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Cancer in children and adolescents in Europe: Developments over 20 years and future challenges

K. Pritchard-Jones[a,*], P. Kaatsch[b], E. Steliarova-Foucher[c], C.A. Stiller[d], J.W.W. Coebergh[e]

[a]Section of Paediatric Oncology, Institute of Cancer Research & Royal Marsden Sutton, Surrey SM2 5PT, UK
[b]German Childhood Cancer Registry (GCCR), University of Mainz, Germany
[c]Descriptive Epidemiology Group, International Agency for Research on Cancer, Lyon, France
[d]Childhood Cancer Research Group, Department of Paediatrics, University of Oxford, Oxford, UK
[e]Department of Public Health, Erasmus University Medical Center Rotterdam, The Netherlands

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ABSTRACT

This special issue contains 18 articles describing population-based analyses of incidence and survival for cancer among children and adolescents in Europe over the period 1978–1997. The analyses were derived from the large database of the ACCIS project (Automated Childhood Cancer Information System), which was built through collaboration of 62 population-based cancer registries in 19 European countries. Data on 88,465 cancers in children and 15,369 in adolescents (age 15–19 yrs) were included in the various analyses, making this the largest database on cancer in these age-groups in the world. National data were grouped into five European regions to allow comparisons of incidence and survival, for all cancers and by tumour type, including analysis of trends in both over time. This overview paper focuses on the comparability of the data from multiple registries and describes the potential confounding factors. Age-standardised annual incidence rates of many, but not all, cancers in children and adolescents are clearly rising. There are geographical differences in survival for the majority of tumour types. Survival rates increased for nearly all types of cancer in children and adolescents. The implications of these findings for aetiological factors and treatment delivery for cancer in children and adolescents are discussed.

1. Introduction

This special issue describes variation in incidence of and survival from cancer in children and adolescents in Europe over the period 1978–1997, with follow-up of vital status until the late 1990s. The estimates are based on the large database of the ACCIS project (Automated Childhood Cancer Information System),[1] which was built through collaboration of 62 population-based cancer registries in 19 European countries. All together 730 million person-years of observation are included in the childhood age range (0–14 years) and 88 million person-years at adolescent age (15–19 years). Data on 88,465 cancers in children and 15,369 in adolescents were included in various analyses, making this by far the largest database on cancer in these age-groups in the world.

This special issue adds to the results of the previous comparative studies, notably the International Incidence of Childhood Cancer[2,3] with respect to Europe, and the population-based survival studies from the Eurocare project.[4,5] Detailed analyses for specific subgroups of tumours, defined according to the International Classification of Childhood Cancer (ICCC)[6] were complemented by those for additional entities of clinical or epidemiological interest. In adolescents, cancer incidence and survival has rarely been described on

* *Corresponding author:* Tel.: +44 208 661 3498; fax: +44 20 8661 3617.
E-mail address: Kathy.Pritchard-Jones@icr.ac.uk (K. Pritchard Jones).
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such a large scale. Incidence rates and survival have been compared among five European regions to identify geographical patterns. This is the first time that incidence time trends in children and adolescents were examined in such an extensive pan-European format.

2. Overview of information sources

Within the ACCIS project, special emphasis was placed on evaluation of data quality and comparability. This was a long process coordinated by the International Agency for Research on Cancer (IARC) and the ACCIS Scientific Committee, requiring active cooperation from the cancer registries. Data comparability is especially important because quantitative data on cancer in children and adolescents are scarce and small changes in absolute numbers represent a large relative difference. In the process of data evaluation, the ACCIS Scientific Committee therefore had to exclude substantial proportions of cases and person-years because of insufficient comparability (Steliarova-Foucher, Kaatsch, Lacour et al., this issue). Long traditions in cancer registration and pan-European efforts of standardisation within the European Network of Cancer Registries (ENCR)[7] resulted in much improved comparability between registries, although it is still imperfect. In various articles of this special issue questions have been raised on the extent of true comparability of the results, given the differences in medical practices, registration criteria, tumour diagnosis and classification across the areas of participating registries and their improvements over time. For example, there seem to be small, but systematic differences in incidence of childhood cancer between paediatric and general cancer registries, possibly related to varying case ascertainment and referral. Such differences were especially apparent for thyroid carcinomas and, retinoblastoma. While some geographical variation may be affected by differences in exposure to underlying risk factors, some can be partially explained by differences in diagnostic or classification criteria. For example, the high incidence rates observed in the North can in part be explained by differences in data production since the Nordic countries have long-standing nationwide compulsory registration with a relatively high level of automation, and the possibility of linkage with all population databases. In contrast, the incidence and survival figures in registries without access to national mortality databases may be biased and deficient follow-up for vital status might overestimate survival [Steliarova-Foucher, Kaatsch, Lacour et al., this issue]. Only more detailed analyses, using additional statistical and clinical information could verify these assumptions and quantify their effect. In particular, comparison of pathology review processes across the participating areas for certain tumour types (lymphomas, brain tumours, soft tissue sarcomas, bone tumours, thyroid carcinomas) would help to quantify the role of such differences in variation of the incidence rates. Despite these described limitations in comparability, the scale of this project has produced indicators of reference for the European population of children and adolescents and suggested avenues for improvement of current data collection and future research.

