Childhood cancer survival in Europe 1999–2007: results of EUROCARE-5—a population-based study

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Summary

Background Survival and cure rates for childhood cancers in Europe have greatly improved over the past 40 years and are mostly good, although not in all European countries. The EUROCARE-5 survival study estimates survival of children diagnosed with cancer between 2000 and 2007, assesses whether survival differences among European countries have changed, and investigates changes from 1999 to 2007.

Methods We analysed survival data for 157 499 children (age 0–14 years) diagnosed between Jan 1, 1978 and Dec 31, 2007. They came from 74 population-based cancer registries in 29 countries. We calculated observed, country-weighted 1-year, 3-year, and 5-year survival for major cancers and all cancers combined. For comparison between countries, we used the corrected group prognosis method to provide survival probabilities adjusted for multiple confounders (sex, age, period of diagnosis, and, for all cancers combined without CNS cancers, casemix). Age-adjusted survival differences by area and calendar period were calculated with period analysis and were given for all cancers combined and the major cancers.

Findings We analysed 59 579 cases. For all cancers combined for children diagnosed in 2000–07, 1-year survival was 90·6% (95% CI 90·2–90·9), 3-year survival was 81·0 % (95% CI 80·5–81·4), and 5-year survival was 77·9% (95% CI 77·4–78·3). For all cancers combined, 5-year survival rose from 76·1% (74·4–77·7) for 1999–2001, to 79·1% (77·3–80·7) for 2005–07 (hazard ratio 0·973, 95% CI 0·965–0·982, p<0·001). The greatest improvements were in eastern Europe, where 5-year survival rose from 65·2% (95% CI 63·1–67·3) in 1999–2001, to 70·2% (67·9–72·3) in 2005–07. Europe-wide average yearly change in mortality (hazard ratio) was 0·939 (95% CI 0·919–0·960) for acute lymphoid leukaemia, 0·959 (0·933–0·986) for acute myeloid leukaemia, and 0·940 (0·897–0·984) for non-Hodgkin lymphoma. Mortality for all of Europe did not change significantly for Hodgkin's lymphoma, Burkitt's lymphoma, CNS tumours, neuroblastoma, Wilms' tumour, Ewing's sarcoma, osteosarcoma, and rhabdomyosarcoma. Disparities for 5-year survival persisted between countries and regions, ranging from 70% to 82% (for 2005–07).

Interpretation Several reasons might explain persisting inequalities. The lack of health-care resources is probably most important, especially in some eastern European countries with limited drug supply, lack of specialised centres with multidisciplinary teams, delayed diagnosis and treatment, poor management of treatment, and drug toxicity. In the short term, cross-border care and collaborative programmes could help to narrow the survival gaps in Europe.

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Introduction

The EUROCARE project produces population-based cancer survival and related information that depicts the situation in Europe as accurately as possible. It encourages the participation of all European cancer registries that have good-quality survival data.

Survival after childhood cancers is now generally good and better than for adults. Previous EUROCARE studies estimated that during 1995–2002, 5-year all-cancer survival was 56% for adults,[1] and 81% for children.[2] However, large differences exist between countries: ranging from 48% to 62% for adults, and 75% to 86% for children.[1,2] Survival improved between the late 1990s and the early 2000s, particularly for acute lymphoid leukaemia and CNS cancers.[2]

EUROCARE-5 assessed the largest European population yet, with a much greater participation of cancer registries from eastern Europe. Here, we present EUROCARE-5 survival data for children diagnosed with cancer between 2000 and 2007, assess whether survival differences between European countries have changed, and investigate whether survival for the main childhood cancers has changed from previous periods.

Materials and methods

Study design and data collection

The EUROCARE-5 database contains data for 157 499 cancers diagnosed in European children (age 0–14 years; 14 years is usually the cutoff used in studies of childhood cancer) from Jan 1, 1978, to Dec 31, 2007, with data for whether the patient is alive or date of death updated to Dec 31, 2008. The data were provided by 74 population-based cancer registries in 29 countries: Denmark, Finland, Iceland, Norway, and Sweden(grouped as northern Europe); Bulgaria, Estonia, Hungary, Latvia, Lithuania, Poland, and Slovakia (eastern Europe); Austria, Belgium, France, Germany, Netherlands, and Switzerland (central Europe); Croatia, Italy, Malta, Portugal, Slovenia, and Spain (southern Europe); and England, Ireland, Northern Ireland, Scotland, and Wales (UK and Ireland). All cancer registries collected data according to a standardised protocol and sent them for central analysis anonymously so no ethical approval was required for the study.

Most countries had national cancer registration. Six (Belgium, Italy, Poland, Portugal, Spain, and Switzerland) had partial registration (one or more local or regional registries). Ten specialised childhood cancer registries contributed: England and Wales, Germany, Hungary, France (for solid cancers), France (haematological cancers), Piedmont and Marche in Italy, the Childhood Cancer Registry covering Barcelona, the Comunitat Valenciana covering Alicante, Castellon and Valencia, and the Girona Registry in Spain.

Cancers were grouped into 15 diagnostic categories defined by the International Classification of Childhood Cancers (ICCC) third edition,[3] with the addition of all cancers combined. Only malignant cancers were included—for example, malignant intracranial and intraspinal neoplasms (III and Xa) were included, whereas non-malignant intracranial or intraspinal neoplasms such as craniopharyngioma, meningioma, ganglioglioma, and benign teratoma were excluded. Pilocytic astrocytoma—the most common CNS neoplasm in children—was also excluded from most analyses because the International Classification of Disease for Oncology third edition (ICD-O-3)[4] assigns it a borderline behaviour code.

Statistical analysis

Only observed survival (not adjusted for country-specific mortality) is presented,[5] which in children corresponds very closely to relative survival since competing risks of death are negligible. Survival for 2000–07 was estimated from all cases diagnosed during this period, irrespective of the potential follow-up, using the complete survival approach.[6] Survival estimates were calculated with the actuarial method and SEER*stat software.

We used the corrected group prognosis method[7] for survival comparisons adjusted for multiple confounders (sex, age, and period of diagnosis, with further adjustment for casemix for all cancers combined except CNS cancers). We first calculated 5-year survival estimates for patients with a given combination of covariates with the Cox model.[8] We then calculated country-specific adjusted survival as a weighted average of the 5-year survival expected in each country for each of the adjustment covariate combinations. The weightings were the numbers of patients in the whole sample with each covariate combination at the start of follow-up. The covariates were sex (male reference), age (1–4 years reference), period of diagnosis (2000–03 reference), and country (France reference). We used Stata (version 10) to produce survival estimates by the corrected group prognosis method. We investigated interactions between country and diagnostic period, but they were not significant (data not shown).

Many countries provided all cases diagnosed in the national population, while the six countries with partial registration were under-represented in the European pool. To overcome this geographical bias, survival for Europe as a whole was estimated by weighting the country-specific survival estimates with weightings proportional to the population of 0–14 year-old children in each country in 2000–07. This approach assumes that the population covered by partial cancer registration is representative of the country as a whole. A single set of country weightings was used and applied to each sex, age group, and calendar period.

We estimated differences in survival time with the period survival method[9] for three follow-up periods: 1999–2001 (period of diagnosis Jan 1, 1995–Dec 31, 2001), 2002–04 (period of diagnosis Jan 1, 1998–Dec 31, 2004), and 2005–07 (period of diagnosis Jan 1, 2001–Dec 31, 2007). We used SEER*stat software (version 8.0.1) for these analyses.

To ensure comparability between sexes, European regions, and time periods, for the analyses of survival time for a given cancer, we standardised to the age distribution of all European children diagnosed with that cancer in 1999–2007. In general, we used four age classes (<1 years, 1–4 years, 5–9 years, and 10–14 years). However, for neuroblastoma we grouped together 5–9 years and 10–14 years because the disease generally occurs in young children, giving three age groups (<1 year, 1–4 years, and 5–14 years). Only one age-specific category was used for retinoblastoma (0–4 years) and osteosarcoma (10–14 years).

We estimated age-standardised survival time for Europe as a whole by weighting region-specific survival estimates with weightings proportional to number of 0–14 year-old children in each region in 2000–07. We used a Cox proportional hazard model[8] for each diagnostic group to obtain the average yearly reduction in mortality (hazard ratio [HR]) for 1999–2007 for each region and for

Europe as a whole, adjusted by region (using central Europe as the reference), sex, year of diagnosis, and age.

We used ten diagnostic categories to adjust for casemix in the analysis of all cancers combined: acute lymphoid leukaemias (ICCC category Ia, reference), acute myeloid leukaemias (Ib), Hodgkin's lymphoma (IIa), non-Hodgkin lymphoma (IIb), CNS cancers (III), kidney (ICDO C64.9, C65.9), eye and orbit (ICDO C69), bone (ICDO C40–41), soft tissue (ICDO C49), and all remaining cancers. The categories for CNS cancers were: ependymoma and choroid plexus tumour (IIIa), astrocytomas (IIIb; reference), intracranial and intraspinal embryonal tumours (IIIc), and a final category consisting of other gliomas (IIId), other specified intracranial or intraspinal neoplasms (IIIe), and unspecified intracranial and intraspinal neoplasms (IIIf). We used Stata (version 10) for the proportional hazards models.

Role of the funding source

The sponsor had no role in the study design, data collection, data analysis, data interpretation, or in writing the report. GG, LB, and SR had access to the raw data. The corresponding author had full access to all of the data and had final responsibility to submit for publication.

