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Quality, comparability and methods of analysis of data on childhood cancer in Europe (1978–1997): Report from the Automated Childhood Cancer Information System project

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ABSTRACT

In collaboration with 62 population-based cancer registries contributing to the Automated Childhood Cancer Information System (ACCIS), we built a database to study incidence and survival of children and adolescents with cancer in Europe. We describe the methods and evaluate the quality and internal comparability of the database, by geographical region, period of registration, type of registry and other characteristics. Data on 88,465 childhood and 15,369 adolescent tumours registered during 1978–1997 were available. Geographical differences in incidence are caused partly by differences in definition of eligible cases. The observed increase in incidence rates cannot be explained by biases due to the selection of datasets for analyses, and only partially by the registration of non-malignant or multiple primary tumours. Part of the observed differences in survival between the regions may be due to variable completeness of follow-up, but most is probably explained by resource availability and organisation of care. Further standardisation of data and collection of additional variables are required so that this study may continue to yield valuable results with reliable interpretation.

1. Introduction

In European populations, about 1% of all malignant neoplasms occur in patients aged less than 20 years.[1] This low frequency represents a major difficulty for studies of putative risk factors and clinical management, and the problem is further accentuated when the number of cases is split into a wide variety of tumour types, most of which are uncommon in adults. As a result, international data on childhood and adolescent cancer are sparse.[2–6]

The Automated Childhood Cancer Information System (ACCIS) is a European project aimed at collection, analysis,

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interpretation and dissemination of data on cancer incidence and survival of children and adolescents in Europe.[7] To date, the ACCIS database contains data from some 80 population-based cancer registries, which cover about 50 % of the population aged 0–14 years and about 25% of the population aged 15–19 years living in the 35 participating countries. Over 160,000 childhood and adolescent cancers were diagnosed during the period 1970–2001 in the 1300 million person-years of observation. The wide coverage and large size of this study permit identification of geographic and temporal differences in incidence across Europe, and so provide useful information for generating aetiological hypotheses.[8] Simultaneously, differences in population-based survival of various groups of patients help to identify areas for improvement in the management of childhood and adolescent cancer patients.[5,6,9]

However, valid conclusions about differences in cancer incidence or survival between populations and over time can be drawn only from comparable datasets of high quality with complete registration and follow-up. This paper describes the methods of data collection and analysis and evaluates internal quality and comparability of the part of the ACCIS database that was selected for detailed analyses of incidence and survival of individual and combined tumour types. It also discusses the extent to which the comparison of incidence rates and survival may be influenced by the differences in methods of registration and follow-up and identifies priorities for further improvement of data comparability across Europe.

2. Material and methods

2.1. *Setting up the ACCIS database*

Some 100 European population-based cancer registries were invited to participate in the ACCIS study. Acceptable data were received from 78. To participate, the registries submitted a file of records for all cancer cases incident over a specified registration period (from about 1970 onwards) in children (aged 0–14 years at diagnosis) and adolescents (age 15–19 years) resident in the defined registration area at the time of diagnosis. All malignant and non-malignant tumours of the central nervous system (CNS) defined in the International Classification of Childhood Cancer[10] (ICCC) were to be included. Non-malignant tumours of the meninges and the pituitary and pineal glands were also included (see Appendix). Each record contained identification and demographic variables (registration number, sex, age, date of birth), data concerning the incident cancer (date of incidence, topography, morphology, behaviour and grade) and information on follow-up (date of last contact and vital status at this date). The participating registries also supplied population data and a questionnaire describing registration methods, coding systems and data sources for respective data items, to aid understanding and interpretation of their data.

