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Childhood cancer survival in Europe: an overview

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Abstract

Other articles in this issue of the *European Journal of Cancer* have described population-based survival analyses of specific types of childhood cancer included in the EUROCARE database, diagnosed since 1979. The present paper summarises the relevant estimates and comments on intercountry differences, focusing on possible distortions in the intercountry comparisons based on data produced by the cancer registries. Potential biases include a lack of exhaustiveness of both case ascertainment and follow-up for living status and also a lack of consistency in the use of classification of the childhood cancer types. Nevertheless, despite such biases, consistent differences are observed between European countries in the probability of survival following the diagnosis of a paediatric cancer. In most cases, poor population-based survival rates are probably explained by inadequacies in the adoption and implementation of therapeutic protocols that have been proved to be effective. In some instances, the cause of unsatisfactory estimates was the inclusion of a sizeable proportion of children with cancer in clinical trials which were found to be ineffective. A regression analysis of incidence, mortality and survival rates during 1978–1989 over the whole EUROCARE database strongly indicates that the prognostic improvements over time are real and cannot be attributed to changes in diagnostic procedures.

Keywords: Childhood cancer; Population cancer registries; Survival; Time trends; Geographical variation; Cancer care; Incidence; Prevalence; Mortality

1. Introduction

The rationale for creating most population-based cancer registries has not changed since William Farr — more than one and a half centuries ago — set up the Registrar General in Great Britain [1]:

> Diseases are more easily prevented than cured and the first step to prevention is the discovery of ... causes. The Registry will show ... these causes by numerical fact and measure the intensity of their influence and will collect information on the laws of vitality ... in the two sexes at different ages and the influence of civilisation, occupation, locality, season and other physical agencies, either in generating disease and inducing death, or improving the public health.

The expectation proved to be correct. Furthermore, for childhood cancer, incidence data from registries have led to findings which are relevant to aetiology. Worldwide, with the exception of lymphomas, the ratio between the highest and lowest incidence rates does not exceed 5 (a ratio which is orders of magnitude smaller than the corresponding ratio for many adult cancers); genetic factors and ethnic variation account for some of these differences; rates for several cancers are slightly,

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but consistently and significantly, higher in boys than in girls; socioeconomic status is positively associated with acute lymphatic leukaemia (ALL) and perhaps negatively associated with neuroblastoma; no temporal trend in the incidence rate has been detected, with the exception of AIDS-related cancers in Africa and possibly ALL in children aged 0–4 years [2]. The apparent increase in cancers of the central nervous system (CNS) with time is largely if not totally attributable to refinements in the diagnostic approaches. In addition, for childhood cancers, with some exceptions — e.g. bilateral retinoblastoma — the contribution of hereditary factors to the overall carcinogenic burden is limited [3].

The potential of using cancer registries to evaluate health management through estimates of survival rates on a population basis was perceived later. In the United States, SEER (an acronym whose first letter represents 'Surveillance') estimates have been available since the early 1970s [4]. In the same period, in Europe, population-based data were available only for a few areas (e.g. England and Wales and the Scandinavian countries). During the last decade, a number of European analyses have appeared, thanks to a concerted action — called EUROCARE — of European population-based cancer registries [5]. The major aim of the EUROCARE project is to establish the extent of survival differences between European countries and their reasons, using standardised methods allowing for intercountry comparisons [6]. This has been a major task: for historical reasons, throughout the European countries the level of health planning and the attention given to it as well as the evaluation of medical interventions have been quite heterogenous, for oncology as well as for medicine generally.

By providing estimates of survival, cancer registries have become important in the assessment of the effectiveness and efficiency of cancer care in the populations that they serve, thus contributing important information allowing a rational allocation of resources for health and research. This function of the cancer registries is particularly important for children with cancer, for whom nowadays the probability of being cured and having a 'normal life' is many times higher than it was in the 1960s. Progressively more effective therapeutic regimens have become available during the last 30–40 years, such that their effectiveness in population settings needs to be investigated.

Thus, cancer registries help in the assessment of whether the standard of delivery of care to children with cancer is optimal for that time of diagnosis and whether in the past progressively more efficient therapeutic regimens have been adopted in a timely manner. Comparisons with the efficacy observed in clinical trials is also possible. The articles published in this issue of the *European Journal of Cancer* were produced in order to provide an answer to some or all of these questions.