Correct interpretation of the results obtained is of utmost importance because of the burden that cancer represents for the young patients, their families and the whole society. The differences in incidence and survival described in this special issue should be interpreted in a positive way, as an identification of the needs for future epidemiological and clinical research as well as further improvements in clinical organisation.

3. Variations in incidence

The total age-standardised incidence was 139 per million children for Europe overall, for the period 1988–1997 (Stiller, Marcos-Gragera, Ardanaz et al., this issue), varying from 131 per million in the British Isles to 160 per million in Northern Europe and from 116 per million to 173 per million between indi-

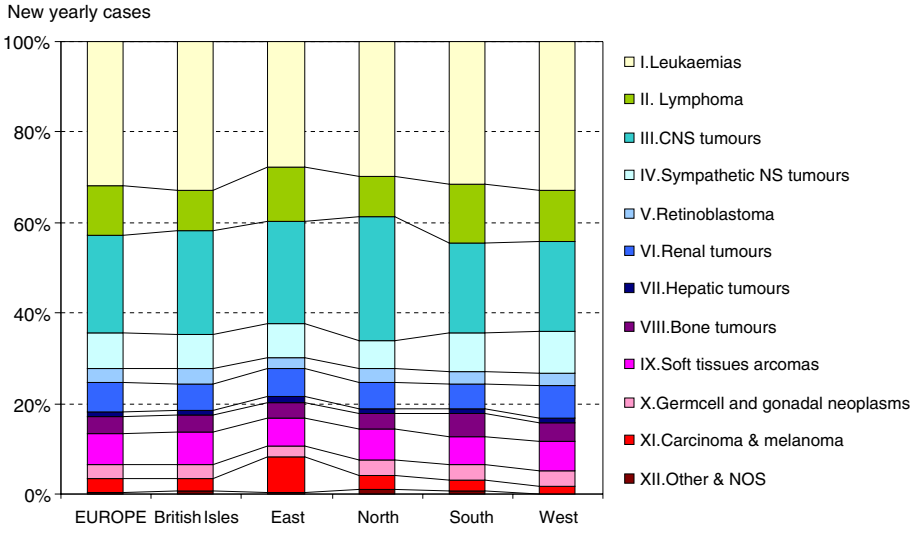

Fig. 1 – New yearly cases of cancer in children aged 0–14 years, showing contribution of various cancer types as defined by the International Classification of Childhood Cancer[6] to the total incidence in Europe, 1988–1997. The proportions are based on the age-standardised rates (world standard). Source: ACCIS.

vidual countries. Nevertheless, the relative ranking and proportional distribution of tumour-specific incidence rates was rather similar across the regions (Fig. 1). There were some exceptions; e.g. the marked excess of carcinomas in the East, wholly attributable to the high incidence of thyroid carcinoma in Belarus. The greatest range of regional incidence rates was for central nervous system (CNS) tumours, from 27 per million in the West to 44 per million in the North. Some of the variation for CNS tumours was due to differences in the registration of non-malignant tumours. However, there was still a wide range of inter-regional variation in the incidence rates when only malignant CNS tumours were considered. Differences in diagnostic practices probably accounted for much of this variation, but geographical differences in underlying risk factors cannot be ruled out.

