Long-term survival and cure fraction estimates for childhood cancer in Europe (EUROCARE-6): results from a population-based study

*Laura Botta, Gemma Gatta, Riccardo Capocaccia, Charles Stiller, Adela Cañete, Luigino Dal Maso, Kaire Innos, Ana Mihor, Friederike Erdmann, Claudia Spix, Brigitte Lacour, Rafael Marcos-Gragera, Deirdre Murray, Silvia Rossi, on behalf of the EUROCARE-6 Working Group**

Summary

Background The EUROCARE-5 study revealed disparities in childhood cancer survival among European countries, giving rise to important initiatives across Europe to reduce the gap. Extending its representativeness through increased coverage of eastern European countries, the EUROCARE-6 study aimed to update survival progress across countries and years of diagnosis and provide new analytical perspectives on estimates of long-term survival and the cured fraction of patients with childhood cancer.

Methods In this population-based study, we analysed 135 847 children (aged 0–14 years) diagnosed during 2000–13 and followed up to the end of 2014, recruited from 80 population-based cancer registries in 31 European countries. We calculated age-adjusted 5-year survival differences by country and over time using period analysis, for all cancers combined and for major cancer types. We applied a variant of standard mixture cure models for survival data to estimate the cure fraction of patients by childhood cancer and to estimate projected 15-year survival.

Findings 5-year survival for all childhood cancer combined in Europe in 2010–14 was 81% (95% CI 81–82), showing an increase of three percentage points compared with 2004–06. Significant progress over time was observed for almost all cancers. Survival remained stable for osteosarcomas, Ewing sarcoma, Burkitt lymphoma, non-Hodgkin lymphomas, and rhabdomyoscarcomas. For all cancers combined, inequalities still persisted among European countries (with age-adjusted 5-year survival ranging from 71% [95% CI 60–79] to 87% [77–93]). The 15-year survival projection for all patients with childhood cancer diagnosed in 2010–13 was 78%. We estimated the yearly long-term mortality rate due to causes other than the diagnosed cancer to be around 2 per 1000 patients for all childhood cancer combined, but to approach zero for retinoblastoma. The cure fraction for patients with childhood cancer increased over time from 74% (95% CI 73–75) in 1998–2001 to 80% (79–81) in 2010–13. In the latter cohort, the cure fraction rate ranged from 99% (95% CI 74–100) for retinoblastoma to 60% (58–63) for CNS tumours and reached 90% (95% CI 87–93) for lymphoid leukaemia and 70% (67–73) for acute myeloid leukaemia.

Interpretation Childhood cancer survival is increasing over time in Europe but there are still some differences among countries. Regular monitoring of childhood cancer survival and estimation of the cure fraction through population-based registry data are crucial for evaluating advances in paediatric cancer care.

Funding European Commission.

Introduction

5-year observed survival of childhood cancer in Europe improved from 76·1% during 1999–2001 to 79·1% during 2005–07. Despite major progress in eastern European countries, disparities among states persisted,[1] and survival varied widely by cancer type. 5-year survival from sarcomas, neuroblastoma, and CNS tumours rarely exceeded 70%, remaining stable over time. Survival after childhood cancer in the 2000s was generally good and the estimated prevalence of adults who had had childhood cancer (childhood cancer survivors) was approximately 70 and 80 per 100 000 population in Italy and the USA, respectively.[2,3]

Improved survival and the growing population of childhood cancer survivors have drawn increasing attention to long-term cancer sequelae. For several paediatric cancers, an excess risk of death is well documented to persist for many years after diagnosis due to treatment effects, second malignancies, or host features.[4–6] However, population-based cancer registries have rarely been the source of data on long-term survival, mortality rate, and cure fraction for childhood cancer because of the need for large sample sizes and long follow-up periods, which are seldom available.[7,8] The EUROCARE project has estimated cancer survival since the diagnostic year of 1978, with increasing coverage of the European population. The EUROCARE-6 database contains about 220 000 records of childhood cancer diagnosed from 1978 to 2013. The magnitude of this European cohort and the long period covered make

Lancet Oncol 2022; 23: 1525–36

Published **Online** November 15, 2022 https://doi.org/10.1016/S1470-2045(22)00637-4

*Members are listed in the appendix (p 15)

Evaluative Epidemiology Unit, Department of Research, Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, Milan, Italy (L Botta MSc, G Gatta MD); **Digestive Cancer Registry of Burgundy, INSERM U1231, University of Bourgogne, Dijon, France** (L Botta); **Editorial board, Epidemiologia e Prevenzione, Milan, Italy** (R Capocaccia MSc); **National Disease Registration Service, NHS Digital, London, UK** (C Stiller MSc); **Spanish Registry of Childhood Tumours** (A Cañete MD) **and Department of Paediatrics** (A Cañete), **University of Valencia, Valencia, Spain; Cancer Epidemiology Unit, Centro di Riferimento Oncologico (CRO) IRCCS, Aviano, Italy** (L Dal Maso PhD); **Department of Epidemiology and Biostatistics, National Institute for Health Development, Tallinn, Estonia** (K Innos PhD); **Epidemiology and Cancer Registry, Institute of Oncology Ljubljana, Ljubljana, Slovenia** (A Mihor MD); **Division of Childhood Cancer Epidemiology, Institute of Medical Biostatistics, Epidemiology and Informatics (IMBEI), University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany** (F Erdmann PhD, C Spix PhD); **French National Registry of Childhood Solid Tumors, CHU Nancy, Vandœuvre-lès-Nancy, France** (B Lacour MD); **Inserm UMRS-1153, CRESS team 7, University of Paris Cité, Paris, France** (B Lacour); **Epidemiology Unit and Girona Cancer Registry, Department of**

Health, Catalan Institute of Oncology, Girona Biomedical Research Institute, Girona, Spain (R Marcos-Gragera PhD); **Consortium for Biomedical Research in Epidemiology and Public Health, Madrid, Spain** (R Marcos-Gragera); **Josep Carreras Leukemia Research Institute, Girona, Spain** (R Marcos-Gragera); **National Cancer Registry Ireland, Cork, Ireland** (Prof D Murray MPH); **School of Public Health, University College Cork, Cork, Ireland** (Prof D Murray); **Department of Oncology and Molecular Medicine, Istituto Superiore di Sanità, Rome, Italy** (S Rossi MSc)

Correspondence to: Laura Botta, Evaluative Epidemiology Unit, Department of Research, Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, 20133 Milan, Italy **laura.botta@istitutotumori.mi.it**

See Online for appendix

Research in context

Evidence before this study

Cure (ie, the complete eradication of the cancer) is the primary goal of childhood cancer care. Estimating the proportion of children effectively cured of their cancer has, however, been hindered by the persistence of long-term mortality due to the adverse effects of treatments. Nevertheless, in the past 15 years, many studies have provided solid estimates of long-term, non-cancer mortality among patients with childhood cancer. These data facilitate estimation of the proportion of cured children by disentangling mortality due to cancer progression from that attributable primarily to the adverse effects of treatments. We searched PubMed from inception to Aug 3, 2022, for English-language research articles using a combination of the following keywords: "childhood cancer" AND ("proportion cured" OR "cure fraction" OR "cure model"). We found only one study reporting cure fraction for acute lymphoblastic leukaemia. In the past 20 years, most European countries have increased registration from partial to national, with coverage now accounting for up to 85% of the childhood population (about 70 million children), making it possible to more accurately describe the burden of childhood cancer in Europe. Moreover, the long period of observation of EUROCARE has allowed long-term survival and the proportion of cured children to be more accurately estimated to better inform on the progress of childhood cancer care.

Added value of this study

This study provides updated population-based estimates of childhood cancer survival variability over time and within 31 European countries, with much wider representativeness, compared with the past, of eastern European countries. 5-year survival for all childhood cancer combined increased by three percentage points in 7 years, and increases varied among individual childhood cancer entities. Survival disparities among countries persisted and were larger for some cancer types that have a poor prognosis and require complex treatments. To our knowledge this study presents, for the first time, cure fraction estimates for patients with childhood cancer, which increased over time. A new survival model estimated a long-term mortality rate attributable to causes other than the diagnosed cancer of about two per 1000 patients per year, ranging from about zero for retinoblastoma to about ten for CNS malignant cancers. Model-based estimates of 15-year survival and their increase over time were provided. These new indicators are aimed at improving understanding of progress in Europe and at stimulating future research from new observational and population-based studies.