Collection of data started in mid-2000. All information received by November 2002 was included in the ACCIS database, stored at the International Agency for Research on Cancer (IARC) and consolidated in September 2003. Analyses presented in this issue are based on this version and disregard any later data submissions from cancer registries. The early closing date of the study in some registries results in part from early date of data submission. All versions of the database contain anonymous records and any particular case can be identified only in the originating registry. All contributing registries agreed to participate in this project, which was approved by the ethical committee of the IARC. All records were verified and standardised centrally in collaboration with the registries concerned. The ACCIS Scientific Committee evaluated overall quality and comparability of all submitted datasets.

2.2. *Selection of datasets for analyses*

Central verification of data aimed at detection of errors, both random and systematic. Logical consistency between variables was verified using standard[10] and new procedures. Unspecified tumours were converted to specified whenever possible, according to the Guidelines of European Network of Cancer Registries (ENCR).[11] Registrations of retinoblastoma and Wilms' tumours were reviewed to identify bilateral cases.

Coding of records was standardised. Most valid basis of diagnosis was simplified to four values: microscopically verified (MV), clinically diagnosed, reported from death certificate only (DCO), and unknown. In the registries that do not have access to information permitting identification of new registrations from death certificates the proportion of DCO cases could not be calculated (see Table 2). If necessary, topography and morphology were converted to the second edition of the International Classification of Diseases for Oncology (ICD-O-2).[12] The International Classification of Childhood Cancer[14] [the conversion table is reprinted in the Annex] was then used to present results. The multiple primary tumours were identified (and redefined, if necessary) in compliance with the IARC/IACR recommended definition.[12] Length of survival time in days was calculated centrally as the difference between the date of diagnosis and death (if deceased), or closing date (if alive by that date). In the registries, where the follow-up interval exceeded 1 year, the survival time was extended by a half of the follow-up interval for those subjects with latest date of follow-up before the closing date of the study ('lost to follow-up'), to account for the average time at risk of dying, according to the actuarial assumption underlying the survival analysis method.[15]

Population data originated from reports published officially by statistical offices of the respective countries (Table 1). The accuracy of the estimated population at risk is fundamental to the calculation of valid rates of incidence. For each registration area, the population figures were provided for every combination of covered calendar year, sex and single year of age. When, exceptionally, population data for single calendar years were not available, they were estimated using linear interpolation. If population figures were unavailable for single ages in some calendar years, the census data were used to estimate the proportion of each year of age and these were applied to the available age groups. Population data were examined for consistency of temporal changes by sex and age to discern any random errors due to data transfer. Most of these procedures were conducted using standard software[10,16] or tailored macros in Stata[17] and Excel.[18]

Table 1 – Background information on the cancer registration procedures in the cancer registries selected as comparable and included in the analyses of incidence and survival in children (age 0–14 years) and adolescents (age 15–19 years) (Source: ACCIS)

Country and covered region	Year start	Country coverage (%)	Incidence date definition	Topography codes	Morphology codes	Multiple primaries definition	Follow-up procedures	Source of population data
BELARUS, National	1999	100	ENCR	ICD-O-2	ICD-O-2	IARC/IACR	Active follow-up using medical records and death certificates. Patient's vital status reviewed at least once a year.	Ministry of Statistics and Analysis of the Republic of Belarus
DENMARK, National	1943	100	other	ICD-O-1	ICD-O-1, ICD-O-2	IARC/IACR	Patients data linked with central population registry and death registry at least once a year.	Denmark statistics
ESTONIA, National	1968	100	ENCR	ICD-8, ICD-O-1, ICD-O-2	ICD-O-1, ICD-O-2	IARC/IACR	Automatic annual link of the registry's database with death certificate database. Date of death or emigration recorded. Complementary manual linkage.	Statistical Office of Estonia, Tallinn
FINLAND, National	1953	100	ENCR	ICD-7, ICD-9	Motnac, 1951	IARC/IACR	Annual computerised record linkage with population registry for date of death and emigration and with the files of Statistics Finland for causes of death.	Statistics Finland
FRANCE, Brittany	1991	5	ENCR	ICD-O-2	ICD-O-2	–	Changes in vital status notified to the registry. Complementary data from physician and medical records. Vital status verified actively once in 3 years.	INSEE, France
FRANCE, Lorraine	1983	4	ENCR	ICD-O-2, ICD-O-3	ICD-O-2, ICD-O-3	IARC/IACR	Medical records and certificates of death used in active and passive follow-up every 3–4 years.	INSEE, France
FRANCE, PACA & Corsica	1905	7	other	ICD-O-1, ICD-O-2	ICD-O-1, ICD-O-2	other	Passive follow-up.	INSEE, France
FRANCE, Rhone Alps	1987	10	ENCR	ICD-O-2	ICD-O-2	other	Follow-up is based on medical records (once a year) and contact with treating physician (every 5 years). Follow-up incomplete for some 10% of cases.	INSEE, France