Cancer incidence in adolescents (aged 15–19 years) was greater than in children, at 186 per million in Europe as a whole, for the period 1988–1997 with wide variations between regions: from 169 per million in the East to 210 per million in the North. In this age group, lymphomas were the most frequent diagnostic group overall and in each region, followed by epithelial tumours (Stiller, Desandes, Danon et al., this issue). In general, the tumours of childhood as well as adulthood were rare in adolescents. The incidence of carcinomas starting to increase from adolescence into adulthood is probably related to the external factors identified in adults. For example, geographical variations in incidence of melanoma and skin carcinomas can certainly be explained by the extent of UV exposure in relation to prevailing skin type (de Vries et al., this issue).

The estimated incidence rates were of reasonable stability due to the large numbers of cases, even for relatively small tumour groups. It was possible to clearly describe differences in incidence between the sexes across age groups and over time. Overall cancer incidence was higher among boys than among girls at all ages, including adolescents (Stiller, Marcos-Gragera, Ardanaz et al. and Stiller, Desandes, Danon et al., this issue). However, several tumours visibly predominated in girls: renal tumours, (Pastore, Znaor, Spreafico et al., this issue), thyroid carcinoma (Steliarova-Foucher, Stiller, Pukkala et al., this issue) and melanomas (de Vries et al., this issue). The sex specific differences provide clues for aetiology of tumours, which may be related to differences in sex chromosome or hormonal activity. Similarly, variation of incidence with age helps to identify potential causal factors in relation to the developmental maturity of the human body.

We believe that most differences in incidence reflect true variations in underlying risk factors (in interaction with host features), although random variation cannot be excluded. In addition to variation in the incidence of thyroid carcinoma, almost exclusively related to the Chernobyl accident (Steliarova-Foucher Stiller, Pukkala et al., this issue), variation in underlying risk factors would probably explain the low incidence of Ewing's sarcoma in children in Northern Europe compared with the South (Stiller, Bielack, Jundt et al., this issue) and the less marked childhood peak in lymphoid leukaemia at age 2–4 years in the East compared with other European regions (Coebergh et al., this issue). How many of these differences are due to genetic predisposition or due to exposure and/or susceptibility to environmental factors remains unexplained. Collection of other data items is necessary, such as immunophenotype, which is now coded in the third edition of the International Classification of Diseases for Oncology (ICD-O-3)[8] and classified in separate entities within the new International Childhood Cancer Classification.[9]

Analyses of trends in incidence of childhood cancers, based on 77,111 cases diagnosed during 1978–1997, show that the overall incidence rate has increased significantly ($p < 0.0001$) from an ASR (age-standardised rate) of 120 per million children in 1978–1982 to 141 per million in 1993–1997 (Kaatsch et al., this issue). The average annual percentage change (AAPC) across Europe was 1.1% and shows no sign of slowing in the most recent quinquennium. The rising trend was observed in all five geographical regions and in the majority of the disease groups (in order of AAPC): soft tissue sarcomas (1.8%), brain tumours, tumours of the sympathetic nervous system, germ-cell tumours, carcinomas, lymphomas, renal tumours, and leukaemias (0.6%). Little change was seen in the incidence of bone tumours, hepatic tumours, and retinoblastoma.

These temporal changes appear to be real to the extent that lack of awareness of childhood cancer should no longer have been a major issue in Europe since the early 1980s and many of the contributing registries had started before the study period. Selection of cancer registries for the analyses of time trends did not seem to affect the incidence trends (Steliarova-Foucher, Kaatsch, Lacour et al., this issue). It is possible that improving diagnostic methods might have contributed to part of this increase. In particular, non-invasive diagnosis of CNS tumours might have inflated the rates in the areas where the novel techniques were widely applied during the study period (Peris-Bonnet et al., this issue). For other tumour types, the improvement in diagnostic methods would most likely result in a more precise characterisation of a tumour, rather than an overall increase of incidence. This was exemplified by the reduction of the proportion of unspecified tumour types over the study period.

The increase in incidence of childhood cancer in this project does not seem to be related to the organised screening programs for neuroblastoma, because such activities were only implemented in some regions or towards the end of the study period. However, awareness of available tests in other areas or periods might have translated into some of the increase of neuroblastoma in young children in West and South of Europe [Spix et al., this issue].