Implications of all the available evidence

The continuing but not huge survival increases in the study period, and the persisting large disparities in prognosis across European countries, indicate that much can be gained by contrasting inequalities in access to the best currently available diagnostic procedures and treatments. The proportion of cured patients should become a further indicator of progress in cancer care. Collaboration between the clinical and epidemiological world must be intensified to be more effective with actions at the European and country level. Stage, treatments, and their long-term side-effects are important grounds for such a collaboration. The International Benchmarking of Childhood Cancer Survival by Stage Project (BENCHISTA) might show a successful way to achieve such a collaboration. BENCHISTA will promote the widespread adoption among cancer registries of the Toronto guideline to code stage at diagnosis in childhood cancer. The project is designed to understand the reasons for variation in childhood cancer survival among countries and to highlight any areas that require improvement in childhood cancer care.

it possible to assess long-term survival and temporal patterns and to estimate the proportion of children who were cured of cancer.

Through the EUROCARE-6 study, covering 85% of the European paediatric population, we present new data, showing progress in survival for childhood cancer cases diagnosed during the period 2000–13 and geographical differences for the most recent period of diagnosis. In addition, we assess long-term survival (up to 15 years) and, to our knowledge, for the first time, the cure fraction (the proportion of patients no longer at risk of dying from progression or relapse of the diagnosed cancer) for all the major groups of paediatric cancers.

Methods

Study design and data collection

EUROCARE-6 is a population-based study. Data on 137 421 cancers in European children (aged 0–14 years) diagnosed from Jan 1, 2000, to Dec 31, 2013, and followed up for vital status to Dec 31, 2014, were provided by 80 cancer registries from 31 European countries, covering on average 85% of the European paediatric population (69 161 377 of 81 171 700 children in the year 2010). All cancer registries collected individual data according to a standardised protocol[9] and, after pseudonymisation, sent them for centralised analysis. After applying quality check procedures, 135 847 childhood cancer cases were considered valid for survival analysis. In addition, each cancer registry provided life tables showing the background mortality in the general population of the administrative territory covered by the registry.

The participating countries were Austria, Belgium, Bulgaria, Croatia, Cyprus, Czechia, Denmark, England, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Malta, the Netherlands, Northern Ireland, Norway, Poland, Portugal, Scotland, Slovakia, Slovenia, Spain, Switzerland, and Wales. All but three countries had national population-based cancer registration. Italy and Spain had partial registration covering 54% and 60%, respectively, of

the entire childhood population. Portugal, on the other hand, thanks to the aggregation of three registries, had total registration covering the entire paediatric population, excluding the Azores. Data from nine specialised childhood cancer registries were included: the childhood cancer registries of Germany, Hungary, France (solid cancers and haematological cancers), Greece (leukaemia, lymphoma, and CNS tumours diagnosed since 2010), Switzerland, and Piedmont (Italy); the Spanish Registry of Childhood Tumours (RETI-SEHOP) covering Madrid and Barcelona; and the Comunitat Valenciana Childhood Cancer Registry covering Alicante, Castellon, and Valencia.

We grouped cancers using the major categories defined by the International Classification of Childhood Cancers (ICCC), third edition,[10] and also analysed all cancers combined. We provide the main analyses for malignant cases only. Tumours of uncertain and benign behaviour of the CNS and intracranial neoplasms are described in the appendix (p 6) only, because not all countries collected these data or sent them to the EUROCARE-6 project. We excluded pilocytic astrocytomas coded as malignant from the malignant tumour analyses because they are defined by the third edition of the International Classification of Diseases for Oncology (ICD-O-3) as borderline behaviour tumours.

To assess differences in 5-year observed survival by country for each childhood cancer, we analysed survival in the period of follow-up 2010–14 because 5 years of follow-up data were not available for patients diagnosed in 2010–13. These estimates include the survival of 4-year cohorts of patients diagnosed from 2006–09 to 2010–13 and followed up to 2014 (period analysis;[11] appendix p 2), based on data from 80 cancer registries covering at least the whole period 2007–10.

To evaluate time trends, we estimated 5-year observed survival in 2004–14, during three time periods: patients in follow-up in 2004–06, 2007–09, and 2010–14, based on cases diagnosed in 2000–06, 2003–09, and 2006–13, respectively (trend analysis; appendix p 2). We divided time into three intervals of different follow-up length to include more cases in the most recent period. We estimated proportions of cured patients and modelled and projected 15-year survival from observed survival data of four diagnosis cohorts (1998–2001, 2002–05, 2006–09, and 2010–13; long-term analysis). Time trends and long-term survival analyses were based on 62 cancer registries covering at least the whole period 2001–10.

Statistical analysis

We calculated observed survival by European countries and for the pool of all participating cancer registries without adjusting for country-specific all-cause mortality because background mortality for children in Europe is very low and does not substantially differ among countries. Since sufficient follow-up was not available for recently diagnosed patients, we computed survival estimates using the actuarial method and adopted the period approach[11] to provide more up-to-date and reliable predictions of 5-year cohort survival.

The age distribution of patients with cancer can vary between countries and over time. Therefore, to improve comparability, we calculated age-standardised survival estimates for all ages combined using the direct method. For the trend and by-country analyses, we derived weights from the cancer-specific age distribution of each ICCC category of all children diagnosed during 2000–13 and 2006–13, respectively (appendix pp 9–10). Moreover, since casemix differences can affect comparisons among countries and over time for all cancers combined, we calculated 5-year observed survival adjusting for casemix using 11 diagnostic categories (acute lymphoid leukaemias, acute myeloid leukaemias, Hodgkin lymphomas, non-Hodgkin lymphomas, CNS tumours, neuroblastoma, nephroblastoma, retinoblastomas, bone tumours, soft tissue sarcomas, and all remaining cancers in the ICCC list).[1] We were unable to estimate age and casemix-adjusted survival for 15 countries due to the small number of cases in some age and cancer-specific strata, so they are not presented as results. We calculated the I^2 statistic to provide a synthetic metric to describe heterogeneity among countries for different cancers. I^2 is the most common measure for heterogeneity that describes the percentage of total variation across countries due to heterogeneity rather than chance.[12] We performed the Z test to evaluate differences between the first and last period analysed in the time-trend analysis.

We used a Cox proportional hazards model for each diagnostic group to obtain the hazard ratio of death for each period adjusted for country, sex, and age group. The proportional-hazards assumption was tested with Schoenfeld residuals; we do not present the results for six diagnostic groups that fail to comply with this assumption. The interactions between periods and age classes for the cancer selected were not included because they were not statistically significant (data not shown). The significance threshold for p values was set at 0·05.

To estimate the cure fraction and projected 15-year survival for the most recent cohorts, we applied a variant of a standard mixture cure model to observed survival data from four diagnosis cohorts including up to 15 years of follow-up, where available. Standard mixture cure models assume that patients are divided into cured patients—ie, those who do not die of cancer—and patients who were expected to die of cancer, with a related estimable risk of death distributed according to a pre-specified parametric distribution.[13] Such models assume that cumulative relative survival will plateau at a particular time after diagnosis (ie, on achieving cure), and patients surviving to this time are expected to have the same life expectancy as their cancer-free contemporaries. Since relative survival for children practically coincides with observed survival, we applied the mixture cure model to observed survival data. For several childhood cancers,