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Table 1 – *continued*

Country and covered region	Year start	Country coverage (%)	Incidence date definition	Topography codes	Morphology codes	Multiple primaries definition	Follow-up procedures	Source of population data
FRANCE, Doubs	1976	1	other	ICD-O-1, ICD-O-2	ICD-O-1, ICD-O-2	IARC/IACR	Follow-up based on systematic monthly review of death certificates in the registration area and in local press. Active follow-up for survival studies mainly from population offices.	INSEE, France
FRANCE, Herault	1985	1	ENCR	ICD-O-2	ICD-O-2	–	Non-systematic follow-up.	INSEE, France
FRANCE, Isere	1979	2	ENCR	ICD-O-2	ICD-O-2	IARC/IACR	–	INSEE, France
FRANCE, Manche	1994	1	other	ICD-O-2	ICD-O-2	IARC/IACR	Follow-up for cases incident in 1994 and 1995 only. Based on monthly matching of registry file with cancer death certificates and annual verification of regional population office after a formal request.	INSEE, France
FRANCE, Bas-Rhin	1975	2	ENCR	ICD-O-2	ICD-O-2	IARC/IACR	Follow-up based on systematic monthly review of death certificates (all causes) in the registration area. Cases without date of death followed-up actively every 5 years through regional population office.	INSEE, France
FRANCE, Haut-Rhin	1988	1	ENCR	ICD-O-2	ICD-O-2	IARC/IACR	Follow-up for cases incident in 1988–1991 only. Vital status from population offices, hospital records and postal survey.	INSEE, France
FRANCE, Somme	1982	1	ENCR	ICD-O-2	ICD-O-2	IARC/IACR	Active follow-up through medical records and population offices in the département every 3 years.	INSEE, France
FRANCE, Tarn	1982	1	ENCR	ICD-O-2	ICD-O-2	IARC/IACR	–	INSEE, France
GERMANY, NCR (only former East)	1976	100	ENCR	ICD-O-2	ICD-O-2	IARC/IACR	Follow-up for cases incident in 1970–1987. Passive follow-up conducted yearly. Losses to follow-up varied 1–5%, and some 30% in year 1987.	Staatliche Zentralverwaltung für Statistik, Berlin, Germany