The increasing incidence trends presented in this special issue refer to the period 1978–1997. According to more recent data in the registries contributing to this special issue, the tendency does not seem to change.[10–12] Increasing incidence was also reported in other parts of world.[13] However, it is extremely important that analysis for further time periods is conducted on a European level to validate these observations. In particular, changes in registration completeness should be evaluated formally, in order to exclude or quantify the potential effect of improving registration, which was not possible in this study.

While some of the increase in childhood cancer incidence could be attributable to improvements in diagnosis and completeness of registration, the consistent increase over the

study period suggests the presence of sustained changes in risk factors. Such changes probably include prenatal and perinatal factors such as changing foetal growth patterns related to rising maternal age at first pregnancy, possibly changing exposure to sex hormones and increasing birth weight. Altered patterns of childcare, resulting from improving socio-economic conditions and the decreasing number of children per family, might have lowered stimulation of immunity to infections in infants and may have given rise to the more frequent occurrence of 'uncommon response to common infections'.[14] Research in etiology, demography and biology might ascertain the nature of these risk factors. At a population level, collection of further data items such as age of the mother at birth, birthweight, number of siblings, serious infections, socio-economic status, would help to refine some of these hypotheses.

4. Variations in survival

Overall 5-year survival was 72% for all children registered in the 54 population based cancer registries contributing to the analysis of the period 1988–1997 (Sankila et al., this issue). In seven of the 12 ICCC disease groups the five-year overall survival was below 75%. Combined with their relatively greater incidence, leukaemias, CNS tumours, sympathetic nervous system tumours (mainly neuroblastoma) and soft tissue sarcomas accounted for more than three quarters of all deaths within 5 years of diagnosis (Fig. 2). Survival improved significantly over the period 1978–97 used for analysis of trends, from 54% for cases diagnosed during 1978–82 to 75% for those diagnosed in 1993–97 (Magnani et al., this issue). These results are concordant with those obtained from the Eurocare data in the period 1978–89.[15] From the mortality data, presented for 23 European countries in the period 1955–1997,[16] early improvements in the North and West were followed by other European countries, with the most recent progress in the East. Within ACCIS, the improvement was statistically significant in all European regions and was most rapid in the East. The greatest reduction over time in mortality at 5 years (more than 50%) was observed for leukaemia (the combined group, and acute lymphoblastic leukaemia in particular), lymphomas (the combined group and non-Hodgkin's lymphomas), retinoblastoma, hepatic neoplasms and germ cell tumours. The lowest reduction in mortality (around 30%) was seen for CNS tumours and soft tissue sarcomas (Magnani et al., this issue). The extent of the reduction in mortality depended on the baseline survival in the reference period 1978–1982, which was already relatively favourable for some tumour groups, such as Hodgkin's disease, retinoblastoma or thyroid carcinoma.

Geographical comparisons in 5 year survival were based on outcomes for nearly 50,000 children diagnosed over the period 1988–1997 (Sankila et al., this issue). Five year survival varied between the five geographical regions from 62% to 77%. The region defined as East generally exhibited lower survival rates than the other defined regions of Europe. The ranking among the European regions hardly changed over the study period, with highest survival in the North and the West and lowest in the East.

In comparisons between North, South, West and British Isles, the North often had the highest survival figures and the lowest were seen in South and British Isles. Differences in overall survival were small (from 71% to 77%) but significant due to the large numbers of cases. Some of this difference could have been caused by differences in the registration practices and completeness of follow-up, as discussed below. In comparisons by ICCC tumour groups between these four regions, substantial differences were seen between the regions with highest versus lowest 5-year survival for neuroblastoma (from 50% to 67%), and hepatic tumours (from 54% to 83%). Smaller differences were seen in CNS tumours (from 63% to 72%), renal tumours (from 81%