	Eligible cases diagnosed in 2000–13	Invalid cases excluded from survival analysis				Valid cases for survival analysis	Data quality indicators						Analysis type*
		Major errors	Death certificate only	Incidentally detected at autopsy	Alive cases with unknown survival time		Multiple primaries	Minor errors†	Lost to follow-up‡	Microscopic confirmation	Morphology not otherwise specified§	Non-malignant CNS tumours¶	
Austria	2411	0	13 (0·5%)	0	0	2398	25 (1·0%)	94 (3·9%)	0/569	2323 (96·9%)	103 (4·3%)	0/464	Period; trend; long term;
Belgium	3356	0	0	1 (<0·1%)	59 (1·8%)	3296	28 (0·8%)	112 (3·4%)	13/1023 (1·3%)	3153 (95·7%)	53 (1·6%)	362/770 (47·0%)	Period
Bulgaria	1947	2 (0·1%)	93 (4·8%)	0	0	1852	5 (0·3%)	106 (5·7%)	0/360	1763 (95·2%)	120 (6·5%)	37/311 (11·9%)	Period; trend; long term
Croatia	1608	0	5 (0·3%)	0	9 (0·6%)	1594	7 (0·4%)	83 (5·2%)	0/309	1491 (93·5%)	207 (13·0%)	39/356 (11·0%)	Period; trend; long term
Cyprus	211	1 (0·5%)	7 (3·3%)	0	0	203	0	13 (6·4%)	0/72	190 (93·6%)	5 (2·5%)	0/19	Period
Czechia	2401	1 (<0·1%)	19 (0·8%)	60 (2·5%)	9 (0·4%)	2312	18 (0·8%)	388 (16·8%)	0/517	2080 (90·0%)	217 (9·4%)	73/456 (16·0%)	Period; trend; long term
Denmark	2327	1 (<0·1%)	0	1 (<0·1%)	1 (<0·1%)	2324	44 (1·9%)	85 (3·7%)	2/535 (0·4%)	2175 (93·6%)	362 (15·6%)	363/597 (60·8%)	Period; trend; long term
Estonia	412	0	2 (0·5%)	1 (0·2%)	0	409	1 (0·2%)	15 (3·7%)	1/88 (1·1%)	393 (96·1%)	17 (4·2%)	55/119 (46·2%)	Period; trend; long term
Finland	2147	20 (0·9%)	0	2 (<0·1%)	0	2125	21 (1·0%)	70 (3·3%)	0/492	2074 (97·6%)	77 (3·6%)	290/529 (54·8%)	Period; trend; long term
France	24 552	24 (<0·1%)	0	7 (<0·1%)	46 (0·2%)	24 475	103 (0·4%)	827 (3·4%)	221/5740 (3·9%)	23 138 (94·5%)	376 (1·5%)	2660/5950 (44·7%)	Period; trend; long term
Germany	25 156	2 (<0·1%)	0	0	667 (2·7%)	24 487	304 (1·2%)	1024 (4·2%)	525/5844 (9·0%)	23 302 (95·2%)	311 (1·3%)	2417/5825 (41·5%)	Period; trend; long term
Greece	1763	27 (1·5%)	0	0	0	1736	4 (0·2%)	17 (1·0%)	1/354 (0·3%)	1701 (98·0%)	13 (0·7%)	56/192 (29·2%)	Period; trend; long term
Hungary	3236	9 (0·3%)	0	1 (<0·1%)	2 (<0·1%)	3224	22 (0·7%)	574 (17·8%)	42/686 (6·1%)	3138 (97·3%)	19 (0·6%)	300/838 (35·8%)	Period; trend; long term
Iceland	129	0	0	1 (0·8%)	0	128	0	3 (2·3%)	0/28	115 (89·8%)	11 (8·6%)	30/46 (65·2%)	Period; trend; long term
Ireland	1782	0	3 (0·2%)	2 (0·1%)	0	1777	13 (0·7%)	133 (7·5%)	0/387	1658 (93·3%)	52 (2·9%)	184/448 (41·1%)	Period; trend; long term
Italy (cancer registry pool)‖	8662	0	6 (<0·1%)	1 (<0·1%)	17 (0·2%)	8638	44 (0·5%)	396 (4·6%)	53/2358 (2·3%)	7784 (90·1%)	695 (8·4%)	688/1791 (38·4%)	Period; trend; long term
Latvia	633	2 (0·3%)	31 (4·9%)	7 (1·1%)	0	593	4 (0·7%)	39 (6·6%)	0/88	537 (90·6%)	95 (16·0%)	3/135 (2·2%)	Period; trend; long term
Lithuania	873	1 (0·1%)	10 (1·1%)	0	0	862	5 (0·6%)	56 (6·1%)	0/157	823 (95·5%)	51 (5·9%)	13/147 (8·8%)	Period; trend; long term
Malta	169	5 (3·0%)	2 (1·2%)	0	0	162	1 (0·6%)	16 (9·9%)	0/44	153 (94·4%)	3 (1·9%)	6/29 (20·7%)	Period; trend; long term

(Table 1 continues on next page)

	Eligible cases diagnosed in 2000–13	Invalid cases excluded from survival analysis				Valid cases for survival analysis	Data quality indicators						Analysis type*
		Major errors	Death certificate only	Incidentally detected at autopsy	Alive cases with unknown survival time		Multiple primaries	Minor errors†	Lost to follow-up‡	Microscopic confirmation	Morphology not otherwise specified§	Non-malignant CNS tumours¶	
(Continued from previous page)													
Netherlands	6621	114 (1·7%)	0	17 (0·3%)	0	6490	121 (1·9%)	242 (3·7%)	0/1505	6097 (93·9%)	112 (1·7%)	787/1635 (48·1%)	Period; trend; long term
Norway	2115	26 (1·2%)	2 (0·1%)	2 (0·1%)	0	2085	28 (1·3%)	161 (7·7%)	0/478	1942 (93·1%)	130 (6·2%)	344/647 (53·2%)	Period; trend; long term
Poland	10263	3 (<0·1%)	62 (0·6%)	3 (<0·1%)	54 (0·5%)	10141	58 (0·6%)	270 (2·7%)	0/2490	9346 (92·2%)	1420 (14·0%)	0/1945	Period; trend; long term
Portugal (cancer registry pool)‖	2504	3 (0·1%)	0	0	4 (0·2%)	2497	9 (0·4%)	62 (2·5%)	0/667	2409 (96·5%)	72 (2·9%)	0/417	Period; trend; long term
Slovakia	1526	0	7 (0·5%)	11 (0·7%)	0	1508	12 (0·8%)	179 (11·9%)	0/430	1475 (97·8%)	47 (3·1%)	130/356 (36·5%)	Period; trend; long term
Slovenia	544	0	0	1 (0·2%)	0	543	8 (1·5%)	42 (7·7%)	0/133	532 (98·0%)	15 (2·8%)	31/108 (28·7%)	Period; trend; long term
Spain (cancer registry pool)‖	7292	16 (0·2%)	6 (<0·1%)	6 (<0·1%)	29 (0·4%)	7235	35 (0·5%)	360 (5·0%)	131/1869 (7·0%)	6734 (93·1%)	168 (2·3%)	499/1518 (32·9%)	Period; trend; long term
Switzerland	2658	0	0	1 (<0·1%)	2 (<0·1%)	2655	27 (1·0%)	112 (4·2%)	20/603 (3·3%)	2488 (93·7%)	42 (1·6%)	265/604 (43·9%)	Period; trend; long term
England	16727	1 (<0·1%)	14 (<0·1%)	0	0	16712	274 (1·6%)	683 (4·1%)	0/3647	15550 (93·0%)	327 (2·0%)	951/3494 (27·2%)	Period; trend; long term
Northern Ireland	772	0	2 (0·3%)	0	0	770	10 (1·3%)	40 (5·2%)	0/171	630 (81·8%)	81 (10·5%)	105/215 (48·8%)	Period; trend; long term
Scotland	1651	0	3 (0·2%)	2 (0·1%)	0	1646	15 (0·9%)	204 (12·4%)	1/328 (0·3%)	1524 (92·6%)	62 (3·8%)	96/324 (29·6%)	Period; trend; long term
Wales	973	0	3 (0·3%)	0	0	970	32 (3·3%)	41 (4·2%)	0/267	809 (83·4%)	87 (9·0%)	81/232 (34·9%)	Period; trend; long term
Total EUROCARE-6 pool (80 cancer registries)	137421	258 (0·2%)	290 (0·2%)	127 (0·1%)	899 (0·7%)	135847	1278 (0·9%)	6444 (4·7%)	1098/32239 (3·4%)	127527 (93·9%)	5350 (3·9%)	10865/30517 (35·6%)	..