GERMANY, GCCR (East and West) GERMANY, GCCR (only former West)	1991 1980	100	other	ICD-O-2	ICD-O-2	other	Active follow-up once a year through hospitals, physicians, family. Losses to follow-up are traced via population registry 3 years after last contact at the latest.	Statistical yearbooks. Federal Statistical Office (ed.). Metzler-Poeschel, Stuttgart, Germany
HUNGARY, National	1971	100	ENCR	Tumour types, ICD-O-2	Tumour types, ICD-O-2	-	Follow-up based on annual reports from regional childhood oncology centres. Active seach for losses to follow-up at least once a year.	Central Statistical Office of Hungary: Demographical yearbook of Hungary, Budapest
ICELAND, National	1955	100	other	ICD-O-2	ICD-O-1, ICD-O-2	other	Vital status updated automatically from National Statistics Office once a month.	Icelandic National Roster
IRELAND, National	1994	100	ENCR	ICD-O-2	ICD-O-2	IARC/IACR	Registry files matched automatically with death certificate file once a year (automated cancer registration).	Central Statistics Office. Census 91 and 96. Stationery Office, Dublin
ITALY, Piedmont paediatric	1965	6	ENCR	ICD-O-2	ICD-O-2	other	Vital status checked every 3 years in municipal population offices.	Official files from ISTAT (census years) or intercensus estimates
ITALY, Marche	1990	2	ENCR	ICD-O-1	ICD-O-1	IARC/IACR	Vital status checked every 3 years in regional population offices.	Sistema Statistica Nasionale, Instituto Nasionale di Statistica (ISTAT), Rome
ITALY, Ferrara	1991	0.5	ENCR	ICD-O-2	ICD-O-2	IARC/IACR	Vital status checked every 2 years in consultation with regional population offices and healthcare files.	Emilia Romagna Regional Statistical and Informative Unit (see: www.regione.emilia-romagna.it)
ITALY, Latina	1983	1	ENCR	ICD-9	ICD-O-2	IARC/IACR	Vital status verified in regional population offices every 2–3 years. Causes of death from Nominative Registry of all causes of death.	Official files from ISTAT (census years) or intercensus estimates
ITALY, Liguria	1986	1	ENCR	ICD-O-1	ICD-O-2	other	Follow-up for date of death or emigration within Italy was conducted through the Municipality Roster and Ligurian Mortality Registry.	Assessorato Bilancio-Finanze, Andamento della popolazione, Servizio Statistica, Comune di Genova, Census and intercensual estimates.
ITALY, Lombardy	1976	1	ENCR	ICD-O-2	ICD-O-2	IARC/IACR	Active follow-up through regional population offices, hospital records, other.	ISTAT

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Table 1 – *continued*

Country and covered region	Year start	Country coverage (%)	Incidence date definition	Topography codes	Morphology codes	Multiple primaries definition	Follow-up procedures	Source of population data
ITALY, Macerata	1991	0.5	ENCR	ICD-O-2	ICD-O-2	IARC/IACR	Vital status checked every 3 years in the municipalities offices of resident population.	National Statistic system ISTAT, Rome
ITALY, Parma	1978	1	ENCR	ICD-O	ICD-O-2	IARC/IACR	Population offices consulted once a year to determine vital status of the regional residents.	ISTAT 1981 and ISTAT 1991
ITALY, Piedmont general	1985	1	ENCR	ICD-O-2	ICD-O-2	other	Follow-up through annual automatic linkage with municipal population registry and active follow-up in population registries of other Italian cities.	Sistema Statistico Nationale. Citta di Torino Ufficio di Statistica. Annuario Statistico 1997
ITALY, Ragusa	1981	1	ENCR	ICD-O-1	ICD-O-1	IARC/IACR	Vital status verified yearly in regional population register. Death certificates for all causes of death received quarterly from local health authority.	Censuses 1981, 1991 and intercensual estimates, ISTAT, Rome
ITALY, Sassari	1992	1	ENCR	ICD-10	ICD-O-2	IARC/IACR	Vital status verified in regional population and all causes mortality registries annually.	ISTAT
ITALY, Tuscany	1985	2	other	ICD-O-2	ICD-O-2	other	Vital status through automatic linkage with regional mortality registry. Bi-annual active search for alive cases through regional population office and regional health authority database.	Censuses of the 1981 and 1991 and intercensual estimates taking into account births and deaths and the migration rate for Central Italy, provided by the Tuscany Region
ITALY, Umbria	1994	1	ENCR	ICD-O-2	ICD-O-2	other	Annual check of vital status in regional population offices and death certificates.	Umbria in figures; Sistema statistico Nazionale, Perugia, Italy
ITALY, Veneto	1987	3	other	ICD-O-1	ICD-O-1	IARC/IACR	Registry data linked with all causes mortality files. Complementary search through population file of regional health units and population offices. Average interval of checks: 3 years.	Municipal registries estimates of population at 31st December. National Institute of Statistics