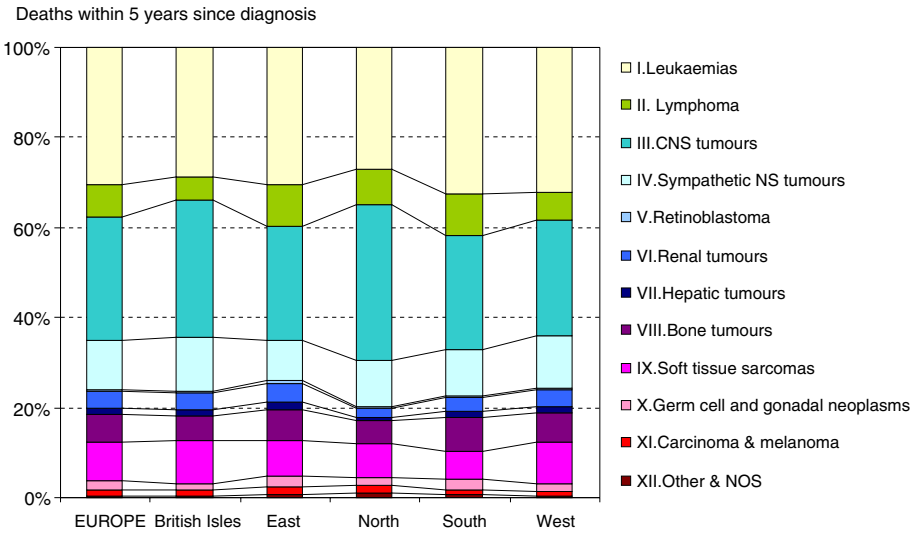

Fig. 2 – Deaths within 5 years since diagnosis showing contribution of various cancer types as defined by the International Classification of Childhood Cancer[6] to the total number of deaths. Based on the actual numbers of deaths observed among children aged 0–14 years at diagnosis in the contributing registration areas of Europe during 1988–1997 and followed up for 5 years. Source: ACCIS.

to 91%), germ cell tumours (from 81% to 90%), leukaemia (from 70% to 78%) and in lymphomas (from 81% to 88%), (Sankila et al., this issue).

Overall 5-year survival for adolescents (aged 15–19 years) was 73%, similar to the 72% reported for children [Stiller, Desandes, Danon et al., this issue]. However, this similarity can be attributed to the higher proportion of tumours with favourable prognosis (such as Hodgkin's disease and epithelial tumours) in adolescents than in children. Adolescents had substantially lower 5-year survival than children for leukaemia (44% versus 73%) and bone tumours (48% versus 61%), but somewhat higher survival for CNS tumours (70% versus 64%). There is increasing evidence that adolescents with cancers that are biologically similar to those found in children have higher survival when treated on the more intensive protocols developed for children rather than adults,[17] yet this practice is still not widespread. The geographical differences in survival were similar to those seen in children.

When interpreting differences in survival among patient groups, some considerations should be taken into account. First, the completeness of follow-up may influence the outcome, with incomplete follow-up possibly overestimating the outcome, due to the actuarial method of calculation (Steliarova-Foucher, Kaatsch, Lacour et al., this issue). Second, the extent and significance of any difference must be evaluated in terms of its clinical meaning. Third, the differences in survival observed between the regions represent comparisons of average outcome, yet within-region variation between countries may be just as great (Fig. 3). Nevertheless, grouping the countries into the regions in this special issue may help to discover certain similarities between the registries and countries of the same region. Such differences indicate that there is room for improvement, although the reasons for observing the differences may not always be well understood. In addition to success in treatment, survival will also be influenced by other factors, as shown in Fig. 3.

In Fig. 3, 5-year survival, estimated for selected countries based on the data available in ACCIS, is shown with 95% confidence intervals to illustrate the statistical variability of each estimate. Overlapping confidence intervals suggest that the estimates of national survival rates are broadly consistent with each other. Each estimate also reflects the case composition and (in)completeness of ascertainment and follow-up within the available datasets, which affects comparability of these figures. For example, the higher proportion of non-malignant cases in the CNS (with presumably better prognosis) may in part explain the higher survival recorded in Nordic countries. But there might also be differences between the regions in pathological definition of a tumour (its degree of malignancy), which would influence the final case-mix. A positive association between incidence and survival indicates that in the high incidence areas more cases with favourable prognosis may have been registered and such effect of overdiagnosis was seen, for example in neuroblastoma (Spix et al., this issue). The relatively lower survival seen in some countries reflects a multitude of factors, ranging from relative (lower) wealth of the country and its residents through health policy to organisation of medical care and treatment