Results

We extracted and analysed two datasets from the EUROCARE-5 database. The first included data for 60 415 children diagnosed with cancer between 2000 and 2007 for which all 74 cancer registries had data. Table 1 shows the main characteristics by country of this dataset, with principal data quality indicators. After checking and correcting,[10] 836 cases were excluded (table 1). Thus, we included 59 579 cases in the analysis. Of these, 56 305 (94·5%) were microscopically verified. For most countries (except Iceland, Northern Ireland, and Latvia), more than 90% of cases were microscopically verified. About 2% of children diagnosed from Jan 1, 2000, to Dec 31, 2003, had been censored before 5 years; for most cancer registries, this proportion was less than 1%, and only for two registries did it exceed 4%. Overall, 1612 (2·7%) cases had unspecified ICCC codes. Based on these numbers we were able to calculate the crude incidence rates for each country. Crude incidence rates for cancers diagnosed between 2000 and 2006 ranged widely between countries (9·1–17·8 per 100 000 per year), similar to the rates reported for the same registries for the period 1998–2002 (10·9–19·5 per 100 000 per year).[11]

From this first dataset, for all cancers combined for children diagnosed in 2000–07, overall survival at 1 year was 90·6% (95% CI 90·2–90·9), survival at 3 years was 81·0% (95% CI 80·5–81·4), and survival at 5 years was 77·9% (95% CI 77·4–78·3; figure 1). For most haematological cancers, 5-year survival was high (ranging from 84% to 95%), except for acute myeloid leukaemia where only 62·7% (95% CI 60·5–64·9) of children survived for 5 years (table 2). 5-year survival for retinoblastoma was high. Survival was also good for nephroblastoma and other non-epithelial renal tumours, mostly nephroblastoma; other renal tumours accounted for 173 (3·4%) cases. For other solid tumours, survival decreased (table 2).

5-year survival for CNS cancers for all of Europe was modest (57·5%, 95% CI 56·1–58·8), with little difference between diagnostic groups (table 2). As differentiating between benign and malignant tumours is difficult, the survival data between countries might not be directly comparable.

Therefore the survival analysis by country including CNS tumours is presented in the appendix. When pilocytic astrocytoma was included, survival increased to 77·0% (95% CI 69·4–82·2) for astrocytomas, and to 66·2% (61·5–70·4) for CNS cancers (see appendix).

For most cancers, survival dropped steeply after the first year from diagnosis, so there was a large gap between 1-year and 3-year survival (figure 1). This trend was particularly evident for acute myeloid leukaemia, CNS cancers, neuroblastoma, rhabdomyosarcoma, osteosarcoma, and Ewing's sarcoma. For the last three, survival also fell steeply from the third to the fifth year after diagnosis.

The Europe wide (country-weighted) 5-year survival analysis from the first database showed that no difference existed between boys and girls for all cancers combined (77·5% [95% CI 76·9–78·2] for boys *vs* 78·3% [77·6–79·0]), but 5-year survival of girls with Burkitt's lymphoma was lower than that for boys (p=0·039), whereas 5-year survival was higher for girls with acute lymphoid leukaemia than for boys (p=0·007; table 2). Children aged younger than 1 year had the lowest 5-year survival for several cancers, particularly acute lymphoid leukaemia, acute myeloid leukaemia, non-Hodgkin lymphoma, ependymoma, embryonal CNS cancers, and all CNS cancers. As expected, children younger than age 1 year with neuroblastoma had good survival (91·1% [89·6–92·5]) whereas less than 60% of older children survived for 5 years. 5-year survival was worst for children aged 10–14 years with astrocytomas, nephroblastoma, and Ewing's sarcoma (table 2).

We extracted the second dataset to estimate 5-year survival for the major diagnostic categories, for the different regions, and for cases diagnosed during the longer period from Jan 1, 1995, to Dec 31, 2007. This analysis was therefore restricted to only 43 cancer registries that had data for at least from Jan 1, 1996, to Dec 31, 2006. Belgium, Croatia, France, Latvia, and Portugal were excluded from this analysis. The second dataset included data for 69 420 childhood cancers. From this dataset, 1273 cases were excluded because they were only discovered on reading the death certificate or at autopsy, were censored just after diagnosis, or had data with major non-recoverable errors (details not shown). Thus, 68 147 cases were used for analysis of trends of 5-year survival.

Based on the analysis from this second dataset, for all cancers combined, 5-year survival rose from 76·1% (95% CI 74·4–77·7) in 1999–2001 to 79·1% (77·3–80·7) in 2005–07, with HRs falling significantly each year (p<0·0001; table 3). The improvement was evident in all regions but the reduction in HR was significant for eastern Europe, central Europe, northern Europe, and the UK and Ireland. 5-year survival for acute lymphoid leukaemia improved significantly and the average yearly reduction in mortality was significant for Europe as a whole, northern Europe, eastern Europe, and the UK and Ireland. 5-year survival in Europe also increased significantly for acute myeloid leukaemia and for non-Hodgkin lymphoma (table 3). Survival increased significantly for non-Hodgkin lymphoma and Burkitt's lymphoma in eastern Europe, for acute myeloid leukaemia in central Europe, and for neuroblastoma in northern Europe (table 3). Survival did not improve significantly for any other diagnostic category.

The HR increased significantly for neuroblastoma in central Europe, osteosarcoma (10–14 years of age) in southern Europe (despite a small number of cases), and Hodgkin's lymphoma in eastern Europe. For osteosarcoma we did a post-hoc analysis: when we restricted our analysis to long bone osteosarcomas—which have better prognosis than short bone disease—HR fell, and the increase in mortality was no longer significant. The HR for Wilms' tumour did not change significantly but the HR for the wider ICCC VIa category (nephroblastoma and other non-epithelial

renal tumours) was significant for UK and Ireland (HR 1·114, 95% CI 1·013–1·224; p=0·026). In our analysis we separated Wilms' tumours—because they have specific treatment protocols—from other renal non-epithelial tumours, which have a worse prognosis (48·7% [95% CI 38·8–57·9] for other renal tumours *vs* 90·6% [89·4–91·7] for Wilms' tumour).

For acute lymphoid leukaemia, most central and northern European countries, the UK, Malta, and Italy, had 5-year survival (adjusted for age, sex, and period of diagnosis) higher than the European mean, whereas Bulgaria, Estonia, Latvia, Lithuania, and Slovakia had the lowest (<80%; figure 2). We analysed acute lympoid leukaemia on a country basis because it is the most common cancer in children, is curable, and standard protocols are available. Furthermore, biases in data quality are minor.

To ensure that comparisons can be done between regions and with earlier periods, we also report in the appendix survival data for CNS tumours including 3172 children with pilocytic tumours (M9421/1).The Swedish National Cancer Registry did not supply reliable data for CNS tumours, and was thus excluded from the analyses of all cancers combined and CNS cancers. Countries varied widely in how they attributed malignancy of CNS tumours and how they collected data for CNS benign and borderline cases from population-based registries. The appendix shows indicators of data comparability, quality, and survival of patients with CNS tumours for each country. We have removed CNS tumours from all-cancers for comparisons of survival between countries. For CNS tumours, survival was poor (58%, 95% CI 52·3–62·5) and large gaps exist between countries (appendix). When pilocytic astrocytoma (which accounts for 25% of all CNS tumours) was added, between-country survival differences narrowed slightly.

For most countries, 5-year survival for all cancers combined (without CNS tumours) ranged between 80% and 85% (figure 3). Austria, Norway, and Switzerland had the highest survival (>84%); all eastern European countries except Poland had low survival (60–77%). Iceland also had low survival but was based on few cases, with a wide 95% CI.

Discussion

5-year survival for all cancers combined is increasing in Europe—as reported in previous EUROCARE studies[2,12]—with HR falling on average by 3% per year. The most notable improvements were in eastern Europe, where 5-year survival rose from 65% in 1999–2001 to 70% in 2005–07.

Despite these improvements, there are still survival disparities between countries and European regions, but with few exceptions, survival was lowest in eastern Europe. Many factors could explain the poor survival in eastern Europe. The first is lack of resources: these countries have lower GDP than countries in other European regions.[13] This shortcoming is likely to have several effects. Drugs might be unavailable, or supplies might run out so that treatment has to be halted before completion.[14] Specialised centres for childhood cancers might not have enough beds or resources to treat all the patients in their catchment areas,[15] and poorer countries might not be able to afford the multidisciplinary teams typical of paediatric oncology units in richer countries.[16] Treatment could be delayed because diagnosis is delayed[17] or patients might die of toxic effects of drug[14] because modern equipment is not available to accurately measure serum drug concentrations.

All these difficulties were mentioned by health professionals in Bulgaria and Estonia when asked to comment on the poor survival in their countries (T Aareleid and N Dimitrova, unpublished). Furthermore, in Bulgaria the number of paediatricians dropped[18] during 2001–07 and the country did not have a national cancer plan.[19] However, a full range of complex paediatric care—including allogeneic bone-marrow transplantation—became available in Estonia in 2005. Furthermore, Estonian paediatric oncology centres now collaborate with the Nordic Society of Pediatric Hematology and Oncology, and have adopted the society's treatment protocols for acute myeloid leukaemia and acute lymphoid leukaemia (T Aareleid, unpublished).

Poland, which had the best all-cancer survival in eastern Europe, nevertheless had difficulties during the EUROCARE-5 study period, during which a new health-care funding system was introduced, leading to shortcomings in health-care delivery.[20] A Polish national cancer plan was introduced in 2006, aimed at improving standard treatments for children among other goals.21 The Polish Society of Pediatric Oncology and Hematology has been raising standards of care for Polish children with cancer and is also advocating—together with the European Society of Pediatric Oncology—for European standards of care for these young patients.[17]

The relatively good survival for Hungarian children might be partly a result of the work of the Hungarian Pediatric Oncology Group, which was established in 1971.[22] The Hungarian health insurance system pays for cytostatic drugs only for children registered and treated according to Hungarian Pediatric Oncology Group guidelines. Initiatives have cut waiting times for diagnostic examinations and sped up diagnoses. The Hungarian Pediatric Oncology Group regularly scrutinises foreign treatment protocols for safety, efficacy, and suitability to local circumstances and sets standards for supportive care and for training specialist doctors and nurses.[23] Such an approach might usefully be applied in other countries with similar resource limitations and health organisation difficulties.