Data are n, n (%), or n/N (%). For invalid cases, the denominator for the percentages is the number of eligible cases. For data quality indicators, the denominator for the percentages is the number of valid cases, unless specified otherwise. Age at diagnosis was 0–14 years. *Trend and long-term analysis refers to inclusion of cancer registries that covered at least the whole period 2001–10; period analysis refers to inclusion of cancer registries that covered at least the whole period 2007–10; time trends and long-term survival analyses were based on 62 cancer registries and period analyses were based on 80 cancer registries. †Minor errors: unlikely combinations of site–morphology, age–site, or sex-site. ‡Proportion of patients diagnosed during 2005–08, censored before Dec 31, 2013, with less than 5 years of follow-up; the proportion is calculated for cases diagnosed during 2005–07 in Croatia, where the follow-up closing date was Dec 31, 2012. §Refers to the following categories in the International Classification of Childhood Cancer (ICCC), third edition: unspecified and other specified leukaemias; unspecified lymphomas; unspecified intracranial and intraspinal neoplasms; unspecified malignant renal tumours; unspecified malignant hepatic tumours; unspecified malignant bone tumours; unspecified soft tissue sarcomas; other unspecified malignant tumours. ¶Proportion of patients diagnosed with non-malignant cancers of the CNS (defined using the ICCC category of CNS and miscellaneous intracranial and intraspinal neoplasms) out of the total cases of tumours of the CNS; pilocytic astrocytomas were included as non-malignant even when coded as malignant. ‖In Spain, Portugal, and Italy, registries are local rather than national, and were pooled together; in Portugal the three registries participating in EUROCARE cover the whole country (excluding the Azores), which is not the case in Spain and Italy.

Table 1: **Data checks on childhood cancer cases diagnosed during 2000–13 in Europe included in EUROCARE-6**

however, no such point of cure was evident from our data due to the risk of non-cancer mortality in the long term. Conventional cure models were therefore not applicable or fitted the data poorly, because the definition of cure and the assumption underlying the conventional model did not fit the childhood cancer. We therefore also fitted a different model for all childhood cancer entities by adding an extra parameter to account for long-term constant risk of non-cancer death, assumed to be common across countries, periods, ages, and sexes. Accordingly, we assumed both patients who were or were not cured of cancer to have a constant mortality rate attributable to long-term risk of non-cancer death. Hence, in this model, the cure fraction represents exactly the fraction of patients who did not die because of cancer. The cumulative survival derived from the model is given by the expression:

$$S_k(t) = [\pi_k + (1-\pi_k) S_u(t)] \exp(-\mu t)$$

For **SEER*Stat** see https://seer.cancer.gov/seerstat/

where $S_k(t)$ is the observed survival at time t of the k-th cohort of diagnosis, π_k is the cohort-specific cure fraction, μ is the long-term risk of death affecting both cured and uncured patients, and $S_u(t)$ is the cumulative survival function of uncured patients due to cancer mortality. We used both Weibull and log-normal distributions to model the failure time of fatal cases. By definition, μ potentially affects all patients at diagnosis but was most evident in patients who had been cured, since the direct effect of cancer mortality in uncured patients was predominant. The model assumes that only the proportion π_k varies across the cohorts of diagnosis, whereas the survival function $S_u(t)$ and the long-term risk are constant over the cohorts of diagnosis. We estimated model parameters by the maximum likelihood method, using grouped data assuming a binomial error structure. Results are shown from either the Weibull or log-normal survival function $S_u(t)$, depending on which fit best in terms of higher likelihood. We removed parameter μ, collapsing to the standard cure model, when its contribution to likelihood was not significant. We performed the Z test to evaluate differences between cure fraction estimated in the first and last period.

For statistical analyses, we used SEER*Stat software (version 8.3.9) and STATA version 17.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

For the survival analysis, we included 135 847 childhood cancer cases, after excluding major errors (missing, invalid, or inconsistent information: 258 [0·2%] of 137 421 childhood cancer cases), cases registered only from a death certificate (290 [0·2%] of 137 421) or diagnosed incidentally at autopsy (127 [0·1%] of 137 421), and patients alive with unknown survival time (899 [0·7%] of 137 421; table 1). The proportion of microscopically verified cases was 127 527 (93·9%) of 135 847 childhood cancer cases overall and was above 90% in all countries except Northern Ireland, Iceland, and Wales. The proportion of non-malignant CNS tumours ranged from zero, in four countries, to over 50% in each of the four Nordic countries (Norway, Iceland, Finland, and Denmark). 1098 (3·4%) of 32 239 children diagnosed from Jan 1, 2005, to Dec 31, 2008, had been censored before 5 years. For most cancer registries, this proportion was less than 1%, exceeding 5% for only three registries (Germany, Hungary, and Spain). Overall, 5350 (3·9%) of 135 847 childhood cancer cases had an unspecified ICCC category, with this proportion being more than 10% in five countries (Croatia, Denmark, Latvia, Poland, and Northern Ireland) (table 1).

Figure 1 shows 5-year age-standardised survival trends, by diagnostic group and for all cancers combined, in the period 2004–14. For all cancers combined, 5-year survival linearly and significantly improved over time from 78% (95% CI 78–79) in 2004–06 to 81% (81–82) in 2010–14. The increases over time were statistically significant for seven of 12 cancer types assessed. Acute myeloid

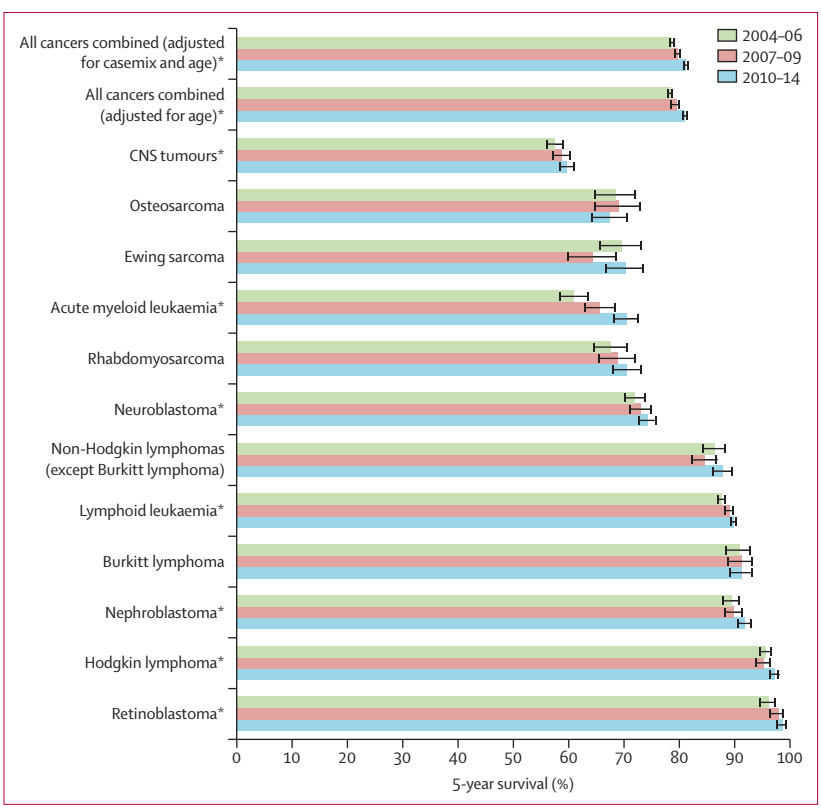

Figure 1: **Age-adjusted 5-year observed survival for all childhood cancers combined and major ICCC entities for the follow-up periods 2004–06, 2007–09, and 2010–14**

Errors bars show 95% CIs. ICCC=International Classification of Childhood Cancer. *Significant differences between the first and the last period defined using p<0·05.

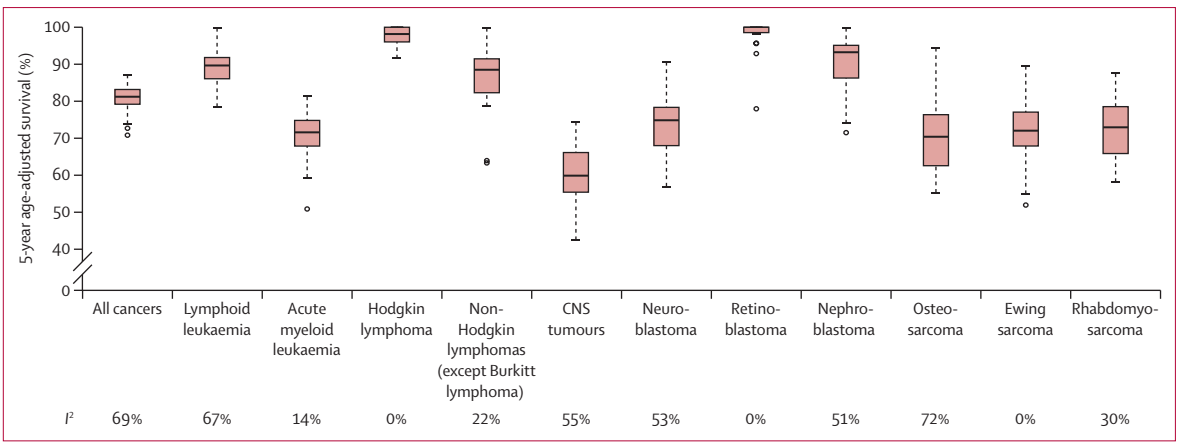

Figure 2: **5-year age-adjusted survival, period analysis 2010–14, by all cancers combined and major ICCC entities**
The boxes indicate the IQR and the centre lines represent the medians of the distributions. The whiskers indicate variability outside the upper and lower quartiles and are calculated by multiplying the IQR by 1·5. The circles denote outliers. Heterogeneity among countries is indicated with the I^2 statistic.