2. Some cautionary notes

Despite providing much information, the data presented in this publication must be assessed with care. Quality of cancer registration (including the exhaustiveness of case ascertainment and the precision in the use of the codes of international disease classifications, particularly for cancer subtypes), as well as the completeness of follow-up, may affect the survival estimates. Present comparisons are unlikely to be biased by differences in case ascertainment, since incidence rates were similar in all countries, although some countries only provided regional data and a small number of cases. Nevertheless, in some countries, children entering clinical trials in outstanding institutions (who are more likely to benefit from treatment) are more likely to be registered by a cancer registry than children treated in other institutions. The extent of this selection bias can vary between countries, depending on the methods used for obtaining the individual data. The anticipation of a particular cancer is less likely to be a source of bias in Europe where, for a variety of reasons, there have been no screening programmes for the early diagnosis of childhood cancers, with the exception of neuroblastoma [20].

The use of a common classification in all of the cancer registries allows a standardisation in diagnosis. Cases without microscopical confirmation were less than 10% in the European pool [21]. The proportion of cases for whom subtypes could not be specified was low, with some exceptions; in Estonia, unspecified subtypes accounted for approximately a quarter of all leukaemias and soft-tissues sarcomas. Unspecified lymphomas represented a fifth or more of all lymphomas in Finland, France and Poland, and the proportion of unspecified intracranial neoplasms exceeded 10% in most European countries. Moreover, no systematic analysis aimed at the validation of diagnoses between countries has been carried out. The proportion of children lost to follow-up, was in most countries 2% (which is reasonable for population-based registries): the corresponding high estimates in The Netherlands and in Switzerland (around or above 10%) may simply reflect the small number of cases in these national databases. The high proportion reported by the German registry (around 5%) may have had a greater impact on the overall estimates due to the weight of the German data in the EUROCARE database.

3. Intercountry comparisons

An overview of intercountry differences in survival for the most common cancer types (for which random variability is expected to be limited) in 1985–1989 is shown in Table 1. Data from Austria, Iceland and Switzerland, as well as non-haemopoietic cancers from The Netherlands, have been omitted because of small numbers.

Table 1
Death risk ratios for cases diagnosed in each country in 1985–1989 versus the mean 5-year survival from the weighted European pool, both genders together[a]

	ALL	ANLL	HD	NHL	Astrocytoma	PNET	Neuroblastoma[b]	Wilms' tumour	Osteosarcoma[c]	Ewing's sarcoma	Rhabdo-myosarcoma	Germ cell and gonadal
Denmark	=	↓	↓	↓	↑	↓	↓	=	↑		=	
England	=	=	=	=	=	↓	↓	↑	↓	=	↓	↑
Estonia	↓			↓	↓							
Finland	↑	↑		=		=	↑	↑			↓	
France	↓						=	↑				
Germany (West)	↑	↑	↑	↑	=	=	↑	↑	↑	↑	=	↑
Italy	↑	=	↓	↓	↑	↑	↑	=	=		=	↑
Poland	↓							↓				
Scotland	=	↑	↓	↑	=	=	↓	↑		↑	↓	
Slovakia	↓	↓	↓	↓	↓	↓	=					↓
Slovenia	=	↓	↑	↑	↓		↓				↑	
Spain	=	↓		=	↓	=	=			=		
Sweden	↑			↑	↑	↑						
The Netherlands	↑	=		=								

PNET, primitive neuroectodermal tumours; RR, relative risk; HD, Hodgkin's disease; NHL, non-Hodgkin's lymphoma; ALL, acute lymphoblastic leukaemia; ANLL, acute non-lymphocytic leukaemia.
↓ Survival worse than Europe, RR >1.15; = survival close to Europe, RR 0.85–1.15;
↑ Survival better than Europe, RR <0.85.
[a] Symbols represent the death risk ratio of each country versus the mean age-adjusted 5-year survival from the weighted European pool, both genders. Symbols are absent for countries with a number of cases less than or equal to 10, or where age-standardised survival could not be calculated because of a lack of cases in one or more age classes.
[b] Based on survival for the age group 0–4 years only.
[c] Based on survival for the age class 10–14 years only.

Germany exhibited high survival levels for most cancer types, but this may have been influenced by the relatively high proportion of children lost to follow-up and by the possible selection of patients entering some clinical trials (for an example, see the thyroid cancer article by Storm and colleagues [22]. In addition, Sweden, Finland and Italy showed generally increased survival rates compared with the European pool. South Sweden may be representative of the whole of Sweden; however, this is not likely to be the case for Italy, where survival data from the Piedmont and other Northern regions seems to be higher than in Southern Italy [7]. In Scotland and Slovenia, some cancers were above the European average and this was well balanced by a number below the average. In contrast, relatively poor survival for most of the considered sites was noted in England, Spain, Estonia, Poland, Slovakia and, unexpectedly, Denmark.