MALTA, National	1991	100	ENCR	ICD-O-2	ICD-O-2	other	Follow-up by linkage with mortality database and review of death certificates.	Central Office of Statistics, Malta, Annual Demographic Reviews of the Maltese Islands, census of population and housing in Malta, 1995 (www.magnet.mt/home/cos/index.html)
NETHERLANDS, National	1989	100	ENCR	ICD-O-1	ICD-O-2	IARC/IACR	Follow-up for the patients aged 0–14 at diagnosis conducted in a framework of a special ad hoc study.	Statistics Netherlands
NETHERLANDS, Eindhoven	1995	7	ENCR	ICD-O-1	ICD-O-1	IARC/IACR	Follow-up for vital status through links with municipal health administration, central genealogy registry of all deaths, other paediatric oncology centres.	Statistics Netherlands
NETHERLANDS, DCOG	1973	100	other	-	Four histology groups	other	Follow-up for vital status conducted actively (attending physician) and passively (national death registry) once a year.	Statistics Netherlands
NORWAY, National	1952	100	ENCR	ICD-7, ICD-O-2	MOTNAC, ICD-O-2	IARC/IACR	Follow-up conducted in a framework of a special *ad hoc* study. Survival time was provided by the registry.	Statistics Norway
SLOVAKIA, National	1976	100	ENCR	ICD-O-1	ICD-O-1	other	Passive followed-up for vital status through compulsory notifications from clinicians and autopsy reports. Complementary active follow-up by manual matching of all death certificates for the entire country.	Statistical Office of Slovak Republic, Bratislava
SLOVENIA, National	1950	100	ENCR	ICD-10	WHO24.1, ICD-O-1, ICD-O-2	IARC/IACR	Follow-up for vital status at least once a year by automatic linkage of the registry records with population register of the country. Childhood cancer patients also followed-up through special out-patient department of the Institute of Oncology in Ljubljana.	Statistical Office of Republic of Slovenia, Ljubljana
SPAIN, National	1990	55	other	ICD-O-1	ICD-O-1	other	Active follow-up for vital status once a year through treating physicians. Date of death obtained from hospitals.	National Institut of Statistics of Spain

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Table 1 – *continued*

Country and covered region	Year start	Country coverage (%)	Incidence date definition	Topography codes	Morphology codes	Multiple primaries definition	Follow-up procedures	Source of population data
SPAIN, Albacete	1991	1	ENCR	ICD-O-2	ICD-O-2	IARC/IACR	Date of death collected manually once a year in the mortality registry of all causes of death in the region.	Proyeccion de Poblacion del Instituto Nacional de Estatistica (www.ine.es)
SPAIN, Asturias	1982	2	ENCR	ICD-O-2	ICD-O-2	IARC/IACR	Annual follow-up for date of death by automatic linkage (date of birth and sex) with mortality database of cancer deaths (1982–1994) and all causes (1985–1994).	SADEI. Caracteristica de la poblation de Asturias; Censo de poblacion de Asturias (1991); Padron municipal de habitantes
SPAIN, Basque Country	1986	15	other	ICD-O-2	ICD-O-1	other	Vital status verified by linkage of the registry file with mortality dataset for period 1986–2000.	EUSTAT (Basque Institute of Statistics) censo de poblacion y vivienda, 1991. Gioberno Vasco Vitoria Gasteiz
SPAIN, Canary Islands	1993	4	ENCR	ICD-O-2	ICD-O-2	IARC/IACR	–	National Institut of Statistics of Spain
SPAIN, Girona	1994	1	ENCR	ICD-O-1	ICD-O-2	IARC/IACR	Vital status verified yearly by automatic record linkage with mortality database covering the Catalonia region.	Institut d'Estatistica de Catalunya (www.idescat.es)
SPAIN, Granada	1985	2	other	ICD-O-2	ICD-O-2	other	Active follow-up for *ad-hoc* survival studies through death certificates, hospital discharge records and other clinical records. Linkage with Spain, National.	Instituto de estadistica de Andalucia. Un siglo de demografia en Andalucia: la poblacion desde 1900. Sevilla, IEA,1999
SPAIN, Mallorca	1988	1	ENCR	ICD-O-1	ICD-O-1	IARC/IACR	A special follow-up survey for ACCIS study. Vital status verified from hospital or physician records and death certificates of cancer deaths within the island.	L'esperanca de vida a les baleares. Institut balear d'estadistica. Palma, Espana
SPAIN, Navarra	1973	1	ENCR	ICD-O-2	ICD-O-2	other	Follow-up for vital status within the region by monthly manual checks of death certificates, complemented with annual automatic linkage. Other sources: clinical records, other health registries, municipality registry.	Gobierno de Navarra. Departamento de Economia y Hacienda. Servicio de Estadística. Estadística de Población de Navarra. España