leukaemia showed the greatest improvement in survival over time (from 61% [95% CI 58–63] to 70% [68–73], p<0·0001). Survival improvement for CNS tumours was entirely due to ependymoma, particularly for children aged 1–4 years (data not shown). Progress was concentrated in the high-risk ages for neuroblastoma (1–14 years; data not shown). For osteosarcoma there were no significant changes over time. The increases were instead small and not significant for Ewing sarcoma, Burkitt lymphoma, non-Hodgkin lymphomas, and rhabdomyosarcomas. Similar results were found in multivariate analysis when accounting for age, sex, and country (appendix p 11). From the same analysis, we found that sex was not a significant prognostic factor for the cancers for which the proportional hazard assumptions were verified (Hodgkin lymphomas, non-Hodgkin lymphomas, Burkitt lymphoma, osteosarcomas, Ewing sarcoma, and rhabdomyosarcomas). By 2010–14, 5-year survival for all cancers combined was similar for boys and girls, and slightly higher for children aged 1–4 years at diagnosis (83% [95% CI 82–84]) than for infants or older children (both 80%; appendix pp 12–13). Excluding retinoblastoma, survival varied by age across childhood cancer. Among infants (aged <1 year), survival was lowest for lymphoid and myeloid leukaemia, CNS tumours, and Ewing sarcoma, and highest for neuroblastoma. Patients with lymphoid leukaemia or rhabdomyosarcoma aged 10–14 years had lower 5-year survival than younger patients with the same disease, excluding infants with lymphoid leukaemia (appendix p 13).

Crude 5-year survival estimates by country and cancer type, and a bar chart plotting the country-specific 5-year age-adjusted estimates for all childhood cancer, are shown in the appendix (pp 3–8, 14); for all cancer combined, age-adjusted 5-year survival ranged from 71% (95% CI 60–79) in Estonia to 87% (77–93) in Cyprus. Figure 2 shows the distribution of the age-standardised 5-year survival during 2010–14 for childhood cancer with heterogeneity (I^2) among countries. The I^2 statistic was

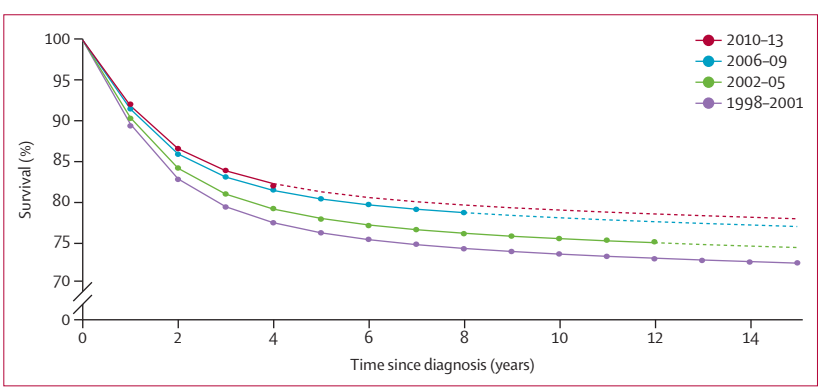

Figure 3: **Observed and modelled survival for all cancers combined in the EUROCARE-6 pool, by period of diagnosis**
Solid dots denote observed survival, solid lines denote modelled survival, and dotted lines represent survival projections to 15 years.

69% for all cancers combined, indicating a high percentage of total variation across countries due to heterogeneity rather than random variation. Among the haematological tumours, heterogeneity was high for lymphoid leukaemia (I^2=67%), but low for non-Hodgkin lymphoma (I^2=22%), acute myeloid leukaemia (I^2=14%), and Hodgkin lymphoma (I^2=0%; figure 2). Differences were more pronounced for solid tumours, with high heterogeneity (I^2>50%) for osteosarcomas, CNS tumours, neuroblastoma, and nephroblastoma. Retinoblastoma and Ewing sarcoma were the solid tumours with the lowest percentage variation due to between-country heterogeneity (I^2=0). The box plot shows a very small variation for retinoblastoma, while we can conclude that the dispersion observed for Ewing sarcoma is attributable to chance and not to real heterogeneity (I^2=0%; figure 2). Adjustment of survival by age and casemix was also done. Such adjustment reduced geographical differences because 15 countries (Croatia, Cyprus, Czechia, Estonia, Finland, Greece Iceland,

	Distribution	Number of cases	Long-term risk of death* (95% CI)	LRS	1998–2001			2002–05			2006–09			2010–13		
					Cure fraction, % (95% CI)	SE	15-year survival projection	Cure fraction, % (95% CI)	SE	15-year survival projection	Cure fraction, % (95% CI)	SE	15-year survival projection	Cure fraction, % (95% CI)	SE	15-year survival projection
All childhood cancers	Log-normal	126729	1·9 (1·4–2·4)	56·4	74% (73–75)	0·5%	72·4%	76% (75–77)	0·5%	74·3%	79% (78–80)	0·5%	77·0%	80% (79–81)†	0·6%	77·9%
Lymphoid leukaemia	Weibull	33857	1·8 (1·0–2·5)	18·3	84% (82–86)	1·2%	81·9%	87% (85–89)	1·2%	87·1%	89% (87–92)	1·3%	86·9%	90% (87–93)†	1·5%	87·3%
Acute myeloid leukaemia	Log-normal	6355	1·5 (0·0–3·1)	4·6	58% (54–61)	1·6%	56·3%	59% (56–61)	1·3%	57·4%	66% (63–68)	1·4%	64·2%	70% (67–73)†	1·7%	68·3%
Hodgkin lymphoma	Weibull	6692	2·0 (1·2–2·8)	10·9	96% (86–100)	5·3%	93·5%	97% (88–100)	4·6%	93·8%	97% (88–100)	4·4%	94·0%	98% (83–100)	8·0%	95·4%
Non-Hodgkin lymphoma	Weibull	5342	3·1 (2·0–4·2)	23·4	82% (77–86)	2·2%	78·0%	86% (81–90)	2·1%	81·7%	87% (83–91)	2·2%	83·0%	89% (84–94)†	2·8%	85·0%
Burkitt lymphoma‡	Log-normal	3140	..	..	86% (80–92)	3·1%	86·0%	89% (83–94)	2·8%	89·1%	91% (85–96)	2·9%	90·7%	91% (84–98)	3·5%	91·1%
CNS tumours	Log-normal	20175	10·7 (8·7–12·7)	87·2	57% (55–59)	1·1%	48·5%	58% (56–60)	1·0%	49·6%	61% (59–63)	1·0%	51·8%	60% (58–63)†	1·1%	51·4%
Neuroblastoma	Weibull	9478	2·9 (1·7–4·2)	33·7	69% (66–72)	1·4%	65·8%	70% (68–72)	1·2%	67·0%	72% (70–75)	1·3%	69·2%	74% (71–78)†	1·6%	71·3%
Retinoblastoma	Weibull	3370	0·8 (0·0–1·5)	3·4	97% (83–100)	7·4%	96·2%	97% (86–100)	5·8%	96·0%	98% (83–100)	7·8%	96·8%	99% (74–100)	12·8%	97·9%
Nephroblastoma	Weibull	7055	1·5 (0·8–2·1)	30·7	89% (85–94)	2·5%	87·4%	89% (85–92)	1·9%	86·7%	92% (87–96)	2·2%	89·7%	92% (87–97)	2·7%	90·2%
Osteosarcoma§	Log-normal	3033	..	0·5	60% (54–64)	2·2%	60·4%	62% (59–66)	1·9%	62·8%	61% (57–65)	2·0%	61·7%	61% (55–67)	3·0%	61·6%
Ewing sarcoma	Log-normal	2813	7·0 (2·2–11·7)	8·6	64% (58–70)	3·1%	57·3%	66% (60–71)	2·8%	59·4%	65% (60–71)	2·7%	58·9%	73% (65–80)†	3·7%	65·5%
Rhabdomyosarcoma	Weibull	4423	4·4 (2·5–6·2)	58·7	68% (64–72)	2·1%	63·8%	68% (64–71)	1·7%	63·4%	70% (67–74)	1·8%	65·9%	71% (66–75)	2·2%	66·3%

95% CIs are asymptotic. ICCC=International Classification of Childhood Cancer. LRS=χ^2 likelihood ratio statistic for the inclusion of the long-term risk of death (μ). SE=standard error. *Number of deaths attributable to causes other than the diagnosed cancer per 1000 patients per year. †Significant differences between the cure fraction estimated in the first and the last period defined using p<0·05. ‡Full model did not converge; the reported results came from the standard cure model. §Parameter μ removed due to a large standard error; the reported results came from the standard cure model.