Factor	Influence
Quality of diagnosis	Lack of verification of malignancy may lead to inclusion of non-cancerous cases, which would improve survival.
Screening	Whether organised or spontaneous, screening would detect cases with more favourable prognosis. In case of neuroblastoma, this leads in some cases to overdiagnosis.
Tumour behaviour	Larger proportion of benign brain tumours (with somewhat better survival) may explain higher survival.
Classification criteria	Classifying less aggressive tumours into categories of more aggressive tumours would improve overall survival. This is a particular problem in CNS tumours but can also affect several other groups. Central review of diagnosis improves precision of classification.
Tumour stage	Larger proportion of tumours with lower stage would lead to a more favourable outcome.
Completeness of follow-up	Incomplete follow-up (e.g. due to strict confidentiality rules, migration) may result in overestimation of overall survival.
Access to medical care	Weak infrastructure, long distance to referral hospital, low socio-economic status, low awareness of general paediatricians may all lead to delayed diagnosis or treatment, and therefore lower survival.
Participation in protocols or clinical trial	Large proportion of cases participating in protocols or controlled clinical trials would result in more favourable survival.

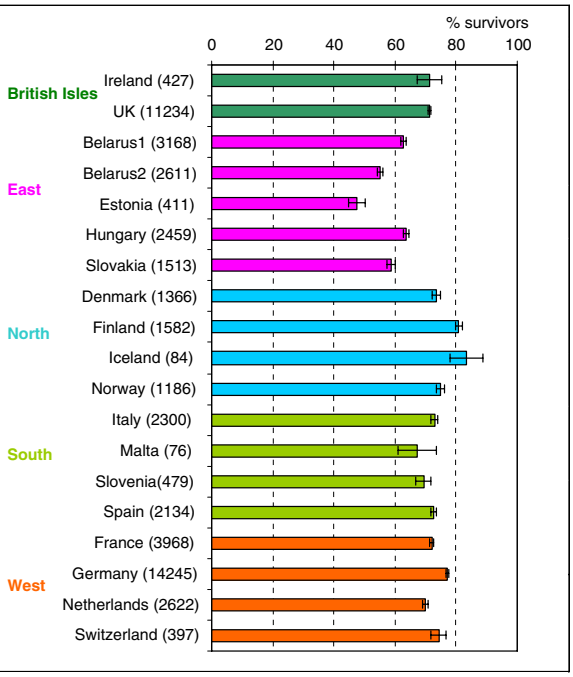

Fig. 3 – Factors influencing the differences in 5-year actuarial population-based survival between the national estimates based on the cohorts of childhood cancer patients aged 0–14 years at diagnosis during 1988–1997 and followed-up in the registries contributing to the analysis of survival [Sankila et al., this issue]. The line sections at the end of the bars represent the 95% confidence interval of the point estimate. Numbers of patients included in the survival analysis are shown in brackets. Two sets of results are shown for Belarus: Belarus1 (including all cases) and Belarus 2 (excluding thyroid carcinomas). Source: ACCIS.

standards. Progress in survival is the result of long term investment in manpower and infrastructure to diagnose and treat children and adolescents with cancer. Developing this infrastructure requires suitably trained personnel with access to continuous professional development, and implementation of clinical trials, which are viewed as the best 'standard of care' in paediatric haemato-oncology. Standards to which nations and organisations may aspire have been highlighted by the best results of large clinical trial groups. However, translation of these successes to entire populations is influenced by allocation of national resources and organisational structures as well as the needs of the specific population and profession. It might be expected that the results of population-based survival be inferior to those reported from large clinical trials, the latter applying more strict eligibility criteria, while a population-based cancer registry also includes cases with late or unusual diagnosis and with severe co-morbidity.

The survival analyses presented in this special issue consider the cohorts of cases diagnosed until 1997 and then followed-up for a few years. It is likely that the situation has further improved in 2006. Given their lower baseline survival, the countries grouped here within the East can be expected to continue to experience the largest increases in survival, as they did during the period of this study. More up-to-date estimates of cancer patient survival can be produced using period survival methodology,[18] and its application to the ACCIS data is underway.