Leukaemia is one the most common and most curable childhood cancers; according to Globocan,[24] about 280 paediatric cases are expected in 2008 in the eastern European EUROCARE countries (ranging from seven in Estonia to 107 in Poland). If the 5-year survival of these patients could be brought up to the European average—surely feasible—all-Europe survival would rise from 86% to 88%. However, the rarity of most childhood cancers[16] creates particular difficulties for small countries—eg, Estonia, Latvia, and Lithuania—which only have about ten cases per year (acute lymphoid leukaemia or CNS cancers). Since good results for these cancers are usually obtained only when treatment is centralised in high-volume centres of excellence,[25] collaborative programmes in which all patients are sent to a single centre could be a solution. Malta—which has good outcomes—is a small country that had a longstanding arrangement with the British National Health Service.[26] The provisions of the European Directive on Cross-Border Healthcare[27] could also facilitate such collaboration. Some small countries also have a very low GDP[13] and health expenditure—eg, health expenditure in Estonia was half that of Malta in 2010, according to WHO.

Survival did not improve for several cancers in Europe (Hodgkin's lymphoma, CNS cancers, neuroblastoma, nephroblastoma, Ewing's sarcoma, and osteosarcoma). Furthermore, we report a significant fall in survival for neuroblastoma in central Europe and osteosarcoma in southern Europe. For neuroblastoma, the decrease seemed to be confined to children aged 1–14 years, whose prognosis was poorer than that of infants. Moreover, the fall occurred in all the central European countries (Austria, Germany, Netherlands, and Switzerland). The division of the study period into three intervals was not related to changes in treatment regimen for several reasons.

Changes from one trial or protocol to the next do not take place at the same time for all cancer types; even for specific cancer types, changes are not necessarily simultaneous across all countries. We believe it would be inappropriate to use the period survival method for analysis by trial era because the periods for analysis relate primarily to follow-up, with incomplete overlap of range of years of diagnosis from one period to the next.

The little or no survival increases for several cancers during 1999–2007 confirm the beliefs of some paediatric oncologists and researchers that the optimisation of present treatments has reached its limits.[16] New research approaches are therefore needed to further improve survival, especially for high-risk groups. New approaches to trial design and greater international collaboration are needed to recruitment enough participants for studies of small and homogeneous subgroups of patients.[16]

All-cancer survival varied widely across Europe, partly because of the large differences in survival for CNS cancers. Data for CNS cancers are difficult to compare reliably because of differences in diagnosis (pathological or clinical),[28] classification (malignant or non-malignant, specified or non-specified neoplasms),[29] and coverage by population-based registries: not all cancer registries collect data for non-malignant CNS tumours. A report addressing possible biases and data quality shortcomings related to CNS cancer registration across Europe is in preparation.

The between-country differences for all-cancer survival are also unlikely to be caused by differences in casemix for some cancers. For example, acute lymphoid leukaemias are almost always precursor cell types; 98% of acute lymphoid leukaemias included in our study were of these types (94–100% by country) and all have similar survival. Thus, differences in the casemix are unlikely to account for the large survival differences between countries for acute lymphoid leukaemia. Survival for non-Hodgkin lymphoma could have been affected by the proportions of unspecified lymphomas. However, the largest decrease in survival for these two forms taken together compared with non-Hodgkin lymphoma alone was 1·3% (in northern Europe), so the difference by European region could not have been substantially affected by the proportions of lymphoma not otherwise specified.

Similar considerations apply to Burkitt's lymphoma, for which survival might be affected by the number of patients with Burkitt's cell leukaemia included in acute lymphoid leukaemia. Many of these cases are late-stage lymphomas with poor survival. However, the inclusion of Burkitt's cell leukaemia under Burkitt's lymphoma did not reduce the differences in survival between European regions. The largest change was a 3·3% decrease for eastern Europe.

The survival data presented by follow-up time and by age or sex are averages of very heterogeneous country-specific estimates. However, childhood cancers are rare, and European estimates based on a very large dataset—as in EUROCARE-5—are likely to be reliable and up to date. The information in figure 1 and table 2 confirm the peculiarities of different childhood cancers and their different prognoses compared with cancer in adults. Difficulties of following up incident cases to ascertain vital status might have partly biased survival estimates. In some cases, registries are aware that a patient is no longer traceable, and this is shown in the proportion of early censored cases, which was highest for Belgium, Germany, and Switzerland (2·2–6·8%). In other cases, no information reaches the registry, so such patients are classed as permanently alive (so-called immortals). Methods for dealing with this difficulty are based on analysis of cancers with a very poor prognosis (eg, lung or pancreatic cancers) or of long-term survival. Such methods are not applicable to childhood cancers. Analysis of adult cancers for all the EUROCARE-5 countries[30]

indicated that a substantial proportion of deaths of cancer patients might have been missed in Croatia, Poland, and—to a lesser extent—Austria, Belgium, and Germany. The proportion of suspected immortals was highest in the Kielce Cancer Registry (32% of Polish cases). When Kielce region was excluded, survival for all childhood cancers combined in Poland fell by 0·8 percentage points. This finding suggests that missing death information is unlikely to substantially bias 5-year survival data for cancers with good or medium prognosis, and is not of particular concern for the analysis of childhood cancers.

The linkage of Estonian Cancer Registry files to the death certificate database was prevented in 2001–07 by data protection regulations.31 As a consequence, some incident cases that could have been identified from death certificates were missing for that period. These cases were usually of cancers with poor prognosis, and their loss has probably caused survival in Estonia to be overestimated. A similar difficulty arose for the Croatian Cancer Registry.[32]

Childhood cancer incidence rates in our study were as high as expected,[11] and similar to those published in CI5C for 1998–2002.[11] Survival estimates can therefore be considered as referring to a complete collection of cases. They can also be taken as fully representative for all the countries with national coverage—the majority in our study. For countries with partial registration (Italy, Poland, Portugal, Switzerland, and Spain), our results refer to well-defined areas within a country and how reliably they can be applied to the whole nation is a matter of assumption. However, this assumption is reasonable, in view of the geographical spread of the registries and the high level of centralisation of care for children with cancer, most of whom are enrolled in clinical trials and concentrated in specialised paediatric oncology hospitals.

Thus, Europe-wide estimates of survival for childhood cancer—even if complicated by shortcomings in data quality and differences in disease definition and casemix—show large inequalities between countries. Reduction of these differences should continue to be a major health priority; new EU and national policies might be needed to achieve such a reduction (panel 1).

This study and the previous EUROCARE and ACCIS population-based studies of childhood cancers are important for assessing how changes to diagnosis, treatment, and health-care organisation affect survival and cure of childhood cancers (panel 2). Pan-European analyses also help to show the difficulties of comparing cancer data between countries, for example for CNS cancers in our study.

Forthcoming studies should assess how much survival differences are caused by variability in diagnostic criteria and how much to registration practices. These studies will require accurate, reliable, up-to-date, standardised data from population-based cancer registries. Maintenance and improvement of this information-gathering system is essential to continue to study basic epidemiological indicators for cancer.

Finally, although reduction of persisting survival inequalities across Europe is important, the long-term quality of life of patients with highly curable cancers should also be improved. Pursuit of this objective requires identification, estimation, and comparison of specific indicators for quality of life. Collaboration between cancer registries and European-wide projects (eg, PanCare and the European Network for Cancer Research in Childhood and Adolescents) will greatly help this ambitious challenge to be met.

Panel 1: Steps to reduce variation in childhood cancer outcomes in Europe

Development and extension of twinning programmes, pairing medical institutions in high-income countries with those in low-income and middle-income countries, as some European paediatric groups have done for central and south American countries.[33–36] These programmes can rapidly improve survival when the collaborating institutions have a long-term commitment and their efforts are supported locally.[15]

Implementation and extension of the European directive on Cross-Border Healthcare[27] particularly to small European countries that lack the resources and infrastructure to treat these diseases and are unlikely to develop such infrastructure because of the very small numbers of children with cancer.

Sustenance of public health research to develop strategies to ensure access to effective treatment. High-resolution studies[37] of adult cancers have suggested detailed reasons for survival inequalities among European adults. Similar studies should be done for childhood cancers, particularly CNS cancers.

Improvement of national registration of childhood cancer, especially in Eastern Europe. Legislative, organisational, and economic difficulties have to be overcome to implement new, and maintain current, population-based childhood cancer registration.[38]

Panel 2: Research in context

Systematic review

Childhood cancers are rare but unlike most rare cancers they can be treated effectively in most cases. Previous EUROCARE studies [2,12] showed large differences between countries for childhood cancer survival, with outcomes usually poor for eastern European children. However, survival for childhood cancers improved between the early 1980s and the early 2000s, particularly for acute lymphoid leukaemia and CNS cancers. EUROCARE-5 includes a larger European population (accounting for 77% of the childhood population of Europe, about 59 million), mainly a result of increased participation of cancer registries from eastern European countries.

Interpretation

5-year survival for all childhood cancers combined improved from 76·1% (95% CI 74·4–77·7, in the late 1990s) to 79·1% (77·3–80·7, in the early 2000s). However, survival disparities between countries and European regions persisted. With few exceptions, survival was lowest in eastern Europe, and survival differences were large for cancers with generally poor outcomes such as acute myeloid leukaemia, ependymoma, and bone and soft tissue sarcomas. CNS tumours showed the largest inequalities across Europe, partly because of difficulties in comparing diagnoses and

classification, suggesting a specific, more detailed analysis is needed. The present situation, reported in previous articles by the EUROCARE and ACCIS projects, could be improved by intensifying international collaboration with twinning programmes and by motivating politicians to create and develop sustainable infrastructure recognising the specific needs of children with cancer. Special programmes should be developed for small countries, such as the Baltic nations, according to their health-care resources and relationships with larger countries.

Contributors

GG designed the study, and wrote the first draft of the article. LB and SR did the statistical analyses. LB, SR, TA, MB-L, JC, ND, ZJ, PK, BL, SM, RM-G, PM, M-JS-P, MiS, MaS, CS, ATa, ATr, OV, and RP-B revised the report. Members of the working group collected data. All authors contributed to data interpretation and wrote the report. All authors reviewed and approved the final version.

Conflicts of interest

We declare that we have no conflicts of interest.