Table 2: **Results of cure models, period 1998–2013: long-term risk of death (μ), trend of cure fraction, and 15-year survival projections by all cancers combined and major ICCC entities**

Ireland, Lithuania, Latvia, Malta, Slovakia, Slovenia, Northern Ireland, and Wales) were excluded due to the small number of cases in some age and cancer-specific strata; therefore, these data are not shown.

Figure 3 and table 2 show the results of the long-term survival analysis. 15-year survival for children with cancer diagnosed during 1998–2001 was 72% (95% CI 72–73) and was estimated to improve to 78% for those diagnosed in the period 2010–13 (table 2). The survival curve for all cancers combined in figure 3 continues to decrease for each of the four periods slightly at a nearly constant rate even after 10 years. The cure fraction of patients could be estimated when accounting for constant long-term risk (μ); for all cancers combined it rose significantly over time from 74% (95% CI 73–75) in 1998–2001 to 80% (79–81) in 2010–13.

For the diagnosis period 2010–13, the estimated cure fraction was high for retinoblastoma (99%; 95% CI 74–100), Hodgkin lymphoma (98%; 83–100), nephroblastoma (92%; 87–97), Burkitt lymphoma (91%; 84–98), lymphoid leukaemia (90%; 87–93), and non-Hodgkin lymphoma (89%; 84–94). It was the lowest for CNS tumours (60%; 58–63). The increase in the cure fraction during 1998–2013 was statistically significant for neuroblastoma and for haematological malignancies, apart from Hodgkin lymphoma and Burkitt lymphoma. The difference between the cure fraction and 15-year survival, attributable to long-term mortality from other causes, was only 2% for all cancer types, but the gap was much wider for CNS tumours (9%) and Ewing sarcoma (7%) in the latest period estimates.

We estimated the yearly long-term non-cancer mortality rate for all children diagnosed with cancer to be 1·9 per 1000 survivors (95% CI 1·4–2·4), becoming the predominant risk of death after 10 years from diagnosis. By comparison, the expected mortality in a comparable sample of the general population, calculated from life tables of all-cause mortality rates, was around 0·2 per 1000 on average. Patients' long-term non-cancer mortality rate was significantly different from zero for almost all the considered entities. We found high long-term mortality risks for CNS tumours (10·7; 95% CI 8·7–12·7), Ewing sarcoma (7·0; 2·2–11·7), rhabdomyosarcoma (4·4; 2·5–6·2), non-Hodgkin lymphoma (3·1; 2·0–4·2), and neuroblastoma (2·9; 1·7–4·2). We observed low values for retinoblastoma (0·8; 0·0–1·5), nephroblastoma (1·5; 0·8–2·1), and acute myeloid leukaemia (1·5; 0·0–3·1; table 2). The model that better fits the observed data was detected using the likelihood ratio test and is reported in table 2. The results came from the standard cure model, without the inclusion of the parameter μ, in the analysis of Burkitt lymphoma because the full model did not converge, and of osteosarcoma because we found an implausible μ estimate with a large standard error. Overall observed survival rates from both cancers remained constant after 11 years from diagnosis (data not shown), and were therefore well fitted by the standard cure model.

Discussion

We analysed survival trends and long-term survival of European children with cancers diagnosed during 1998–2013. Survival significantly increased by 2% or more over time for all cancers combined and for lymphoid leukaemias, neuroblastoma, retinoblastoma, CNS tumours, nephroblastoma, and acute myeloid leukaemia. During the study years, treatment refinements (eg, risk-adapted therapies for leukaemias and radiotherapy for ependymoma in children younger than 3 years,[14] and reductions in toxicity and protocol intensification for high-risk groups) became more prevalent; systemic and centralised treatment were better organised; and adequate supportive care services became better implemented, thus reducing infection and malnutrition, and promoting psychosocial support. These improvements might have contributed to the progress in cancer survival reported.

Large geographical disparities in population-based childhood cancer survival have been shown in the past.[1,15] Unfortunately, significant differences across countries still persisted during the study period assessed in this study. Using a synthetic indicator to express the heterogeneity is important as we can conclude, for example, that the dispersion observed for Ewing sarcoma is attributable to chance and not to real heterogeneity (I^2=0%; figure 2).

The extent to which survival differences result from different distributions of stage at diagnosis or unequal access to effective treatments is still uncertain, because stage information in the contributing cancer registries was not sufficiently complete to be assessed in this study.

Our two-component mixture model was designed to capture the long-term risk of death in children diagnosed with cancer, due to side-effects of cancer treatments, second cancers, risk factors associated with the first cancer carrying an extra risk of death for patients, and the small background mortality (mainly from external or infective causes, about 0·2 per 1000 patients per year) to which individuals in the considered ages of the general population are also subjected. To our knowledge, this is the first application of such a model to childhood cancer survival analysis. Due to the limited follow-up for more recently diagnosed cohorts, we assumed the long-term risk component and parameters defining times to cancer death to be constant within the 15-year study period. Only the cure fraction was allowed to vary across diagnosis cohorts. The model was in good agreement with observed data, while the standard cure model—based on a zero mortality rate at some time after diagnosis—fitted poorly for most of the considered cancer entities.

About two out of 1000 cancer survivors for all childhood cancer combined are estimated to die annually from other causes. This rate was an order of magnitude higher than the expected mortality in a comparable sample of the general population (about 0·2 per 1000 on average). Several studies have investigated the long-term mortality risk of patients with childhood cancer in terms of underlying causes of death, using death certificates and

clinical records. The US Childhood Cancer Survivor Study[16] estimated an excess rate of 2·5 per 1000 of dying from causes other than the first occurring cancer, for cohorts diagnosed during 1982–86 and followed up to 2002. This estimate is similar to the rate of 2·4 per 1000 reported by the pan-European PANCARE study,[6] including all children and adolescents diagnosed with cancer mostly during 1960–2008. However, published data do not allow the estimates to be disentangled by subperiods of diagnosis. Lower estimates of long-term mortality rate were reported by a Swiss population-based study[17] of children diagnosed during 2000–07 (1·4 per 1000), an Italian cohort of cancer survivors diagnosed during 1960–1999 (1·4 per 1000),[18] and a UK study[19] reporting a rate of 1·2 per 1000 for the treatment period 1990–2006. Other population-based studies[20,21] confirmed the persistence of long-term excess mortality attributable to second independent cancers or other causes, but the reported figures could not be compared with those of the present study. According to specific diagnosed cancer, we found the highest level of long-term mortality rates for CNS tumours, consistent with studies done in the UK[19] and in Scotland.[22] For other childhood cancers, the wide confidence intervals or a different classification precluded proper comparisons with all the other cited studies. However, most studies reported higher long-term mortality after diagnosis with Hodgkin lymphoma compared with our estimate (2·0 per 1000).

We interpreted the subgroup of children exposed only to long-term mortality risk as cancer-free patients (ie, those cured of cancer). Persistent excess mortality does not allow identification, for many childhood cancers, of a subgroup of patients defined as cured according to the usual criterion of having the same life expectancy as the general population. Here, we considered an alternative definition of cure[23] as those patients who were not expected to die from progression or relapse of the diagnosed cancer, despite a higher risk of dying from independent cancers or other non-cancer causes, compared with the general population. For these patients, prevention or early diagnosis of possible late effects of treatment and, less likely, secondary cancers, was estimated to be the most effective way to prevent the extra risk of deaths. Patients who were cured accounted for 80% among all patients diagnosed with childhood cancer.

