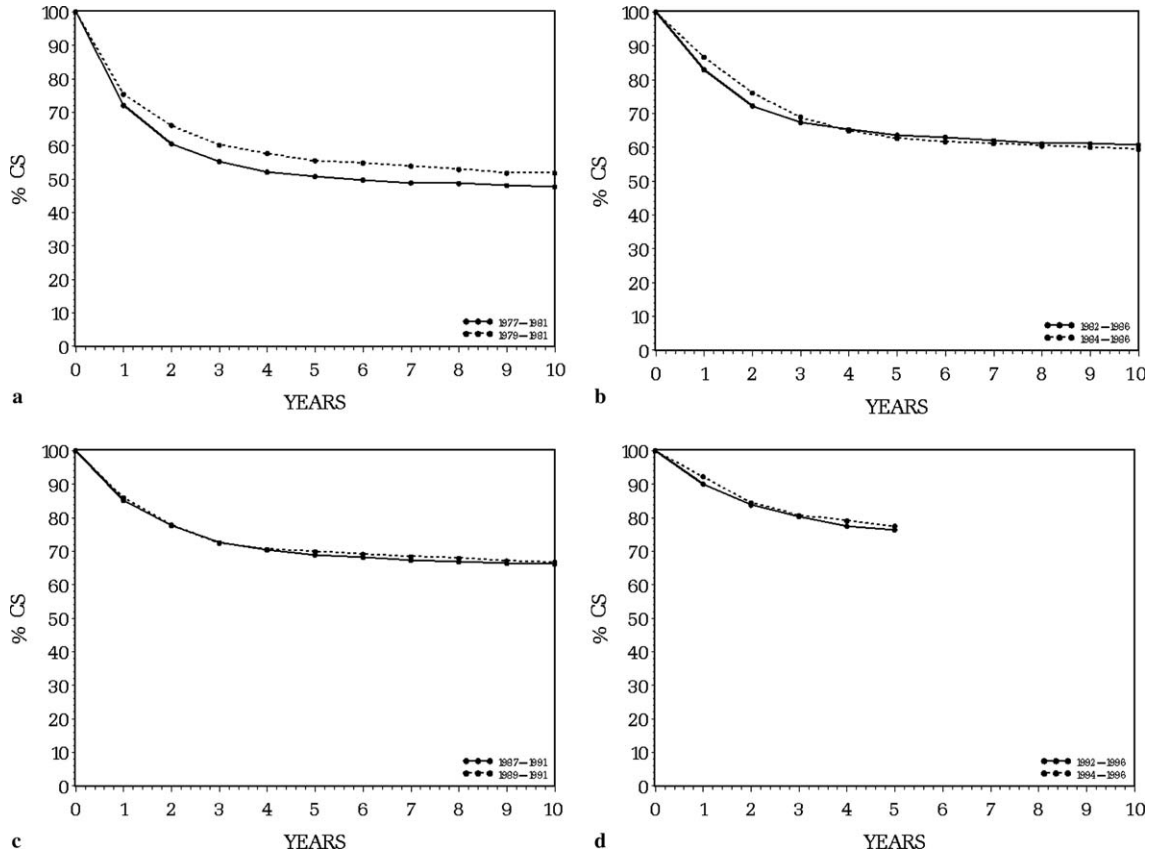

Fig. 1 – Childhood Cancer Registry of Piedmont. Cumulative survival for all cancer types estimated through cohort analysis (solid lines) and period analysis (dashed lines). (a) 1977–1981 cohort and 1979–1981 period; (b) 1982–1986 cohort and 1984–1986 period; (c) 1987–1991 cohort and 1989–1991 period; (d) 1992–1996 cohort and 1994–1996 period.

3.2. *Mixed analysis of trends in long-term survival*

Fig. 2 shows mixed analysis estimates of cumulative survival for total childhood cancer. The cohort of diagnosis 1972–1976 is the only one for which survival estimates could be obtained entirely through cohort analysis, while the 25-year survival projection for the most recent (1997–2001) period was obtained entirely through period analysis. The probability of surviving 25 years after a cancer in childhood has more than doubled compared to cohort analysis estimates from patients diagnosed more than 25 years ago (73% vs. 32%).