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Tables and Figures

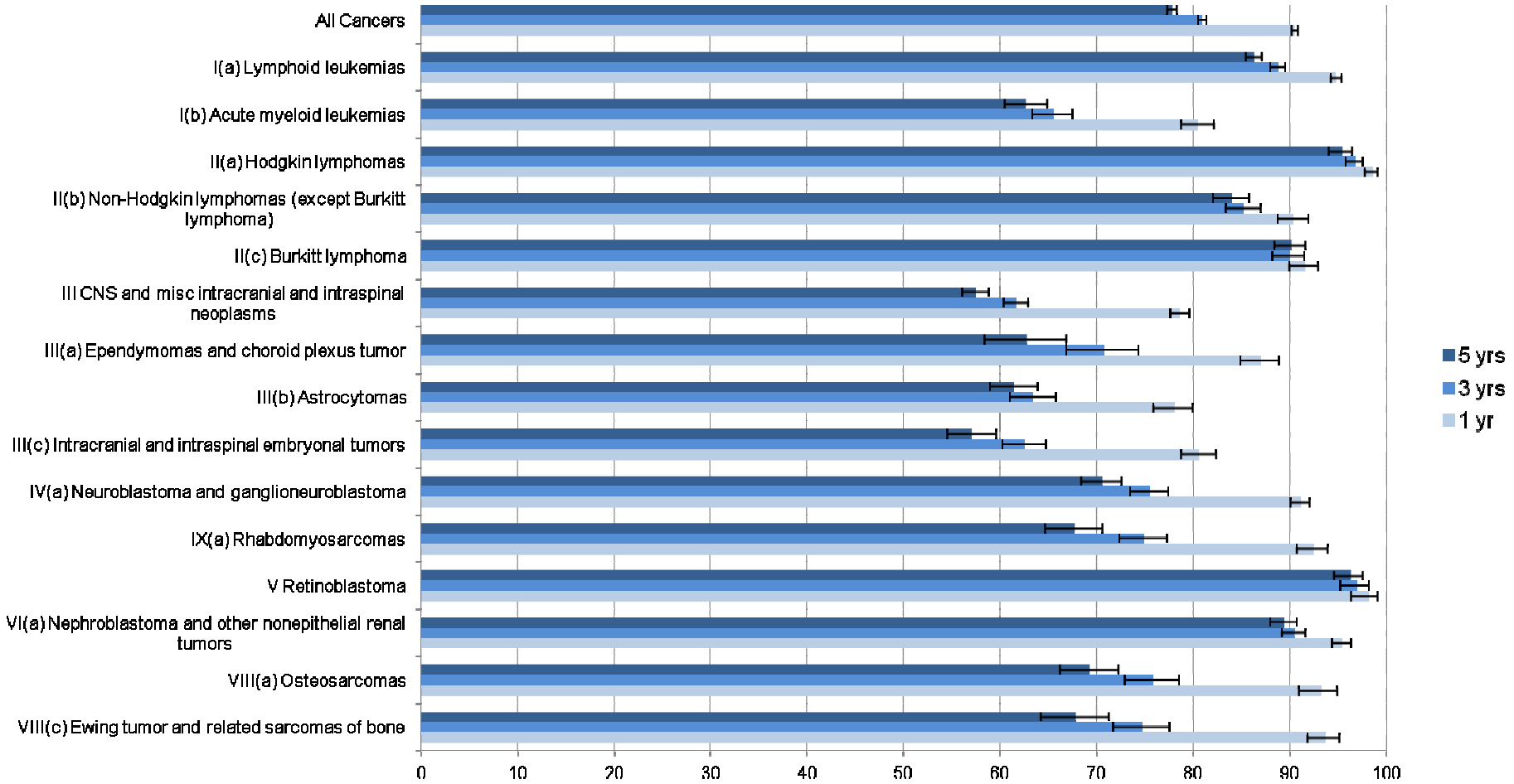
Table 1: Numbers of children diagnosed with cancer by country and region.

Country/European area	Coverage of national population (%)	Total malignant cases diagnosed 2000-2007	Cases with major errors, % (n.)		Cruce incidence (rate per 100,000)	Cases without major errors excluded from analyses						Cases included in the analyses							
					Malignant tumours diagnosed in 2000-2006	Death certificate only, % (n.)		Autopsy, % (n.)		Alive with zero survival time, % (n.)		Number of cases	Microscopic verification, % (n.)		Alive 2000-2003 censored before 5 years, % (n.)		Unspecified cases[1], % (n.)	
Denmark	100·0	1,085	4·7	(51)	13·1	0·0	(0)	<0·1	(1)	0·0	(0)	1,033	96·4	(996)	0·0	(0)	6·4	(66)
Finland	100·0	1,084	<0·1	(1)	15·1	<0·1	(1)	0·5	(5)	0·0	(0)	1,077	98·4	(1060)	0·3	(3)	4·0	(43)
Iceland	100·0	54	7·4	(4)	9·1	0·0	(0)	0·0	(0)	0·0	(0)	50	86·0	(43)	0·0	(0)	14·0	(7)
Norway	100·0	964	1·9	(18)	13·3	0·1	(1)	0·0	(0)	0·0	(0)	945	95·9	(906)	0·4	(4)	1·8	(17)
Sweden	100·0	1,459	0·8	(11)	11·4	0·0	(0)	0·1	(2)	0·0	(0)	1,446	97·4	(1409)	0·0	(0)	7·0	(101)
Ireland	100·0	919	2·5	(23)	13·3	0·1	(1)	0·1	(1)	0·0	(0)	894	91·7	(820)	0·0	(0)	3·7	(33)
UK - England & Wales	100·0	8,725	0·7	(62)	12·8	<0·1	(5)	0·1	(10)	0·1	(11)	8,637	92·3	(7971)	0·2	(21)	1·5	(126)
UK - Northern Ireland	100·0	346	4·0	(14)	11·0	0·6	(2)	0·0	(0)	0·0	(0)	330	88·8	(293)	0·0	(0)	8·5	(28)
UK - Scotland	100·0	954	1·0	(10)	13·0	0·3	(3)	0·1	(1)	0·1	(1)	939	94·4	(886)	0·0	(0)	3·2	(30)
Austria	100·0	1,423	2·2	(32)	13·5	0·9	(13)	0·0	(0)	0·0	(0)	1,378	98·5	(1357)	0·0	(0)	3·7	(51)
Belgium	55·5	1,231	0·0	(0)	15·6	0·0	(0)	0·0	(0)	2·2	(27)	1,204	97·3	(1171)	0·0	(0)	1·5	(18)
France	100·0	11,410	0·5	(60)	13·6	0·0	(0)	0·0	(0)	0·1	(13)	11,337	93·7	(10625)	0·7	(77)	1·4	(162)
Germany	100·0	13,235	0·0	(0)	13·5	0·0	(0)	0·0	(0)	0·7	(91)	13,144	95·9	(12602)	6·1	(804)	1·0	(130)
Switzerland	29·4	366	0·5	(2)	12·7	0·5	(2)	0·5	(2)	1·1	(4)	356	96·9	(345)	2·2	(8)	2·5	(9)
The Netherlands	100·0	3,382	0·0	(0)	14·3	0·0	(0)	0·2	(8)	0·0	(0)	3,374	95·3	(3216)	0·5	(17)	1·6	(54)
Croatia	100·0	1,068	5·6	(60)	16·8	0·2	(2)	0·0	(0)	0·0	(0)	1,006	93·6	(942)	0·0	(0)	16·1	(162)
Italy	36·0	3,688	0·7	(24)	16·8	0·1	(4)	0·0	(0)	0·1	(4)	3,656	90·8	(3320)	0·8	(28)	7·1	(259)
Malta	100·0	108	0·9	(1)	17·8	1·9	(2)	0·9	(1)	0·9	(1)	103	93·2	(96)	0·0	(0)	1·0	(1)
Portugal	69·7	766	1·2	(9)	9·2	0·0	(0)	0·0	(0)	0·9	(7)	750	94·5	(709)	0·7	(5)	3·1	(23)
Slovenia	100·0	332	0·0	(0)	13·5	0·0	(0)	0·3	(1)	0·0	(0)	331	99·1	(328)	0·0	(0)	0·9	(3)
Spain	33·8	2,278	0·3	(7)	14·4	0·2	(4)	<0·1	(2)	0·8	(18)	2,247	92·7	(2083)	0·8	(19)	2·4	(53)

Bulgaria	100·0	1,134	1·5	(17)	12·2	3·9	(44)	0·0	(0)	0·0	(0)	1,073	96·6	(1036)	<0·1	(1)	6·0	(64)
Estonia	100·0	192	0·5	(1)	11·7	0·5	(1)	0·0	(0)	0·0	(0)	190	97·9	(186)	0·5	(1)	2·1	(4)
Hungary	100·0	1,752	<0·1	(1)	12·7	0·0	(0)	0·0	(0)	0·2	(4)	1,747	98·1	(1714)	0·4	(7)	0·7	(12)
Latvia	100·0	362	4·7	(17)	11·7	5·5	(20)	1·7	(6)	0·0	(0)	319	89·0	(284)	0·0	(0)	15·4	(49)
Lithuania	100·0	495	5·7	(28)	10·7	0·6	(3)	0·0	(0)	0·0	0	464	97·6	(453)	4·3	(20)	5·0	(23)
Poland	11·7	735	3·5	(26)	10·9	0·1	(1)	0·0	(0)	1·4	(10)	698	91·8	(641)	1·9	(13)	7·3	(51)
Slovakia	100·0	868	0·0	(0)	12·9	1·7	(15)	0·2	(2)	0·0	(0)	851	95·5	(813)	0·0	(0)	3·9	(33)
Northern Europe	100·0	4,646	1·8	(85)	12·9	<0·1	(2)	0·2	(8)	0·0	(0)	4,551	97·0	(4414)	0·2	(7)	5·1	(234)
UK-Ireland	100·0	10,944	1·0	(109)	12·8	0·1	(11)	0·1	(12)	0·1	(12)	10,800	92·3	(9970)	0·2	(21)	2·0	(217)
Central Europe	94·7	31,047	0·3	(94)	13·7	<0·1	(15)	<0·1	(10)	0·4	(135)	30,793	95·2	(29316)	2·9	(906)	1·4	(424)
Southern Europe	42·7	8,240	1·2	(101)	14·8	0·1	(12)	<0·1	(4)	0·4	(30)	8,093	92·4	(7478)	0·6	(52)	6·2	(501)
Eastern Europe	48·5	5,538	1·6	(90)	12·0	1·5	(84)	0·1	(8)	0·3	(14)	5,342	96·0	(5127)	0·8	(41)	4·4	(236)
Europe [2]	77·1	60,415	0·8	(479)	13·4	0·2	(124)	<0·1	(42)	0·3	(191)	59,579	94·5	(56305)	1·8	(1027)	2·7	(1612)

ICCC= International Classification of Childhood Cancers. [1] ICCC diagnostic groups: Ie, IIe, IIIf, VIc, VIIc, VIIIe, IXe and XIIb. [2] Data from 29 the European countries in the present study

Figure 1: Country-weighted survival by ICCC diagnostic category for European children diagnosed with cancer 2000-2007



Includes data for 57, 956 cases. Error bars are 95% CIs. ICCC=International Classification of Childhood Cancers.