The main strengths of this study are that it uses population-based data, it is more representative than previous rounds of EUROCARE (because more European registries met the European Network of Cancer Registries standard quality criteria), and it is the most comprehensive assessment of its kind, including the most recently available data from 85% of the overall European paediatric population (EU 27 plus the UK, Norway, Iceland, and Switzerland). The national registries of Cyprus and Greece were included the study. Completeness of coverage was reached by Belgium, Poland, and Czechia, but not by Italy and Spain. Coverage of eastern Europe has risen, but there is still room for improvement. Data from Sweden were not included because of stringent interpretation of the General Data Protection Regulation; however, childhood cancer survival is very high in Sweden, with similar rates to Finland and Norway.[1,24] Data from Luxembourg, Liechtenstein, and Romania were also missing. We do not expect the overall results to be affected because the absence of Sweden and Romania might compensate for each other, but we would expect the heterogeneity of survival in Europe to potentially increase by including these two countries.

The study has several limitations. The analysis does not include adolescents because the cancer distribution among adolescents differs to that of children[25] and because not all childhood population-based cancer registries collect data on patients diagnosed at the ages of 15–19 years. Morphologically poorly defined diagnoses (ie, cancers classed as not otherwise specified) were reported for 5350 (3·9%) of 135 847 childhood cancer cases. Percentages in five countries (Latvia, Denmark, Croatia, Poland, and Northern Ireland) were between 10% and 16%, but only Latvia had 5-year survival of 58% for the not-otherwise-specified cancers, which is lower than the EUROCARE-6 pool average. The proportion of not-otherwise-specified cancers did not affect the crude 5-year survival variability among countries, which ranged from 71% to 91% on inclusion of these cancers, and from 72% to 91% on their exclusion, while maintaining the same heterogeneity indicator I^2 (data not shown).

Childhood cancers are mostly classified in terms of morphology, as coded from the ICD-O-3 classification. Even if the same classification is used by all population-based registries, the lack of a centralised diagnostic service in many countries might affect comparability of data between and within countries. However, more than 30 years of European and worldwide analysis indicates a high level of standardisation, due to the collaboration among paediatric oncologists within national and international networks, the wide participation to multicentric clinical trials, and the common data checking criteria and tools adopted by population-based cancer registries.

The main comparability issue, also addressed in previous EUROCARE studies,[26] is the variability between countries in CNS tumour malignancy coding. For 17 of 31 countries, the proportion of borderline and benign CNS cases exceeded 30% of the CNS cases collected overall. Large gaps between countries in terms of survival of patients with CNS tumours, including or excluding borderline and benign CNS cases, were observed; however, the variability between countries does not seem to be affected by this exclusion.

Another limitation of this study is the absence of proper staging information at diagnosis, reported for most common cancers in the adult population. An ongoing pan-European project[27] is aiming to address this major question by promoting widespread adoption among cancer registries of the Toronto guidelines to code stage at diagnosis in childhood cancer. We are confident that routine collection

of childhood cancer stage will enable cancer registries to better monitor progress in future analyses.

In addition, the absence of treatment information hampers evaluation of how changes in therapy during this timeframe contribute to increased survival and makes it difficult to correctly interpret the long-term risk of death in children, since treatment exposure can determine late effects and related late mortality. The details of each treatment regimen are crucial for this purpose and even where they are not collected by population-based cancer registries, a systematic linkage between national clinical registries and population-based cancer registries might be the solution. Both long-term survival rates and cure fractions are derived from model estimates from 15-year follow-up survival data, without considering causes of death; they are also subject to all of the model's assumptions. Information on cause of death was not available for a fifth of all childhood cancer cases diagnosed during 1998–2013. Moreover, clinical reconsideration of the cause of death has shown that coding rules tend to overestimate the number of deaths attributed to cancer.[28] We expect that the long-term mortality rates and cure fractions yielded by the study can be confirmed or amended in the future, by use of longer follow-up and more complete, reliable information on cause of death from population-based cancer registries.

Finally, these results come 10 years after the end of the study period, with the risk that any recent advances in childhood cancer control might have been missed. Several factors contributed to delays in study conduct. First, the physiological lag in cancer registration in Europe, depending on country-specific operational conditions (resources, organisation of basic health-care flows, and computerisation of processes) resulted in different collection times among countries and in a delay to ensure maximum geographical representativeness (a major strength of the study). Further delays resulted from data quality controls, which involved multiple revisions and submissions but ensured maximum result comparability. In some countries, additional administrative steps were needed to ensure compliance with privacy regulations. Lastly, the limited dedicated resources available for such a comprehensive study also played a role.

Childhood cancer is an emotive topic. As treatment and outcomes improve, there is greater understanding of the long-term impact of childhood cancer diagnoses on child and adult populations. Timely, comprehensive surveillance of childhood cancer survival within Europe and worldwide is essential to bringing new insights into childhood cancer management, encouraging organisational changes within the health-care domain to bridge differences, and evaluating the response to these changes. With the exception of acute myeloid leukaemia, only small improvements in childhood cancer survival were seen during 2004–14. The reasons might include few breakthrough advances in treatments, unequal access to best treatments, and dispersion of patient referrals. Reducing geographical disparities and bringing childhood cancer survival in all countries closer to the best-performing countries will greatly impact the health of patients worldwide. For some small countries, many actions are ongoing[29,30] or envisaged, such as collaboration in international treatment protocols; commitments by local governments to approve new drugs; or reducing bureaucracy associated with accessing high-level treatments unavailable at home, such as proton radiotherapy or haematopoietic stem-cell transplantation. A study conducted with six national cancer registries showed that high dispersion of patients among hospitals (calculated using hospital volumes) increases the risk of death, particularly for CNS tumours.[31] Following the results of that study, Bulgaria is pursuing centralisation of treatment in two centres. The Slovenian Cancer Control Plan for 2022–26 envisions maintaining the high treatment centralisation already in place and aims to introduce comprehensive rehabilitation for patients with childhood cancer. Investment has been made in Poland to improve key dedicated hospital outcomes[32] and in the Netherlands, where centralisation has been implemented, with seven childhood cancer centres joining forces to create a single comprehensive childhood cancer centre.[33]

Centralisation also implies access to second opinion, which takes the form of a review of the histological diagnosis by an expert institution. This procedure is available in many—but not all—European countries, and for some—but not all—types of childhood cancer. We hope that access to second opinion in all the European countries can be facilitated thanks to the European Reference Networks or national or regional societies of paediatric oncology.

Furthermore, improvement is needed of the ICCC[10] and WHO classification of tumours, particularly CNS tumours,[34] to ensure better codification of cancers by the registries.

In conclusion, regular monitoring of childhood cancer survival and estimation of the cure fraction through population-based registry data is crucial in evaluating advances in cancer care for children. Cross-border care, twinning programmes, and implementation of efficient national and pan-European cancer control plans could help to narrow the survival gaps within Europe.

Contributors

GG, LB, RC, and SR drafted the protocol. GG, LB, and SR contributed to data acquisition. GG, LB, and SR had full access to all the data in the study, accessed and verified all the raw data, prepared the data, and performed quality control. LB, SR, and RC performed the analyses. All the authors checked the results. GG, LB, and RC drafted the report. All authors contributed to writing the final report, approved the version to be published, and had final responsibility for the decision to submit for publication. All members of the EUROCARE-6 Working Group had access to the results of all steps of data preparation, quality control, and analyses, and contributed to interpretation of the findings.

Declaration of interests

AC reports consulting fees from EUSA PHARMA outside of the submitted work. All others authors declare no competing interests.

Data sharing

We analysed pseudonymised data collected from 80 population-based cancer registries, after approval by the Ethics Committee of the National

Cancer Institute of Milan (INT73/16; April 21, 2016). We hold these data in trust from each participating registry for the statistical analyses agreed in the EUROCARE-6 protocol, available at http://www.eurocare.it. We are not permitted to share individual data. Aggregated level data, in the form of counts, rates, or survival proportions, can be only shared after express permission from the participating registries. These data should be requested by contacting the corresponding author or the Eurocare Secretariat (eurocare.secretariat@istitutotumori.mi.it).