5. Conclusions and recommendations

The authors of the articles in this special issue have suggested ways for further development of the ACCIS project as a common project of European cancer registries and the organised paediatric haemato-oncology community. These suggestions are summarised below:

First, continuity and further improvement of data collection are necessary to attain better comparability and more precise description of the variation in cancer incidence and survival for children (and adolescents) in Europe. The material to update the current results to the year 2002 or beyond is already available in many cancer registries. A positive impact on quality control in the participating registries during this work was reported (Steliarova-Foucher, Kaatsch, Lacour et al., this issue). Further standardisation is required in data definition (e.g. meaning of date of diagnosis, coding multiple tumours and inclusion criteria, etc.) and in use of the standard classification systems,[8,9] to allow more precise comparison between subgroups of tumours internationally. Improvement of data quality is also an ethical requirement: it is important to ensure that all information contained within the data is used to learn from past experience.

Second, a few more variables should be collected to maximise the value of the routine data collection. For example, in addition to 'date of incidence', 'date of registration' would help to evaluate data flow in a cancer registry and estimate its completeness,[19] which was not possible with data currently available. Data on stage of disease at diagnosis and primary treatment would help to better interpret differences in survival between groups of patients with neuroblastoma [Spix et al., this issue] or Wilms' tumour [Pastore, Znaor, Spreafico et al., this issue]. Collection and careful coding of laterality for the cases of retinoblastoma and Wilms' tumour would help research into identifying external risk factors for these tumours [MacCarthy et al. and Pastore, Znaor, Spreafico et al., this issue]. Records on participation of each case in a clinical trial or a treatment protocol would help to refine the interpretation of geographical and temporal differences in survival.

Third, the proportion of 'unspecified' tumour types should be further reduced; the differences between the regions show that there is room for such improvement. In addition, several cancer registries were not included in the analyses because of too many unspecified tumours. Also, the need for validation of tumour subtypes was identified in several articles in this issue, as the way to allow more precise interpretation of geographical differences and changes over time for the majority of tumour types in children and adolescents (e.g. haematopoietic neoplasms, soft tissue tumours and thyroid carcinoma). Comparison of the criteria for coding behaviour of CNS tumours would probably help to explain at least a part of the difference in incidence rates between the North and other regions. Such improvement in the quality of diagnosis on a population scale is beyond the sole responsibility of the cancer registries and active collaboration with attending oncologists/pathologists is therefore indispensable.

Fourth, there is potential for improvement of follow-up of the patients (for vital status and second primary tumours), in order to remove some uncertainty in interpretation of the reported differences [Sankila et al. and Magnani et al., this issue]. In some countries, this could be achieved by enabling individual linkage of cancer registry records with mortality databases.

Fifth, a need for a continuous support from the European Union (EU) became evident. This special issue is the end result of 6 years work, the first four of which were financed by the EU. Cessation of these funds just when this project was ready to produce important European figures has slowed publication of results considerably. Publishing data for the late nineties in 2006 may seem somewhat obsolete, even though probably not differing much from current data. However, the sustained rise in cancer incidence rise and survival over the study period testify the need for close monitoring of these trends. Plans for continuation of ACCIS depend heavily on the availability of modest funds for coordination of this European endeavor, centralised analysis of data and organisation of truly international publications, as illustrated by this special issue. Direct involvement of cancer registries and clinicians in analysis and interpretation is the way to achieve considerable improvement of data comparability. The production of this special issue necessitated pan-European collaboration and the information produced is indispensable for monitoring progress in the field within the EU.

Sixth, an urgent need for (re-)opening the access to individual data was identified in many countries. The valuable publication European Directive 95/46/EC on data protection[20] opened ways for the variable interpretation of data protection and enlarged rather than diminished disparities within the EU. In some new member states, this Directive replaced the legislative vacuum on the subject and resulted in restriction of access to identifiable data for the cancer registries,

although this might have been available for the previous 50 years. To produce reliable and good quality data, cancer registries need to have access to personal data without explicit consent of patients or parents and need to be able to link data on birth, diagnosis and death for each patient. Information that is thus generated is used to improve care for future patients or possibly prevent future occurrence of some cancers. By disclosing minimum personal information to a limited and identified number of professionals working in a cancer registry, each individual thus contributes to improvement of health status within their society. Collection, storage and linkage of health data, in a well defined framework, is at least as important for the society as the compulsory disclosure of fiscal (financial) data. Increasingly, identity of an individual is hidden to the registrars, which hinders completeness and good quality of incidence and follow-up data. Request of a written consent for inclusion in a cancer registry is not compatible with the production of reliable incidence rates and completeness of registration. A link between the cancer registries and national databases of deceased persons is necessary to ensure high quality of follow-up. Comparability of data across Europe can only be achieved in an environment of trust, where the confidence of personal health data is protected, but accessible. Again, the European Commission has an important role in promoting these principles across Europe. The experience of the Nordic countries clearly shows that data linkage is possible, useful and safe.