The unsatisfactory survival from ALL in France requires some comments. Cancer registries from which the present estimates were derived served only approximately 4% of the French childhood population and excluded areas where internationally famous French large centres are located. Nevertheless, French clinical studies in the early 1980s had reported unsatisfactory outcomes [8] which may have been reflected in the present findings.

For most cancer sites, present analyses have included a comparison between population-based survival in Europe and in other countries, notably the SEER series in the US. In general, it seems that in the most recent time periods, results in Europe were as satisfactory as in the US, thus closing the previous gap. This gap had been observed during the first decades after the introduction of efficacious protocols. In those days, the European lag reflected both the imperfect organisation of childhood cancer care on this side of the Atlantic and the reluctance of some European paediatric oncologists to submit their patients to treatments which were also known to be aggressive and toxic.

With regard to data from the US reported in this issue, survival estimates in European countries have been compared with a sample of the US childhood population which, however, may not be representative of the whole country. This influences the interpretation of present findings. In fact, it is known that in the US ethnicity influences the probability of survival, which is lower in black children [4]. This disadvantage is more likely to be attributable to a differential access to adequate therapeutic regimens rather than to biological factors.

4. Time trends

Table 2 summarises estimates reported in this issue for those cancer types for which absolute numbers were sufficient for an adequate statistical analysis.

Most estimates were statistically significant and all estimates were remarkably consistent. Over a period of

Table 2
Hazard ratios for childhood cancers in Europe according to period of diagnosis

	1978–1981	1982–1985	1986–1989	1990–1992	Countries included in analysis
Acute lymphocytic leukaemia (ALL)	1	0.74[a]	0.61[a]	0.49[a]	Countries with at least 30 cases registered
Acute non-lymphocytic leukaemia (ANLL)	1	0.74[a]	0.55[a]	0.53[a]	Countries with at least 30 cases registered
Chronic myeloid leukaemia	1	0.78	0.70[a]	0.49[a]	Countries with at least 15 cases registered
Hodgkin's disease	1	0.98	0.85	0.53[a]	Countries with at least 30 cases registered
Non-Hodgkin's lymphoma (NHL)	1	0.66[a]	0.47[a]	0.38[a]	Countries with at least 30 cases registered
Tumour of the central nervous system (all)	1	0.84[a]	0.70[a]	0.68[a]	Countries with at least 30 cases registered
PNET medulloblastoma	1	0.85	0.74[a]	0.73[a]	Countries with at least 30 cases registered
Neuroblastoma	1	0.74[a]	0.72[a]	0.63[a]	Countries with at least 30 cases registered
Retinoblastoma	1	1.11	0.60	0.75	Countries with at least 15 cases registered
Wilms' tumour	1	0.93	0.65[a]	0.73[a]	Countries with at least 30 cases registered
Hepatoblastoma	1	0.58[a]	0.40[a]	0.29[a]	Countries with at least 12 cases registered
Osteosarcoma	1	0.64[a]	0.55[a]	0.62[a]	Countries with at least 15 cases registered
Ewing's sarcoma	1	0.80	0.46[a]	0.45[a]	Countries with at least 15 cases registered
Soft-tissue sarcoma (all)	1	0.83[a]	0.69[a]	0.72[a]	Countries with at least 30 cases registered
Rhabdomyosarcoma	1	0.74[a]	0.67[a]	0.68[a]	Countries with at least 30 cases registered
Fibrosarcoma	1	0.89	0.51[a]	0.63	Countries with at least 15 cases registered

[a] 95% confidence interval excludes 1.00.

less than 15 years, survival for all cancer sites has progressively improved.

However, estimates may have been influenced by the exclusion from some cancer type-specific databases of data from some countries because of small absolute number of cases or unavailability of cases diagnosed during some part of the 1978–1992 time period. Future expansions of the database will lead to intercountry comparisons of time trends in survival, thus allowing the investigation of how efficiently different European countries have adopted effective therapeutic protocols.