Acknowledgments

Funding from the European Commission (Work Programme 2017, Grant Agreement 801520 HP-JA-2017, "Innovative Partnership for Action Against Cancer") was used to prepare and clean the EUROCARE-6 database. The salary of LB was granted by the Italian Association of Cancer Research (AIRC) under Investigator Grant 2020 ID.24933 (Principal Investigator GG). The French national cancer registry is supported by endowments from the French National Cancer Institute (INCa), the French Agency of Public Health (Santé publique France), and the National Institute of Health and Medical Research (INSERM) and by grants from the French National Cancer Institute (INCA2014–218) and the National Agency of Research (ANR-10-COHO-0009). The Slovenian cancer registry is supported by the research programme for comprehensive cancer control SLORApro (grant number P3-0429 by Slovenian Research Agency). The work of the Estonian cancer registry was supported by the Estonian Research Council (grant number PRG722). The contribution by LDM was supported by AIRC under grant number 21879. We thank Joanne Mary Fleming for English language editing.

References

1 Gatta G, Botta L, Rossi S, et al. Childhood cancer survival in Europe 1999-2007: results of EUROCARE-5—a population-based study. *Lancet Oncol* 2014; **15:** 35–47.

2 Francisci S, Guzzinati S, Dal Maso L, Sacerdote C, Buzzoni C, Gigli A. An estimate of the number of people in Italy living after a childhood cancer. *Int J Cancer* 2017; **140:** 2444–50.

3 Phillips SM, Padgett LS, Leisenring WM, et al. Survivors of childhood cancer in the United States: prevalence and burden of morbidity. *Cancer Epidemiol Biomarkers Prev* 2015; **24:** 653–63.

4 Olsen JH, Möller T, Anderson H, et al. Lifelong cancer incidence in 47,697 patients treated for childhood cancer in the Nordic countries. *J Natl Cancer Inst* 2009; **101:** 806–13.

5 Merzenich H, Baaken D, Schneider A, et al. Mortality risk among 5-year survivors of childhood cancer in Germany-Results from the CVSS study (Cardiac and Vascular late Sequelae in long-term Survivors of childhood cancer study). *Int J Cancer* 2022; **150:** 67–72.

6 Byrne J, Schmidtmann I, Rashid H, et al. Impact of era of diagnosis on cause-specific late mortality among 77 423 five-year European survivors of childhood and adolescent cancer: the PanCareSurFup consortium. *Int J Cancer* 2022; **150:** 406–19.

7 Gatta G, Rossi S, Foschi R, et al. Survival and cure trends for European children, adolescents and young adults diagnosed with acute lymphoblastic leukemia from 1982 to 2002. *Haematologica* 2013; **98:** 744–52.

8 Shah A, Stiller CA, Kenward MG, Vincent T, Eden TO, Coleman MP. Childhood leukaemia: long-term excess mortality and the proportion 'cured'. *Br J Cancer* 2008; **99:** 219–23.

9 EUROCARE Scientific Direction. EUROCARE-6 protocol for updating population-based cancer survival in Europe. June, 2015. http://www.eurocare.it/LinkClick.aspx?fileticket=99eJdjrCq18%3d&tabid=93 (accessed July 12, 2022).

10 Steliarova-Foucher E, Stiller C, Lacour B, Kaatsch P. International Classification of Childhood Cancer, third edition. *Cancer* 2005; **103:** 1457–67.

11 Brenner H, Hakulinen T. Up-to-date cancer survival: period analysis and beyond. *Int J Cancer* 2009; **124:** 1384–90.

12 Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003; **327:** 557–60.

13 Sposto R. Cure model analysis in cancer: an application to data from the Children's Cancer Group. *Stat Med* 2002; **21:** 293–312.

14 Koshy M, Rich S, Merchant TE, Mahmood U, Regine WF, Kwok Y. Post-operative radiation improves survival in children younger than 3 years with intracranial ependymoma. *J Neurooncol* 2011; **105:** 583–90.

15 Allemani C, Matsuda T, Di Carlo V, et al. Global surveillance of trends in cancer survival 2000-14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. *Lancet* 2018; **391:** 1023–75.

16 Mertens AC, Liu Q, Neglia JP, et al. Cause-specific late mortality among 5-year survivors of childhood cancer: the Childhood Cancer Survivor Study. *J Natl Cancer Inst* 2008; **100:** 1368–79.

17 Schindler M, Spycher BD, Ammann RA, Ansari M, Michel G, Kuehni CE. Cause-specific long-term mortality in survivors of childhood cancer in Switzerland: a population-based study. *Int J Cancer* 2016; **139:** 322–33.

18 Bagnasco F, Caruso S, Andreano A, et al. Late mortality and causes of death among 5-year survivors of childhood cancer diagnosed in the period 1960-1999 and registered in the Italian Off-Therapy Registry. *Eur J Cancer* 2019; **110:** 86–97.

19 Fidler MM, Reulen RC, Winter DL, et al. Long term cause specific mortality among 34 489 five year survivors of childhood cancer in Great Britain: population based cohort study. *BMJ* 2016; **354:** i4351.

20 Garwicz S, Anderson H, Olsen JH, et al. Late and very late mortality in 5-year survivors of childhood cancer: changing pattern over four decades—experience from the Nordic countries. *Int J Cancer* 2012; **131:** 1659–66.

21 Kero AE, Järvelä LS, Arola M, et al. Late mortality among 5-year survivors of early onset cancer: a population-based register study. *Int J Cancer* 2015; **136:** 1655–64.

22 Brewster DH, Clark D, Hopkins L, et al. Subsequent mortality experience in five-year survivors of childhood, adolescent and young adult cancer in Scotland: a population based, retrospective cohort study. *Eur J Cancer* 2013; **49:** 3274–83.

23 Haupt R, Spinetta JJ, Ban I, et al. Long term survivors of childhood cancer: cure and care. The Erice statement. *Eur J Cancer* 2007; **43:** 1778–80.

24 Sørensen GV, Belmonte F, Erdmann F, et al. Late mortality among survivors of childhood acute lymphoblastic leukemia diagnosed during 1971-2008 in Denmark, Finland, and Sweden: a population-based cohort study. *Pediatr Blood Cancer* 2022; **69:** e29356.

25 Ries L, Trama A, Nakata K, Gatta G, Botta L, Bleyer A. Cancer incidence, survival, and mortality among adolescents and young adults. In: Bleyer A, Barr R, Ries L, Whelan J, Ferrari A, eds. Cancer in adolescents and young adults. Cham: Springer, 2017: 7–42.

26 Gatta G, Peris-Bonet R, Visser O, et al. Geographical variability in survival of European children with central nervous system tumours. *Eur J Cancer* 2017; **82:** 137–48.

27 Botta L, Gatta G, Didonè F, Lopez Cortes A, Pritchard-Jones K, the BENCHISTA Project Working Group. International benchmarking of childhood cancer survival by stage at diagnosis: the BENCHISTA project protocol. *PLoS One* 2022; **17:** e0276997.

28 Möller TR, Garwicz S, Perfekt R, et al. Late mortality among five-year survivors of cancer in childhood and adolescence. *Acta Oncol* 2004; **43:** 711–18.

29 Vaitkevičienė G, Matuzevičienė R, Stoškus M, Žvirblis T, Ragelienė L, Schmiegelow K. Cure rates of childhood acute lymphoblastic leukemia in Lithuania and the benefit of joining international treatment protocol. *Medicina (Kaunas)* 2014; **50:** 28–36.

30 Paapsi K, Baburin A, Mikkel S, Mägi M, Saks K, Innos K. Childhood cancer incidence and survival trends in Estonia (1970-2016): a nationwide population-based study. *BMC Cancer* 2020; **20:** 30.

31 Gatta G, Botta L, Comber H, et al. The European study on centralisation of childhood cancer treatment. *Eur J Cancer* 2019; **115:** 120–27.

32 Dudek-Godeau D, Kieszkowska-Grudny A, Kwiatkowska K, Bogusz J, Wysocki MJ, Bielska-Lasota M. Analysis of changes in cancer health care system in Poland since the socio-economic transformation in 1989. *Rocz Panstw Zakl Hig* 2016; **67:** 445–54.

33 Reedijk AMJ, van der Heiden-van der Loo M, Visser O, et al. Site of childhood cancer care in the Netherlands. *Eur J Cancer* 2017; **87:** 38–46.

34 Girardi F, Allemani C, Coleman MP. Worldwide trends in survival from common childhood brain tumors: a systematic review. *J Glob Oncol* 2019; **5:** 1–25.