Finally, a common European approach is particularly important for research into rare diseases such as cancer in children and adolescents. As shown in the ACCIS project, important reference data can be generated within Europe through the cancer registries and health professionals who help to create the primary data. The added value is a step forward in understanding the cancer burden in young people.

Conflict of interest statement

None declared.

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S V Petrovich, O Budanov (Belarus); H Storm, N Christensen (Denmark); T Aareleid (Estonia); T Hakulinen, R Sankila, E Pukkala (Finland); E Le Gall, I Tron (Brittany, France), B Lacour, E Desandes (Lorraine, France), J L Bernard, P Pillon, J C Gentet (PACA and Corsica, France), F Freycon, C Berger (Rhone Alps, France), L Remontet (Francim, France), A Danzon, M Mercier (Doubs, France), J P Daurès, B Tretarre (Herault, France), F Ménégoz (Isère, France), A V Guizard (Manche, France), M Velten (Bas-Rhin, France), A Buemi (Haut-Rhin, France), N Raverdy (Somme, France), M Sauvage, P Grosclaude (Tarn, France); P Kaatsch, B Eisinger, R Stabenow (Germany); D Schuler, Z Jakab, G Borgulya (Hungary); L Tryggvadottir, J G Jonasson, K Bjarnadottir (Iceland); H Comber, F Dwane (Ireland); C Magnani, G Pastore (Piedmont, Italy), F Pannelli, C Pascucci (Marche, Macerata, Italy), S Ferretti (Ferrara, Italy), E Conti, V Ramazzotti, M C Cercato (Latina Province, Italy), M Vercelli, A Puppo (Liguria, Italy), P Crosignani, G Tagliabue, A Tittarelli (Lombardy, Italy), V De Lisi, P Sgargi (Parma, Italy), R Zanetti, S Patriarca (Piedmont, Italy), R Tumino (Ragusa, Italy), M Budroni, D Piras (Sassari, Italy), E Paci, E Crocetti (Tuscany, Italy), F La Rosa, F Stracci (Umbria, Italy), P Zambon, S Guzzinati (Veneto, Italy); M Dalmas (Malta); JWW Coebergh, J van Dijck, A Wit, H de Ridder-Sluiter (Netherlands); F Langmark, A Johansen, A Andersen (Norway); I Plesko (Slovakia); M Primic Žakelj, V Pompe-Kirn (Slovenia); R Peris-Bonet, B Giner (Spain), E Almar Marques, A Mateos Ramos (Albacete, Spain), J Ramon Quiros Garcia, A Cañada Martínez (Asturias, Spain), I Izarzugaza (Basque, Spain), A Alemán Herrera (Canary Islands, Spain), P Viladiu, R Marcos, A Izquierdo (Girona, Spain), C Martínez Garcia (Granada, Spain), A Obrador, I Garau (Mallorca, Spain), E Ardanaz (Navarra, Spain), J Borràs, J Galceran (Tarragona, Spain), J de la Bárcena Guallar, M C Martos Jiménez (Zaragoza, Spain); G Jundt (Basel, Switzerland), C Bouchardy, M Usel (Geneva, Switzerland), J Allemann, H Frick (Graubünden and Glarus, Switzerland), T Fisch, S Ess (St Gallen Appenzell, Switzerland), F Joris, D de Weck (Valais, Switzerland); S Yalcin Eser (Izmir, Turkey); CA Stiller, MFG Murphy, GJ Draper (England and Wales, UK), A Gavin, C Fox, W Hamill, R Middleton (Northern Ireland, UK), D Brewster, L Bhatti, A McDonald (Scotland, UK). We also acknowledge the collaborators from the other 15 registries, whose data were not included in the analyses.

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