Table 2: Country-weighted 5-year survival by ICCC diagnostic category, sex, and age

Diagnostic category	N. of cases	All children	Girl	Boy	Age <1year	Age 1-4 years	Age 5-9 years	Age 10-14 years
All Cancers	57,956	77·9 (77·4-78·3)	78·3 (77·6-79·0)	77·5 (76·9-78·2)	77·9 (76·4-79·4)	79·3 (78·4-80·0)	77·6 (76·6-78·5)	76·6 (75·7-77·5)
I(a) Lymphoid leukemias	15,860	86·3 (85·5-87·1)	87·6 (86·4-88·6)	85·3 (84·1-86·4)	61·8 (56-67·1)	90·6 (89·5-91·7)	88·1 (86·8-89·3)	77·7 (75·5-79·7)
I(b) Acute myeloid leukemias	3,094	62·7 (60·5-64·9)	62·6 (59·3-65·7)	62·6 (59·4-65·6)	53·5 (47·0-59·6)	65·1 (61·4-68·5)	67·9 (63·5-71·9)	59·5 (55·1-63·5)
II(a) Hodgkin lymphomas	3,142	95·4 (94·1-96·5)	94·3 (92·0-96·0)	96·6 (95·5-97·4)	- (-)	95·5 (91·1-97·8)	94·1 (89·9-96·6)	95·8 (94·5-96·8)
II(b) Non-Hodgkin lymphomas (except Burkitt lymphoma)	2,544	84 (82·0-85·8)	84·0 (80·7-86·7)	84·0 (81·5-86·2)	63·3 (49·8-74·0)	78·1 (72·7-82·5)	87·0 (83·8-89·6)	85·4 (82·7-87·8)
II(c) Burkitt lymphoma	1,443	90·2 (88·5-91·7)	85·4 (80·0-89·4)	90·7 (88·8-92·3)	40·1 (40·1-40·1)	89·3 (85·3-92·3)	91·1 (88·8-93·0)	87·2 (84·0-89·8)
III CNS and misc intracranial and intraspinal neoplasms	9,277	57·5 (56·1-58·8)	56·8 (54·7-58·9)	58·0 (56·2-59·7)	48·3 (43·8-52·7)	57·4 (55·0-59·8)	57·0 (54·6-59·3)	60·3 (57·8-62·7)
III(a) Ependymomas and choroid plexus tumor	1,233	62·8 (58·4-66·8)	61·6 (55·1-67·4)	62·5 (56·5-67·9)	42·4 (30·0-54·3)	55·3 (50·6-59·8)	74·7 (66·5-81·1)	76·2 (68·6-82·2)
III(b) Astrocytomas	2,714	61·5 (59·0-63·9)	62·1 (58·7-65·3)	60·7 (57·1-64·1)	64·1 (56·3-70·9)	79·4 (75·6-82·7)	55·6 (51·1-60·0)	49·3 (45·0-53·5)
III(c) Intracranial and intraspinal embryonal tumors	3,119	57·1 (54·6-59·6)	57·1 (53·0-60·9)	57·1 (53·9-60·2)	33·3 (26·6-40·2)	46·5 (42·3-50·5)	67·3 (63·3-71·0)	67·3 (62·2-71·9)
IV(a) Neuroblastoma and ganglioneuroblastoma	4,588	70·6 (68·4-72·6)	71·7 (68·3-74·8)	69·5 (66·7-72·1)	91·1 (89·6-92·5)	58·7 (54·8-62·5)	52·1 (45·8-58·0)	55·7 (45·5-64·6)
V Retinoblastoma	1,627	96·4 (94·6-97·6)	96·1 (93·3-97·8)	97·2 (95·5-98·2)	98·3 (96·6-99·1)	94·6 (89·9-97·2)	96·4 (79·9-99·4)	- (-)
VI(a) Nephroblastoma and other nonepithelial renal tumors	3,554	89·4 (88·0-90·7)	89·7 (87·7-91·3)	89·2 (87·0-91·0)	84·3 (80·2-87·6)	91·4 (89·7-92·9)	88·2 (85·4-90·4)	76·7 (66·0-84·5)
VIII(a) Osteosarcomas	1,500	69·3 (66·2-72·3)	72·8 (68·3-76·8)	66·4 (62·1-70·4)	- (-)	59·8 (47·6-70·1)	72·1 (66·7-76·8)	68·5 (64·9-71·9)
VIII(c) Ewing tumor and related sarcomas of bone	1,397	67·9 (64·2-71·2)	66·7 (61·4-71·4)	68·7 (63·7-73·1)	70·6 (58·8-79·6)	73·7 (64·6-80·7)	76·3 (71·5-80·4)	62·1 (57·1-66·6)
IX(a) Rhabdomyosarcomas	2,197	67·7 (64·7-70·6)	64·7 (59·4-69·4)	69·7 (66·1-73·0)	61·0 (49·7-70·5)	71·2 (66·2-75·5)	70·6 (65·5-75·2)	62·3 (56·6-67·5)

Data are % survival (95% CI), unless stated otherwise. For patients diagnosed 2000-07.

Table 3: 5-year age-standardised survival and average annual reduction in mortality from childhood cancers diagnosed in Europe from 1999 to 2007.

Diagnostic category	Region	Number of cases (1995-2007)	%Survival (95%CI)			HR (95%CI) for 1999-2007	p value
			1999-2001	2002-2004	2005-2007		
All cancers	Northern Europe	5,091	78·4 (75·9-80·7)	80·1 (77·6-82·3)	81·2 (78·8-83·3)	0·966 (0·934-0·999)	0·041
	UK and Ireland	18,107	74·4 (73·1-75·7)	76·2 (74·9-77·4)	77·8 (76·5-79·1)	0·971 (0·955-0·987)	0·001
	Central Europe	29,654	78·8 (77·7-79·8)	80·5 (79·5-81·4)	81·0 (80·0-82·0)	0·979 (0·966-0·992)	0·002
	Southern Europe	4,601	79·2 (76·5-81·6)	78·5 (75·9-80·9)	82·1 (79·6-84·3)	0·967 (0·934-1·001)	0·057
	Eastern Europe	8,363	65·2 (63·1-67·3)	66·8 (64·5-68·9)	70·2 (67·9-72·3)	0·970 (0·950-0·990)	0·003
	All Europe	65,816	76·1 (74·4-77·7)	77·3 (75·4-78·8)	79·1 (77·3-80·7)	0·973 (0·965-0·982)	<0·001
Ia Lymphoid leukaemia	Northern Europe	2,305	84·8 (82·0-87·2)	87·9 (85·4-90·1)	86·7 (84·1-88·9)	0·970 (0·910-1·034)	0·351
	UK and Ireland	5,022	81·5 (79·7-83·2)	87·0 (85·3-88·5)	89·4 (87·9-90·8)	0·911 (0·871-0·953)	<0·001
	Central Europe	8,565	86·1 (84·7-87·3)	90·0 (88·8-91·1)	90·1 (88·9-91·2)	0·960 (0·927-0·996)	0·028
	Southern Europe	1,202	83·6 (79·8-86·8)	86·0 (82·3-89·0)	87·2 (83·5-90·1)	0·944 (0·865-1·030)	0·195
	Eastern Europe	2,003	69·7 (65·8-73·2)	75·8 (72·0-79·1)	80·3 (76·8-83·3)	0·919 (0·875-0·964)	0·001
	All Europe	19,097	82·2 (79·5-84·4)	86·3 (84·0-88·3)	87·6 (85·4-89·5)	0·939 (0·919-0·960)	<0·001
Ib Acute myeloid leukaemia	Northern Europe	445	66·9 (56·8-75·2)	71·4 (61·3-79·3)	67·3 (57·2-75·5)	0·995 (0·915-1·082)	0·912
	UK and Ireland	1,005	65·6 (59·2-71·3)	61·1 (54·8-66·8)	66·5 (59·4-72·6)	0·957 (0·904-1·013)	0·129
	Central Europe	1,525	60·8 (55·4-65·7)	62·8 (57·4-67·7)	67·3 (61·9-72·1)	0·940 (0·900-0·982)	0·005
	Southern Europe	218	79·1 (63·5-88·6)	58·8 (45·3-70·0)	67·4 (51·9-78·8)	1·029 (0·915-1·159)	0·631
	Eastern Europe	398	42·9 (32·2-53·2)	45·4 (36·1-54·3)	49·0 (38·6-58·6)	0·957 (0·897-1·022)	0·189
	All Europe	3,591	63·3 (54·3-70·3)	59·5 (51·3-66·7)	64·4 (55·2-71·8)	0·959 (0·933-0·986)	0·003
IIa Hodgkin lymphoma	Northern Europe	324	95·8 (87·3-98·6)	98·7 (90·4-99·8)	95·0 (86·0-98·3)	1·070 (0·794-1·442)	0·655
	UK and Ireland	914	96·1 (92·6-98·0)	94·4 (90·6-96·6)	97·0 (93·1-98·7)	0·994 (0·846-1·167)	0·937