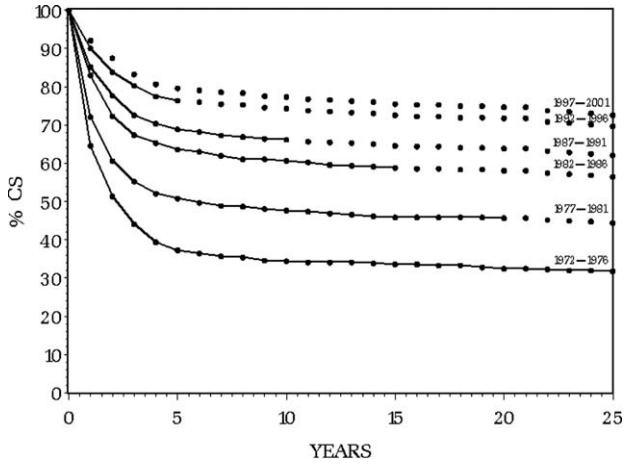

Fig. 2 – Childhood Cancer Registry of Piedmont. Cumulative survival for all cancer types estimated through mixed analysis, combining cohort analysis (solid line) and period analysis (1997–2001) (dots) for cohorts of diagnosis with incomplete follow-up.

Table 2 presents mixed analysis estimates of 5, 10, 15, 20 and 25-year cumulative survival for leukaemia (and ALL), CNS tumours, other childhood cancers, and total childhood cancer. Children with ALL benefited most from the introduction of new diagnostic techniques and treatment protocols. The probability of surviving 5 years after a diagnosis in 1972–1976 was 38% (95% CI: 29–48%); it increased to 77% (95% CI: 70–85%) for the 1987–1991 cohort, and is estimated to reach 87% (95% CI: 81–93%) for the most recent cohort. Twenty-five-year survival estimates for this type of cancer similarly grew from 33% (95% CI: 24–43%) to 83% (95% CI: 77–90%) for the first and last cohorts, respectively. The corresponding figures for CNS and for all other tumours are somewhat lower, but consistent in terms of the markedly improving trend.

As 5-year survival is often considered as a reference time after which survivors are likely to be cured, we also present in Table 3 survival estimates at 10, 15, 20 and 25 years since diagnosis conditioned to 5-year survival. Conditional 10-year survival for ALL improved from 86% (95% CI: 83–88%) for chil-