SPAIN, Tarragona	1980	1	ENCR	ICD-O-1	ICD-O-2	other	Annual automatic linkage with the mortality registry of all causes of death in Catalonia.	Catalonia Statistical Institut
SPAIN, Zaragoza	1960	2	ENCR	ICD-O-1, ICD-O-2	ICD-O-1, ICD-O-2	IARC/IACR	Registry records matched yearly with hospital records and cancer death certificates.	Instituto Nacional de Estatistica. Madrid Censo de poblacion de Zaragoza (1984)
SWITZERLAND, Basel	1970	5	ENCR	ICD-O-1	ICD-O-1	other	Continuous automatic reporting of deaths of the registered patients from national database of deaths. Vital status verified *ad-hoc* for survival studies by contacting control bureau of the community of residence.	Statistisches amt Kanton Basel-Stadt, Statistisches amt Kanton Basel-Landschaft
SWITZERLAND, Geneva	1970	5	ENCR	ICD-O-1, ICD-O-2	MOTNAC, ICD-O-1	other	Continuous verification of vital status through anonymous cancer death certificates and national anonymous mortality data. Active follow-up through population file of Geneva at the end of every calendar year.	Cantonal Office of Statistics (Geneva)
SWITZERLAND, Graubunden & Glarus	1989	3	ENCR	ICD-O-2	ICD-O-2	IARC/IACR	Date of death through questionnaires sent on every 5th anniversary of incidence date to community's population offices. Additional source of information: death certificate and obituaries in newspapers.	Office Federal de la Statistique, Neuchatel, Suisse
SWITZERLAND, St. Gallen Appenzell	1980	8	ENCR	ICD-O-1, ICD-O-2	ICD-O-1, ICD-O-2	other	Vital status verified on the 5th and 10th anniversary of the incidence date of cancer from community registers of residents. Data on death from cancer death certificate of the residents of the registration area and obituaries in newspapers.	Bundessaunt fur Statistik, Schwiz (Swiss Federal Office for Statistics); Census data 1980 and 1990 and intercensual estimates based on registration of births, deaths and population movements