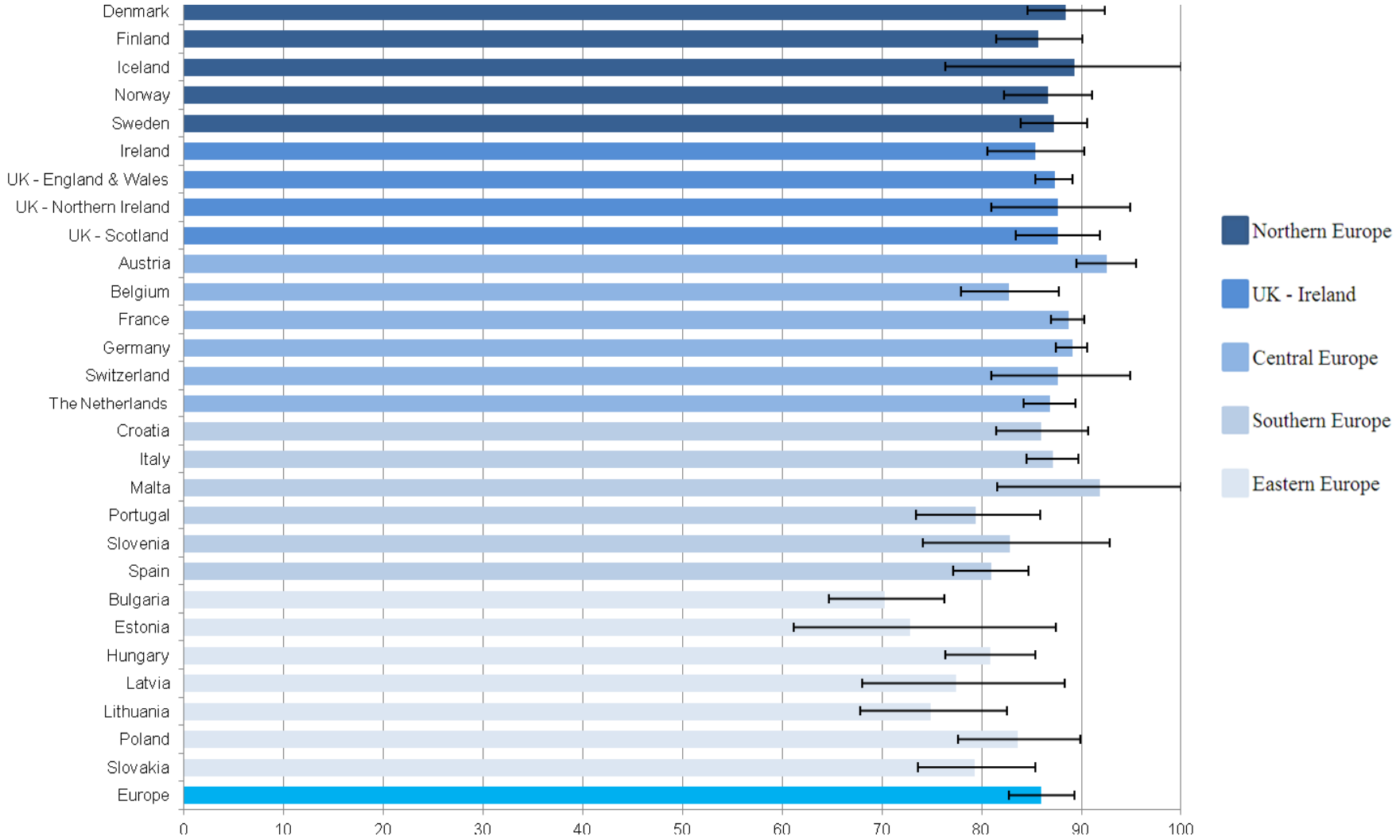
	Central Europe	1,507	96·9 (94·2-98·3)	98·2 (96·2-99·1)	96·8 (93·4-98·5)	0·986 (0·819-1·187)	0·883
	Southern Europe	300	95·7 (87·6-98·6)	94·7 (87·9-97·8)	96·4 (85·9-99·1)	1·012 (0·778-1·317)	0·926
	Eastern Europe	561	90·8 (84·1-94·8)	94·5 (89·5-97·1)	90·6 (82·2-95·2)	1·219 (1·007-1·476)	0·042
	All Europe	3,606	95·5 (90·5-97·8)	96·3 (92·2-98·2)	95·7 (89·5-98·1)	1·053 (0·962-1·153)	0·261
IIb Non-Hodgkin lymphoma (except Burkitt lymphoma)	Northern Europe	364	85·7 (76·9-91·3)	88·9 (78·5-94·4)	87·0 (77·7-92·6)	1·041 (0·892-1·216)	0·606
	UK and Ireland	744	80·6 (74·0-85·7)	83·2 (76·5-88·1)	89·0 (82·8-93·1)	0·914 (0·826-1·011)	0·081
	Central Europe	1,391	84·4 (79·8-88·0)	88·4 (84·2-91·5)	86·5 (82·0-89·9)	0·967 (0·896-1·044)	0·389
	Southern Europe	209	81·3 (67·9-89·5)	81·6 (66·1-90·5)	83·9 (69·7-91·9)	0·986 (0·838-1·160)	0·863
	Eastern Europe	435	64·2 (54·5-72·3)	72·7 (62·5-80·6)	78·3 (68·4-85·4)	0·878 (0·796-0·969)	0·010
	All Europe	3,143	80·1 (72·2-85·8)	83·7 (75·3-89·3)	85·1 (77 - 90·3)	0·940 (0·897-0·984)	0·009
IIc Burkitt lymphoma	Northern Europe	113	95·7 (73·8-99·4)	94·3 (77·7-98·6)	94·5 (89·6-97·1)	1·068 (0·779-1·465)	0·681
	UK and Ireland	336	79·3 (68·9-86·5)	89·5 (81·1-94·3)	92·9 (75·4-98·1)	0·928 (0·807-1·067)	0·296
	Central Europe	779	95·0 (90·5-97·4)	92·9 (87·6-96·0)	94·3 (79·1-98·5)	0·995 (0·863-1·146)	0·944
	Southern Europe	128	92·9 (80·6-97·5)	81·6 (65·8-90·6)	96·4 (77·8-99·5)	0·975 (0·763-1·246)	0·842
	Eastern Europe	108	73·0 (54·1-85·1)	79·4 (62·4-89·4)	84·8 (73·4-91·5)	0·784 (0·629-0·979)	0·031
	All Europe	1,464	89 (72·5-94·0)	88·4 (73·8-94·6)	93·1 (78·0-97·5)	0·938 (0·866-1·015)	0·132
III All CNS tumours	Northern Europe	917	67·7 (60·9-73·6)	66·9 (60·1-72·9)	65·4 (58·1-71·8)	0·996 (0·937-1·058)	0·888
	UK and Ireland	3,045	58·0 (54·1-61·6)	57·3 (53·7-60·8)	54·4 (50·4-58·2)	1·007 (0·978-1·037)	0·622
	Central Europe	4,363	55·1 (51·9-58·2)	59·0 (55·8-62·0)	56·6 (53·3-59·8)	0·993 (0·969-1·016)	0·544
	Southern Europe	678	59·4 (51·8-66·2)	57·6 (49·4-65·0)	64·5 (55·7-72·0)	0·981 (0·921-1·045)	0·554
	Eastern Europe	1,525	51·1 (45·8-56·2)	47·3 (41·7-52·7)	54·5 (48·4-60·1)	0·982 (0·946-1·020)	0·352
	All Europe	10,528	56·7 (51·9-61·2)	57·1 (52·1-61·7)	58·2 (52·9-63·0)	0·996 (0·981-1·012)	0·661
IIIa Ependymoma	Northern Europe	112	56·9 (35·2-73·8)	63·8 (45·2-77·6)	59·0 (31·7-78·5)	1·020 (0·832-1·249)	0·851
	UK and Ireland	393	62·2 (51·9-70·9)	57·0 (46·6-66·1)	61·1 (50·0-70·4)	1·000 (0·918-1·090)	0·993
	Central Europe	608	65·0 (56·6-72·2)	73·2 (64·3-80·3)	70·3 (61·6-77·4)	0·936 (0·858-1·021)	0·138
	Southern Europe	101	53·7 (33·3-70·4)	74·9 (51·8-88·1)	83·2 (57·0-94·2)	0·953 (0·778-1·168)	0·642
	Eastern Europe	182	48·6 (32·8-62·7)	63·8 (43·2-78·6)	57·0 (39·2-71·3)	0·964 (0·848-1·097)	0·582
	All Europe	1,396	59·0 (45·8-70·2)	69·1 (54·4-79·4)	69·1 (53·5-79·2)	0·970 (0·921-1·021)	0·24
IIIb Astrocytoma	Northern Europe	160	64·5 (44·7-78·8)	63·3 (41·1-79·1)	56·3 (40·5-69·5)	1·057 (0·930-1·203)	0·395
	UK and Ireland	1,065	68·8 (62·2-74·4)	61·5 (55·5-66·9)	59·3 (52·2-65·6)	1·042 (0·984-1·104)	0·157
	Central Europe	1,464	58·1 (52·6-63·2)	52·1 (46·5-57·3)	55·5 (50·1-60·5)	1·001 (0·964-1·040)	0·960