Table 2 – Childhood Cancer Registry of Piedmont 1972–2001

Type of tumour and period of diagnosis	N	5		10		15		20		25	
		CS%	95% CI	CS%	95% CI	CS%	95% CI	CS%	95% CI	CS%	95% CI
(a)											
Leukaemia											
1972–1976	155	31	23–39	27	19–34	26	19–33	26	19–33	26	19–33
1977–1981	204	51	44–57	47	40–53	44	37–50	44	37–50	43[a]	36–50
1982–1986	160	60	52–68	57	49–65	56	48–63	56[a]	48–63	55[a]	47–63
1987–1991	147	70	63–78	68	61–76	67[a]	59–74	67[a]	59–74	66[a]	58–74
1992–1996	156	75	68–82	72[a]	65–79	71[a]	64–78	71[a]	64–78	70[a]	63–77
1997–2001	145	85[a]	79–91	82[a]	75–88	80[a]	74–87	80[a]	74–87	79[a]	72–86
Acute lymphocytic leukaemia											
1972–1976	112	38	29–48	33	24–43	33	24–43	33	24–43	33	24–43
1977–1981	161	58	50–65	53	46–61	53	46–61	53	46–61	50[a]	42–57
1982–1986	127	68	60–76	65	57–74	65	57–74	65[a]	57–74	64[a]	55–72
1987–1991	114	77	70–85	75	68–83	75[a]	68–83	75[a]	68–83	75[a]	66–83
1992–1996	123	84	77–90	81[a]	74–88	81[a]	74–88	81[a]	74–88	80[a]	73–87
1997–2001	117	87[a]	81–93	85[a]	78–91	85[a]	78–91	85[a]	78–91	83[a]	77–90
(b)											
Central nervous system tumours											
1972–1976	90	33	23–43.9	31	21–41	28	18–38	27	17–37	26	16–35
1977–1981	131	46	37–54.3	41	33–50	38	30–47	37	29–46	35[a]	27–44
1982–1986	120	65	57–73.5	63	59–71	59	50–68	57[a]	48–66	54[a]	44–63
1987–1991	101	70	61–79.2	65	56–75	63[a]	53–72	60[a]	51–70	57[a]	47–67
1992–1996	115	82	75–88.8	78[a]	70–85	74[a]	70–85	72[a]	63–81	68[a]	58–78
1997–2001	132	73[a]	65–80.4	69[a]	61–77	66[a]	57–75	64[a]	55–73	60[a]	50–70
Other malignant neoplasms											
1972–1976	196	44	37–52	42	35–50	42	35–50	41	33–48	39	32–47
1977–1981	264	53	47–59	52	46–58	52	46–58	52	46–58	50[a]	44–56
1982–1986	196	66	59–72	63	56–70	61	54–68	61[a]	54–68	59[a]	52–66
1987–1991	206	67	61–74	65	59–72	64[a]	58–71	64[a]	57–70	62[a]	55–69
1992–1996	192	75	68–81	74[a]	68–80	73[a]	66–79	72[a]	66–79	70[a]	63–77
1997–2001	208	80[a]	75–86	80[a]	74–85	78[a]	73–84	78[a]	72–84	75[a]	69–82
(c)											
All tumour types											
1972–1976	441	37	32–42	34	30–39	34	29–38	33	28–37	32	27–36
1977–1981	599	51	47–55	48	44–52	46	42–50	46	42–50	44	40–49
1982–1986	476	64	59–68	61	56–65	59	54–63	58[a]	54–63	57[a]	52–61
1987–1991	454	69	65–73	66	62–71	65[a]	60–69	64[a]	60–68	62[a]	58–67
1992–1996	463	76	73–80	74[a]	70–78	73[a]	68–77	72[a]	68–76	70[a]	65–74
1997–2001	485	80[a]	76–83	77[a]	74–81	76[a]	72–80	75[a]	71–79	73[a]	68–77

5-, 10-, 15-, 20- and 25-year cumulative survival (CS%) and 95% confidence interval (95% CI), estimated through mixed analysis, combining cohort analysis and period analysis (1997–2001) for cohorts of diagnosis with incomplete follow-up. Diagnostic groups are: (a) leukaemia and acute lymphocytic leukaemia; (b) central nervous system tumours and other malignant neoplasms; (c) all tumour types.
a Estimated by period analysis.

dren diagnosed in 1972–1976 to 97% (95% CI 95–97%) for children diagnosed in 1997–2001. Leukaemia and ALL showed stable survival after 10 years from diagnosis. However, CNS showed survival percentages still reducing after the first 5 years, with little signs of reaching a plateau.

4. Discussion

In this paper we validated the survival projections obtained through period analysis in the context of childhood cancer, and then used the method to provide current survival estimates and to examine trends in long-term survival. Although several empirical evaluations of period analysis have been published [16,17], only a few have focused on childhood cancers.[19–21] To our knowledge, no systematic validation of period analysis on all paediatric cancers or presentation of survival time trends using mixed analysis have previously been carried out on European data.