5. Comparing incidence, mortality and survival

Describing cancer in a population is a complex problem in which incidence, survival, prevalence and mortality indicate, respectively, the frequency of disease occurrence, prognosis, the burden of cancer and the ultimate consequences of the disease. These indicators are related to each other and any change in one necessarily reflects changes in the other. For example, improving survival results in different trends for incidence and mortality, which would otherwise parallel each other. Looking at the consistency between incidence, mortality and survival trends may lead to a more thorough understanding of the cancer burden and the control of disease. For rare diseases such as childhood cancers, a cross-validation of the reliability of the estimated survival trends is obtained through their consistency with the incidence and mortality trends.

An overview of trends in incidence, mortality and survival for the major diagnostic groups of childhood cancer in Europe for the period 1978–1989 is provided in Table 3. The analysis covered countries with national registries operating during the 1980s, and with mortality and population data available during the same period; Italy has been added in order to provide representation for the Southern European countries.

Trends in incidence have been estimated from the EUROCARE database for each of the six countries, by a linear regression of the incidence rate versus the calendar year. First of all, incidences estimated by country have been pooled together, with weights proportional to the national population, to obtain an average value. The 12-year relative risk between 1989 and 1978 was then estimated as the ratio of the expected pooled incidence rates in 1989 to the one in 1978. The 12th root of the 1989 to 1978 pooled incidence ratio provided the average annual incidence relative risk. The same procedure was used for the corresponding mortality estimates from the official mortality data from the World Health Organization (WHO) database. All available data from 1978 to 1995 have been used to estimate the regression parameters but the annual relative risk of mortality is for the period of 1978–1989. Finally, the annual relative death rates of cancer

Table 3
Trend analysis during 1978–1989 of incidence, survival and mortality from childhood cancer in Europe (pool of Denmark, Estonia, Finland, Germany, Italy and UK)

	Incidence (annual RR)	Survival (annual death ratio)	Mortality (annual RR)
Leukaemias	1.008	0.94	0.953
Hodgkin's lymphoma	1.006	0.99	0.896
Non-Hodgkin's lymphoma	1.022	0.91	0.957
Bone tumours	1.009	0.92	0.958
Kidney tumours	1.018	0.95	0.963
All cancer	1.020	0.95	0.972

RR, relative risk.

patients have been taken from the results of the multivariate analyses shown in the various articles of this issue of the European Journal of Cancer. Estimates for leukaemias have been obtained by a weighted average of the corresponding relative rates obtained for ALL (RR = 0.94), other leukaemias (0.93) and chronic leukaemias (0.95). Those for bone tumours were derived by the average of the relative rates for osteosarcomas (0.92) and Ewing's sarcoma (0.91). Finally, the estimates for Wilms' tumours have been taken as representative of all kidney tumours.

A slight increase of incidence has been observed for all cancer types, whereas mortality has substantially decreased in the same period. The decrease in mortality rates ranged from 2- to 16-fold the corresponding rate of increase estimated for incidence. Survival markedly increased within the 1978–1989 period, as expressed by the annual death ratio. Consistency of survival changes with differential changes in mortality and incidence was very high, with the exception of Hodgkin's lymphoma, where the 5-year survival was over 90% and the mortality very low, leading to an uncertain mortality trend estimate.

These findings confirm that the prognostic improvements in childhood cancer resulting from the EUROCARE data analysis are real and cannot be attributed to changes in the diagnostic accuracy or anticipation of diagnosis. The relationship between temporal trends of incidence, survival and mortality has seldom been analysed in the past. In a recent study on 20 adult cancers in the US, the results were, at best, tenous with little relationship observed between incidence, survival and mortality [9]. The contrast with this data is probably explained by the unique speed with which, in recent decades, new therapeutic protocols have drastically affected the prognosis of childhood cancers.

6. Discussion

An objection which has been raised to a concerted action aimed at measuring population-based survival rates such as EUROCARE-II, [10] is that evaluation of the quality of cancer care can be more reliably and more simply achieved through estimates of the proportion of patients receiving diagnostic and therapeutic protocols whose ability to improve prognosis has been demonstrated in experimental clinical trials. According to this objection, the focus ought to be more on the process than on the outcome. Indeed, such an approach is appealing because it overcomes both the time lag typical of any follow-up study and the potential bias introduced by the inevitably imperfect standardisation of the retrospective classification of clinical and pathological data. Furthermore, characterisation of cancer patients by the therapeutic protocol which is offered to them also contributes to an estimate of possible non-lethal side-effects. In most European countries, the great majority of children with any given cancer type are referred to outstanding institutions where the comparison between subsequent generations of protocols is a continuous process. Children included in 'new' trials often, but not invariably, have a higher survival rate than those who are not included, but other factors can also be important, such as the place of treatment [11]. Given the rarity of childhood cancers, such outstanding institutions have created national and international networks of multicentric collaborative studies. For some, but not all, European countries, estimates are available of the proportion of children being either referred to national or international cancer study groups or actually entering specific multicentric (national or international) clinical trials [12–14]: methods used for such estimates are not strictly comparable; most reported proportions exceeded 75%, but there is a need for a more systematic approach.