	Southern Europe	196	64·9 (48·6-77·1)	55·0 (40·3-67·6)	66·1 (49·4-78·4)	0·932 (0·828-1·049)	0·245
	Eastern Europe	466	75·2 (67·2-81·5)	49·7 (39·3-59·3)	59·1 (46·9-69·3)	1·050 (0·975-1·130)	0·199
	All Europe	3,351	64·3 (55·0-71·8)	54·5 (45·1-62·7)	59·1 (49·2-67·2)	1·017 (0·989-1·045)	0·234
IIIc Embryonal CNS tumours	Northern Europe	256	61·7 (48·4-72·5)	55·3 (42·6-66·3)	64·3 (50·0-75·5)	0·956 (0·856-1·067)	0·416
	UK and Ireland	957	55·3 (48·7-61·5)	61·0 (54·7-66·8)	55·1 (48·4-61·3)	1·014 (0·961-1·069)	0·618
	Central Europe	1,569	55·1 (50·0-59·8)	63·5 (58·4-68·1)	60·0 (54·5-65·1)	0·990 (0·948-1·034)	0·652
	Southern Europe	192	79·8 (60·7-90·3)	53·1 (38·3-65·9)	62·5 (44·3-76·2)	1·076 (0·952-1·216)	0·240
	Eastern Europe	475	37·3 (27·9-46·7)	38·6 (29·3-47·9)	53·0 (42·9-62·2)	0·965 (0·908-1·027)	0·264
	All Europe	3,449	58·3 (48·7-65·7)	56·4 (47·9-64·2)	59 (49·3-67·2)	0·995 (0·968-1·023)	0·709
IVa Neuroblastoma	Northern Europe	491	61·2 (52·1-69·0)	73·4 (65·0-80·1)	79·6 (70·5-86·2)	0·862 (0·786-0·946)	0·002
	UK and Ireland	1,209	66·1 (60·7-70·8)	67·6 (62·5-72·2)	64·7 (58·8-70·1)	0·999 (0·948-1·054)	0·994
	Central Europe	2,376	78·1 (74·7-81·1)	72·7 (68·7-76·2)	70·3 (65·7-74·4)	1·063 (1·014-1·115)	0·011
	Southern Europe	356	65·0 (53·9-74·1)	66·9 (55·5-76·1)	71·9 (60·3-80·7)	0·918 (0·826-1·020)	0·112
	Eastern Europe	621	59·8 (53·3-65·6)	63·3 (55·6-70·1)	61·6 (53·1-69·0)	0·970 (0·904-1·040)	0·389
	All Europe	5,053	69·5 (63·3-74·8)	69·2 (62·3-74·9)	69·0 (61·8-75·0)	0·992 (0·964-1·020)	0·569
V Retinoblastoma*	Northern Europe	196	97·8 (85·3-99·7)	97·6 (84·3-99·7)	95·0 (81·5-98·7)	1·093 (0·620-1·924)	0·758
	UK and Ireland	497	97·5 (92·4-99·2)	97·7 (93·2-99·3)	99·1 (94·1-99·9)	0·812 (0·578-1·140)	0·229
	Central Europe	763	98·8 (95·2-99·7)	97·6 (93·7-99·1)	98·7 (94·8-99·7)	0·949 (0·655-1·374)	0·780
	Southern Europe	109	100 (100-100)	90·8 (67·7-97·6)	100 (100-100)	0·918 (0·516-1·633)	0·771
	Eastern Europe	157	86·5 (70·5-94·1)	84·0 (65·8-93·0)	81·0 (62·5-91·0)	1·132 (0·904-1·417)	0·280
	All Europe	1,722	96·9 (91·5-98·8)	94·0 (83·0-97·9)	97·9 (89·7-98·4)	0·994 (0·860-1·151)	0·944
Wilms' tumours (M-8960)	Northern Europe	418	82·1 (72·9-88·4)	90·0 (81·4-94·7)	85·6 (76·5-91·4)	1·038 (0·908-1·187)	0·585
	UK and Ireland	1,014	95·9 (92·3-97·9)	88·7 (84·0-92·1)	91·2 (86·8-94·2)	1·095 (0·971-1·234)	0·138
	Central Europe	1,781	91·7 (88·5-94·1)	93·2 (90·3-95·2)	94·4 (91·6-96·4)	0·965 (0·874-1·065)	0·481
	Southern Europe	235	87·9 (76·3-94·0)	92·0 (80·1-96·9)	85·7 (72·3-92·9)	1·052 (0·839-1·318)	0·662
	Eastern Europe	458	78·9 (69·4-85·7)	85·8 (77·6-91·1)	83·9 (74·6-90·0)	0·929 (0·825-1·046)	0·224
	All Europe	3,906	89·0 (82·2-93·0)	90·9 (84·5-94·4)	89·8 (83·0-94·0)	1·005 (0·951-1·062)	0·850
VIIIa Osteosarcoma**	Northern Europe	137	66·1 (46·7-79·8)	82·6 (65·2-91·8)	61·8 (43·6-75·6)	0·980 (0·814-1·181)	0·836
	UK and Ireland	320	66·4 (54·8-75·7)	47·2 (36·7-57·0)	67·4 (54·4-77·4)	0·978 (0·889-1·075)	0·646
	Central Europe	548	75·9 (66·9-82·8)	74·1 (64·7-81·4)	70·5 (61·7-77·6)	1·017 (0·919-1·126)	0·742

	Southern Europe	65	82·5 (46·1-95·3)	70·8 (48·1-84·9)	56·8 (26·4-78·7)	1·336 (1·021-1·748)	0·035
	Eastern Europe	176	62·5 (47·3-74·5)	63·5 (45·7-76·9)	56·4 (38·0-71·3)	1·014 (0·894-1·150)	0·826
	All Europe	1,246	73·4 (56·4-83·1)	68·3 (54·1-78·4)	64·3 (48·0-76·7)	1·011 (0·955-1·069)	0·711
VIIIc Ewing sarcoma	Northern Europe	123	73·6 (53·9-85·9)	55·5 (36·5-70·9)	71·1 (51·9-83·7)	0·981 (0·811-1·188)	0·849
	UK and Ireland	363	67·7 (56·3-76·7)	61·5 (51·1-70·4)	67·7 (57·2-76·1)	0·956 (0·865-1·057)	0·383
	Central Europe	686	72·6 (64·9-78·9)	65·0 (57·0-71·8)	69·5 (61·4-76·2)	1·007 (0·938-1·081)	0·849
	Southern Europe	94	76·3 (48·4-90·5)	71·9 (49·3-85·7)	73·8 (51·0-87·2)	1·122 (0·883-1·427)	0·344
	Eastern Europe	216	49·8 (34·7-63·1)	48·2 (32·3-62·4)	46·2 (32·0-59·3)	0·991 (0·894-1·098)	0·861
	All Europe	1,482	69·2 (54·6-79·1)	62·8 (49·3-73·2)	66·6 (53·4-76·5)	0·998 (0·952-1·046)	0·928
IXa Rhabdomyo sarcoma	Northern Europe	261	69·7 (54·2-80·8)	68·0 (52·1-79·6)	69·0 (54·7-79·6)	0·999 (0·882-1·132)	0·992
	UK and Ireland	708	60·3 (52·7-67·0)	73·9 (66·0-80·2)	64·3 (56·6-71·0)	0·997 (0·927-1·073)	0·944
	Central Europe	1,153	70·3 (64·4-75·4)	71·3 (65·4-76·4)	76·1 (70·1-81·1)	0·973 (0·915-1·035)	0·390
	Southern Europe	150	64·6 (49·3-76·3)	75·4 (58·9-86·1)	77·5 (62·1-87·2)	0·862 (0·711-1·046)	0·133
	Eastern Europe	255	54·2 (39·9-66·4)	61·2 (48·6-71·7)	39·3 (25·7-52·6)	1·026 (0·923-1·400)	0·635
	All Europe	2,527	65·0 (54·9-73·2)	70·9 (60·7-78·6)	68·5 (58·5-76·5)	0·985 (0·948-1·025)	0·472

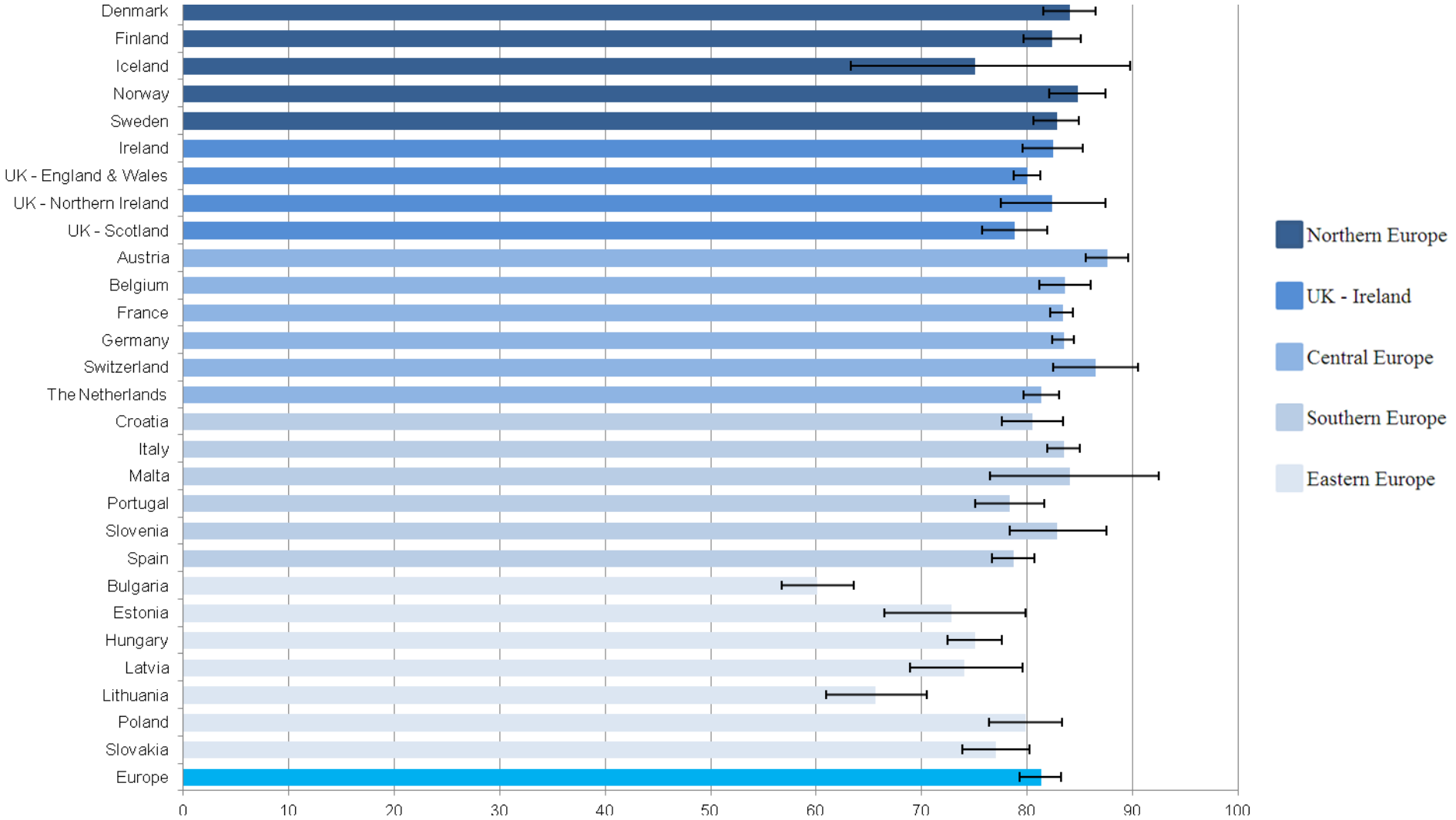
Survival estimated by the period approach. European period survival estimates were region-weighted. Hazard ratio (HRs) adjusted by age, sex, region; CNS and all cancers combined are also adjusted by case mix. * Children aged 0-4 years only. **Children aged 10-14 years only.