Period analysis and cohort analysis are two intrinsically different methodologies, which estimate long-term survival rates using the follow-up experience of different parts of a cancer registry data set. It has been argued that period approach produces more up-to-date survival estimates that provide more valid estimates of future survival probabilities of currently diagnosed patients. In order for these period analysis projections to be valid, (or at least more valid than estimates from cohort analysis), the conditional survival probabilities within defined time intervals following diagnosis

Table 3 – Childhood Cancer Registry of Piedmont 1972–2001

Type of tumour and period of diagnosis	10 (conditional to 5)		15 (conditional to 5)		20 (conditional to 5)		25 (conditional to 5)	
	CS%	95% CI	CS%	95% CI	CS%	95% CI	CS%	95% CI
(a)								
Leukaemia								
1972–1976	86	83–88	84	80–86	84	80–86	84	80–86
1977–1981	92	91–93	86	84–88	86	84–88	85[a]	83–87
1982–1986	95	94–95	93	91–94	93[a]	91–94	92[a]	90–93
1987–1991	97	97–98	95[a]	94–96	95[a]	94–96	94[a]	93–95
1992–1996	96[a]	96–97	94[a]	93–95	94[a]	93–95	93[a]	92–95
1997–2001	97[a]	95–97	95[a]	93–96	95[a]	93–96	93[a]	92–95
Acute lymphocytic leukaemia								
1972–1976	87	84–89	87	84–89	87	84–89	87	84–89
1977–1981	92	91–93	87	85–89	87	85–89	86[a]	84–88
1982–1986	97	96–97	95	94–96	95[a]	94–96	94[a]	93–95
1987–1991	98	97–98	98[a]	97–98	98[a]	97–98	97[a]	96–97
1992–1996	97[a]	96–98	97[a]	96–98	97[a]	96–98	96[a]	94–97
1997–2001	97[a]	96–98	97[a]	96–98	97[a]	96–98	96[a]	94–97
(b)								
Central nervous system tumours								
1972–1976	92	90–94	84	80–87	81	75–84	77	70–81
1977–1981	90	88–92	83	80–86	82	78–84	77[a]	72–80
1982–1986	96	95–97	91	89–93	88[a]	85–90	83[a]	78–86
1987–1991	93	91–94	89[a]	87–91	86[a]	83–88	81[a]	76–85
1992–1996	95[a]	94–96	91[a]	94–96	88[a]	85–91	83[a]	77–87
1997–2001	95[a]	94–95	91[a]	89–93	88[a]	85–90	83[a]	78–87
Other malignant neoplasms								
1972–1976	96	95–96	96	95–97	92	90–93	89	87–90
1977–1981	97	97–97	96	96–97	96	96–97	94[a]	93–94
1982–1986	95	94–96	93	92–94	92[a]	91–93	90[a]	88–91
1987–1991	97	97–97	96[a]	95–96	95[a]	94–95	92[a]	91–93
1992–1996	99[a]	99–99	98[a]	97–98	97[a]	96–97	94[a]	93–95
1997–2001	99[a]	99–99	98[a]	97–98	97[a]	96–97	94[a]	93–95
(c)								
All tumour types								
1972–1976	92	91–93	90	89–91	87	86–89	85	84–87
1977–1981	94	94–94	90	90–91	90	90–91	87[a]	87–89
1982–1986	95	95–96	93	92–93	91[a]	91–92	89[a]	88–90
1987–1991	96	96–96	94[a]	93–94	93[a]	92–93	90[a]	89–91
1992–1996	97[a]	97–98	95[a]	94–96	94[a]	93–95	91[a]	90–92
1997–2001	97[a]	97–98	95[a]	94–96	94[a]	93–95	91[a]	90–92

10-, 15-, 20- and 25-year survival (CS%) and 95% confidence interval (95% CI), conditioned to 5-year survival, estimated through mixed analysis, combining cohort analysis and period analysis (1997–2001) for cohorts of diagnosis with incomplete follow-up. Diagnostic groups are: (a) leukaemia and acute lymphocytic leukaemia; (b) central nervous system tumours and other malignant neoplasms; (c) all tumour types.
a Estimated by period analysis.

must be constant over the subsequent time period (i.e. into the future). If this is not the case, then the estimates will not be completely valid predictions of future survival, but they will still be more valid than those from cohort analysis, unless there is a (unpredictable) change in the direction of the time trends (e.g. if survival stops improving and subsequently deteriorates over time). This is unlikely since recent studies have showed that modern treatments have been effective in reducing mortality both in childhood[29] and later in life,[12] however conclusive evidence could only come from a complete evaluation of treatment-related adverse effects, e.g., second primary malignancies. These are the second most frequent cause of death among 5-year survivors, accounting for less than 20% of all deaths.[12,30] Recent studies from the UK and the USA have estimated overall cumulative risks of the occurrence of a second primary malignancy of 4.2% (within 28 years since diagnosis[31]) and 3.2% (within 20 years[32]), respectively. Similar results were obtained from large European population-based registries.[33,34]