Indeed, at least in the case of childhood cancers, estimating survival rates and estimating the proportion of children entering clinical trials should be considered complementary, and not alternative methods. A (prudent) estimate of the number of avoidable deaths is more likely to induce the health authority to take some decisions regarding the provision of care, whereas a count of the number of children with cancer who are not treated adequately would have an impact in the paediatric oncological milieu. In any case, present findings indicate the need for population-based prospective studies taking into consideration clinical variables at the onset of disease, as well as standardised information on the administration of therapy.

Two important goals are the quantification (and the impact on survival) of complications leading to deviations in the delivery of protocols, such as infection and haemorrhages and the quantification of the fate of children excluded from the networks. In adult patients, an excess of deaths occurring early after diagnosis has been found in the SEER series which are likely to be caused by cancer treatment [15]. Exploratory analyses of early mortality in the childhood cancer EUROCARE database [21] require an extension because the mechanisms of toxicity to the therapies administered to children do not necessarily correspond to those mechanisms in adults.

Throughout cancer-specific analyses, intercountry differences in the probabilities of survival for children diagnosed with cancer have been identified in Europe. Although bias may have ensued from differences in the national databases, many of these differences were not random, i.e. in the late 1980s probability of cure was higher in some European countries than in others.

The consideration of these intercountry differences requires an additional note of caution for those countries where the cancer registries only served a fraction of the population (i.e. The Netherlands, France, Italy,

Spain, Sweden and Switzerland). The representativeness of the latter can be questioned: the organisation for cancer care may be more advanced in those areas where cancer registration has been implemented than in the rest of the country. However, even if not representative of the entire country, present findings are population-based and are therefore indicative of the global management of care in definite areas.

The interpretation of some intercountry differences detected in the present analyses requires additional thoughts and hypotheses. For instance, survival estimates for children with Ewing's sarcoma differed between Germany and England, whereas the results of clinical trials in the two countries were similar [23].

For most childhood cancer sites, survival in European children diagnosed with cancer in the late 1980s has been very similar to corresponding estimates in the US in 1985–1994. This is reassuring. In the field of paediatric oncology, over the last half a century, the US have had a major role in the discovery and application of treatment innovations. Nevertheless, findings in both the US and Europe indicate that access to optimal care differs between subpopulations. Equity should be a goal for the future organisation of the delivery of care.

Trends in the use of effective protocols have also been estimated on the simple basis of mortality rates [16]. As late as 1995, there was still a gap between the US and Europe, albeit less pronounced than in previous periods. These findings are not incompatible with the present estimates, given the long duration of the clinical condition for those children who will eventually die.

Many unanswered questions raised by the present study may find a reply through further surveillance, including high resolution population-based epidemiological studies taking into account individual clinical risk factors associated with prognosis, thus allowing for a rational patient stratification.

Finally, survival is a most important, but not the exclusive, indicator of the adequacy of the delivery of care to children with cancer. At the beginning of the new millennium, therapeutic protocols, albeit effective, are still biologically aggressive: undesirable side-effects are commonly produced in a sizeable number of children being treated. Extrapolation of prudent estimates from Italy [17] and the UK [18] indicate that in Europe the number of adolescents and young adults who have overcome a cancer in childhood is in the order of at least 100 000. Population-based studies on the quality of life of long-term survivors after childhood cancer have been limited. Parallel to the implementation of high resolution population-based estimates of survival rates, there is a need for *ad hoc* investigations in this area, for which the population-based approach provided by cancer registries offers a unique opportunity for achieving reliable estimates of an emerging public health problem.

In conclusion, the information provided in this issue of the *European Journal of Cancer* should be incorporated into approaches evaluating childhood cancer care. A possible model is one suggested some years ago by Donabedian using easily measure criteria [19]. A holistic approach should include consideration of structure (concentration of diagnostic and supportive care and protocol development and adherence, training of paediatric oncologists and other specialists), process (collaborative working groups, assessment of adherence to protocols, development of new protocols, communication, etc.) and outcome. The EUROCARE data must surely have a contributory role in the above.

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