Figure 2: Five-year survival for acute lymphoid leukemia diagnosed in 2000-2007 in European children by country



Includes data for 15,860 cases. Data adjusted by age, sex and period of diagnosis. European estimate was country-weighted.

Figure 3: Five-year survival for all cancers combined (CNS tumours excluded) diagnosed in 2000-2007, in European children by country



Includes data for 50,080 cases. Data adjusted for age, sex, case mix, and period of diagnosis. European estimate was country-weighted.

Appendix

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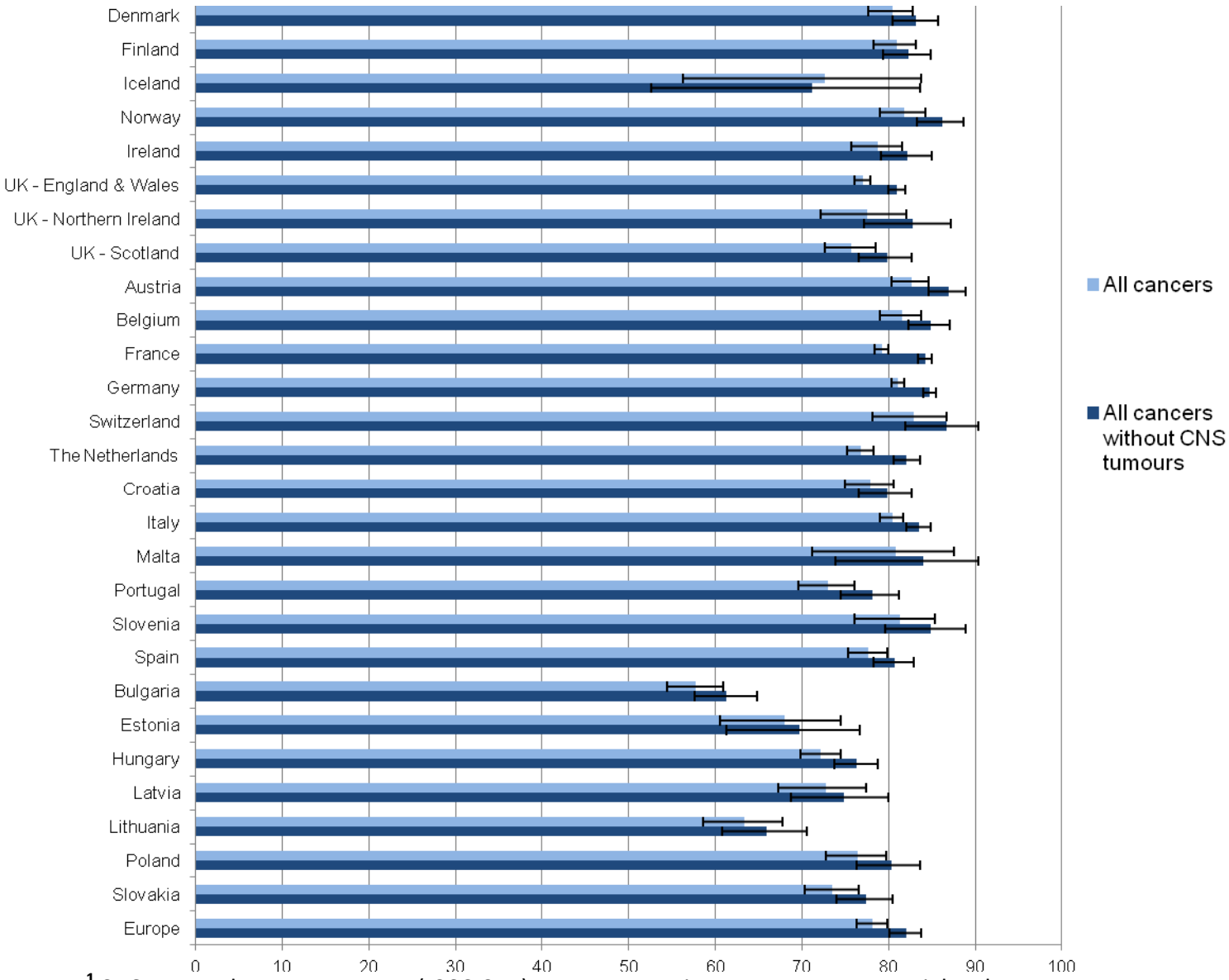
Appendix Table: CNS tumors in children with and without nonmalignant lesions: crude incidence rates and 5-year survival (%) with 95% confident intervals (95% CI), by country, based on 14,940 cases. Period of diagnosis 2000-2007

Country/European area	CNS malignant tumours		CNS malignant tumours 2000-2006 crude incidence rate	CNS malignant tumours and pylocitic astrocitomas		CNS malignant tumours and pylocitic astrocitomas 2000-2006 crude incidence rate	CNS malignant and benign tumours		CNS malignant and benign tumours 2000-2006 crude incidence rate	Microscopically verified cases
	Survival	95% CI		Survival	95% CI		Survival	95% CI		
Denmark	60·6	51·1-68·7	1·6	60·6	51·1-68·7	1·6	77·1	71·3-81·9	3·2	93%
Finland	75·3	69·0-80·5	3·2	77·1	71·1-81·9	3·4	79·5	74·2-83·8	3·9	98%
Iceland	81·8	44·7-95·1	1·5	75·4	46·1-90·2	2·4	80·4	55·4-92·3	3·3	18%
Norway	62·5	54·2-69·7	2·4	71·5	65·0-77·1	3·4	78·3	73·1-82·5	4·6	85%
Ireland	59·7	50·4-67·7	2·0	69·5	62·3-75·6	3·1	70·9	64·1-76·7	3·3	72%
UK - England & Wales	57·1	54·4-59·7	2·1	67·1	64·9-69·2	2·9	71·8	69·9-73·6	3·6	75%
UK - Northern Ireland	55·1	40·7-67·3	1·9	67·5	55·4-76·9	2·8	70·5	59·9-78·8	3·5	71%
UK - Scotland	52·7	43·4-61·1	1·9	61·3	53·3-68·4	2·6	61·3	53·3-68·4	2·6	76%
Austria	63·8	57·4-69·5	2·5	70·4	64·9-75·2	3·2	72·1	66·8-76·7	3·4	95%
Belgium	64·1	56·5-70·7	2·5	72·4	66·3-77·6	3·4	74·1	68·4-78·9	3·8	93%
France	51·8	49·3-54·2	2·0	64·6	62·6-66·5	2·9	70·8	69·1-72·5	3·6	79%
Germany	59·1	56·6-61·5	2·0	70·4	68·4-72·2	2·9	73·9	72·2-75·6	3·4	83%
Switzerland	59·6	43·7-72·3	1·9	61·9	46·6-74·0	2·1	65·4	51·0-76·6	2·3	90%
The Netherlands	46·4	41·8-51·0	2·1	60·7	56·8-64·4	3·0	67·0	63·6-70·2	3·6	79%
Croatia	70·2	62·4-76·7	3·3	72·2	64·9-78·2	3·7	72·2	64·9-78·2	3·7	73%
Italy	61·3	56·7-65·5	2·4	69·5	65·6-72·9	3·1	74·1	70·8-77·1	3·8	74%
Malta	61·2	29·4-82·1	2·7	70·0	41·5-86·5	3·5	71·8	44·3-87·4	3·7	79%
Portugal	49·2	40·2-57·5	1·7	54·5	46·5-61·9	2·1	56·6	48·8-63·8	2·2	91%

Slovenia	57·8	40·9-71·5	1·7	69·4	55·2-79·8	2·4	72·4	59·2-81·9	2·7	100%
Spain	62·6	55·9-68·6	2·5	68·1	62·1-73·3	2·9	70·7	65·2-75·5	3·5	75%
Bulgaria	38·1	30·4-45·8	2·1	42·8	35·2-50·1	2·3	42·8	35·2-50·1	2·3	70%
Estonia	61·7	43·8-75·4	2·3	61·7	43·8-75·4	2·3	61·2	43·9-74·7	2·4	91%
Hungary	55·0	48·8-60·8	2·5	64·8	59·7-69·4	3·4	67·6	62·8-71·9	3·8	91%
Latvia	65·6	52·8-75·7	2·8	65·8	53·1-75·9	2·8	65·8	53·1-75·9	2·8	62%
Lithuania	45·3	36·4-60·8	1·7	53·0	40·6-65·3	1·9	53·6	41·3-66·0	1·9	78%
Poland	61·7	52·3-69·7	2·3	61·8	52·7-69·7	2·4	62·1	52·9-69·9	2·4	77%
Slovakia	52·7	43·2-61·3	2·0	67·6	60·3-73·9	3·0	71·9	65·2-77·4	3·5	78%
Europe [1]	57·7	52·3-62·5	2·1	66·2	61·5-70·4	2·9	70·0	65·7-73·9	3·4	84%

[1] Data from 28 European countries were analyzed, Sweden was excluded. European survival estimates were country-weighted

Appendix Figure: Five-year crude survival for all cancers combined with and without CNS[1] tumours diagnosed in 2000-2007 by country, based on 57,956 cases, in European children (age 0–14 years)



[1] CNS= central nervous system (ICCC-3 III). European estimate was country-weighted