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Table 1 – *continued*

Country and covered region	Year start	Country coverage (%)	Incidence date definition	Topography codes	Morphology codes	Multiple primaries definition	Follow-up procedures	Source of population data
SWITZERLAND, Valais	1989	4	ENCR	ICD-O-1, ICD-O-2	yes, ICD-O-1 & ICD-O-2	IARC/IACR	Vital status verified routinely every 5 years after incidence using questionnaires completed in the population offices of 160 municipalities. Information on death from death certificates of residents. Tracing a case nationally is possible. Follow-up complete for cases incident in 1989–1993.	Recensement federal de la population de 1990. La population des communes. Berne, Suisse
TURKEY, Izmir	1993	4	ENCR	ICD-O-2	ICD-O-2	IARC/IACR	–	Primary heath centers, responsible for registration of all people living in the covered areas, and for forwarding the figures to the Provincial Health Directorate (unpublished data)
UNITED KINGDOM, England & Wales	1962	100	ENCR	ICD-O-2	ICD-O-2	–	Passive follow-up for vital status and emigration facilitated by flagging cancer cases in national population register (NHSCR). Quarterly updates. Sources: death certificates (nationally, all mentioning neoplasms), hospitals, clinical trials. Complementary active requests once a year. Patients followed-up for multiple primary tumours, but data not provided for ACCIS.	Office for National Statistics (mid-year population estimates)
UNITED KINGDOM, Northern Ireland	1993	100	ENCR	ICD10	ICD-O-2	other	Yearly electronic matching of registry files with a file of all deaths from all causes for Northern Ireland. Extra information from death certificates, hospital records, if necessary. Follow-up incomplete for some 10% of cases.	General Registers Office, Oxford House

UNITED KINGDOM, Scotland	1959	100	other	ICD-9, ICD-10, ICD-O-2	ICD-O	other	Follow-up for vital status by linking registry files with national population death records. Emigrations of registered cases notified by the national population register (NHSCR) which flags all registered cancer patients.	General Register Office for Scotland (mid-year population estimates)

–, not available / not applicable
Topography/Morphology codes: the coding systems used to code tumour types during the study period. Using several systems (marked with "yes" in the relevant columns) usually implies that the original codes were converted into the most recent coding system.

Finally, processed data from each registry were evaluated at meetings of the ACCIS Scientific Committee, according to accepted[19] as well as newly developed criteria. Completeness of registration was supported by a reasonable value for the overall incidence rates, no inexplicably low rates for tumour subgroups, consistent information on registration procedures, previous publications, etc. Incidence rates for particular tumour types prone to under-registration, especially in childhood cancer registries, such as brain tumours, retinoblastoma, bone tumours, skin tumours and thyroid cancers, were examined in particular. Quality of the tumour-related information was assessed from percentage of microscopically verified cases and those with diagnostic method unspecified. A low proportion of tumours in the unspecified categories suggested data with high precision of diagnosis and classification. It was not possible to compare the proportion of DCO cases in all registries, but registration procedures were analysed in the registries where DCOs were not registered. Other indicators examined were the overall proportion of the records qualified as 'unlikely', annual frequency distribution of cases, and sex- and age-specific distribution of selected tumour types.

Several indicators were developed to evaluate completeness of follow-up in the registries. The proportion of cases lost to follow-up was based on the codes provided by the registries for the cases declared lost to follow-up before the closing date of the study. The percentage of cases followed-up (follow up 1+ days) represents the proportion of incident cases included in survival analyses. The proportion of cases with follow-up of 5 years or more was calculated as a ratio of the total number of cases with follow-up of at least 5 years and without a date of death prior to closing date of the study (numerator) to total number of cases with follow-up of more than 0 days and without a date of death prior to closing date of the study (denominator). The proportion of cases followed up for at least 5 years indicates the reliability of the estimated 5-year cumulative survival probabilities. The mean follow-up time was calculated for cases with non-zero follow up and not deceased by the closing date of the study. The follow-up indicators relate to the total number of cases not deceased by the closing date of the study (rather than to the total number included in survival analysis), to remove the influence of fatality within a cohort.