In addition to performing an empirical validation of period analysis on the CCRP data, we also assessed the effect of varying the time window width on interval period analysis estimates of cumulative survival. The different options (1, 3 and 5 years) for the width of the time window for period analysis involved a trade-off between using the most recent data available and the (statistical) stability of estimates. Period analysis survival estimates obtained with the narrowest time window lacked precision, and because of the positive historical trends

in survival, they were generally higher than the ones obtained with 3 and 5-year time windows. Three-year time windows produced estimates that were close to those of the cohort analysis, and with reasonable precision. However, since period estimates are meant to be a surrogate for the survival rates later observed for patients diagnosed in a particular period, the most natural comparison is that between period analysis based on a 5-year time window and quinquennial cohorts. These projections slightly underestimated the observed cohort survival, for all periods of diagnosis but one. The magnitude of the difference was generally, but not always, negligible. Brenner[21] showed that for data from 1985 to 1989, 10-year survival estimates from cohort and period analysis were different by 0.6–3.5%, depending on the tumour type. In our analysis the point estimates of 10-year survival in a similar period (1987–1991) was just 0.9% below the observed cohort survival.

To date, validation studies of the use of period analysis for childhood cancer data have focused on 5-year survival (limited to neuroblastoma)[20] and 10-year survival (for the main cancer types),[18,22] although some applications of period[19] and mixed[18,20] analysis have examined 15-year survival. We have evaluated the performance of long-term period estimates for five cohorts of diagnosis, involving survival up to 10 years on three cohorts and up to 15 years on one cohort. Given the reassuring results of this empirical validation, we are confident that the 15-year survival rates obtained by period analysis are valid predictions, although they still slightly underestimate the true figures.

We then used mixed analysis[15] to perform a retrospective analysis of time trends in long-term survival rates. These analyses confirmed the ongoing improvement in long-term childhood cancer survival. Towards the end of last century, 10-year survival reached and passed 75% (80% for leukaemias). Our results for children diagnosed and treated in Piedmont are comparable to the ones from cancer registries in Germany[19] and the USA.[21] Current long-term survival projections up to 25 years were obtained through period analysis using mortality follow-up in the time window 1997–2001.

Limitations of this study include the relatively small number of cases, which prevented more detailed analyses on the less common diagnostic groups, and computation of crude rather than relative survival. However, as for the second issue, patients contributing follow-up experience for the survival estimation were as old as 40 on 31st December 2003, and for the Piedmont general population the cumulative probability of dying before age 40 was 3.7% for males and 1.7% for females in 2000.[35]

In conclusion, we have confirmed the validity of period analysis, and illustrated the use of mixed analysis to estimate trends in long-term survival following diagnosis of childhood cancer. Both methods are useful tools both for purposes of diffusion of results and clinician-patient communication, and for medical resource planning and public health evaluation. In terms of our substantive findings, the probability of surviving 25 years after a cancer in childhood has more than doubled compared to cohort analysis estimates from patients diagnosed more than 25 years ago (73% vs. 32%), providing further evidence of an ongoing improvement in prognosis.

Conflict of interest statement

The authors have no conflict of interest to disclose.

Acknowledgments

The CCRP is supported by the Piedmont Region. This project was partly supported by the "Oncology Special Project", Compagnia di San Paolo FIRMS, by the Italian Association for Research on Cancer (AIRC), by the special program "Ricerca Sanitaria Finalizzata" of the Piedmont Region and by "University of Eastern Piedmont, local research funds 2003". We thank Prof. Neil Pearce for his comments on the draft manuscript. Grateful thanks to Ms. Marinella Nonnato for the careful management of the CCRP data and Ms. Assunta Rasulo for the follow-up.

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