As a result of evaluation, each dataset was either assessed as good quality (comparable) and included in the analyses or excluded. The reasons for the decision were communicated to the registries. Of the 78 cancer registries included in the ACCIS database, 15 were considered to be non-comparable and were therefore excluded from the analyses presented in this and other papers of this volume. Most commonly, the excluded registries showed one or several signs of incompleteness of registration: very low incidence rates, either overall or tumour-specific, and diagnosis based exclusively on microscopic verification. A few registries were excluded on the grounds of unusually high incidence rates in settings where it was not possible to be sure that non-residents had been removed from the dataset. Some datasets were excluded mainly because of an unacceptably high proportion of unspecified tumours, preventing valid international comparisons by tumour group. Finally, a dataset could also be

Table 2 – Datasets contributed by the European cancer registries for the analyses of incidence and survival in children (age 0–14 years) and adolescents (age 15–19 years), with indicators of coverage, data quality and follow-up (Source: ACCIS)

Region	Registry	Period	Time-trend	Person-years						Systematic registration		Number of cases		Basis of diagnosis			NOS	C.a.	Follow-up				Notes
				Age 0–14 years	Age 15–19 years	1978–1982	1983–1987	1988–1992	1993–1997	Non-mal.	Laterality	Age 0–14 years	Age 15–19 years	MV	DCO	Unknown			Closing date	1+ days	5+ years	Median	
		Years				%	%	%	%			*n*	*n*	%	%	%	%	%					
British Isles	IRELAND, National	1994–1997		3417728	1378156	–	–	–	100	*		434	231	96	0	<1	6	<1	31.12.1998	99	0	3	
	UNITED KINGDOM, England & Wales	1978–1995	+	176922141	–	29	27	27	17	*	Rb, Wt	21112	–	91	<1	3	3	0	31.1.2001	98	99	12.3	P Nb
	UNITED KINGDOM, Northern Ireland	1993–1996		1568121	500977	–	–	–	100	*		223	115	77	0	0	27	0	31.12.1999	100	12	1.2	
	UNITED KINGDOM, Scotland	1978–1997	+	20279630	7793722	28	26	23	23			2436	1281	94	<1	0	4	<1	31.12.1999	99	82	10.6	
East	BELARUS, National	1989–1997		20710420	–	–	–	45	55	*	Wt	3200	–	96	0	0	7	0	1.9.2000	99	72	6.6	P
	ESTONIA, National	1978–1997	+	6551135	2110021	25	26	26	24		Wt	810	330	93	<1	0	15	<1	31.12.1998	96	66	7.3	
	HUNGARY, National	1978–1997	+	43147391	–	27	27	25	22	*	Rb, Wt	4875	–	96	–	0	2	<1	1.1.2000	99	72	9.5	P
	SLOVAKIA, National	1978–1997	+	25936857	8433782	25	25	25	24	*	Rb, Wt	3289	1281	94	2	0	8	<1	31.12.1997	91	66	7.9	
	GERMANY, NCR (only former East)	1978–1989	+	38959777	15342870	43	41	16	–	*	Rb, Wt	4831	2640	98	0	<1	5	< 1	31.12.1987	80	64	6.3	S
North	DENMARK, National	1978–1997	+	19093480	7407903	28	25	24	23	*	Rb, Wt	2775	1400	93	<1	2	10	<1	31.12.1997	97	75	9.3	
	FINLAND, National	1978–1997	+	19265469	6789298	26	25	24	25	*	Wt	3012	1295	98	0	<1	9	2	31.12.1998	98	73	8.8	
	ICELAND, National	1978–1997	+	1275103	429753	25	25	25	25	*	Rb, Wt	174	82	98	0	0	5	0	31.12.2000	100	84	10.7	
	NORWAY, National	1978–1997	+	17002822	6188827	26	25	24	24	*		2360	1196	97	<1	<1	11	0	1.1.2000	100	80	10.7	
South	ITALY, Piedmont paediatric	1978–1997	+	13015954	–	32	26	22	20	*	Rb, Wt	1970	–	94	<1	0	6	0	31.12.1999	100	87	11.5	P o2
	ITALY, Marche	1990–1997		1559718	–	–	–	39	61			243	–	88	–	9	10	0	30.9.2000	100	62	6.2	P o3
	ITALY, Ferrara	1991–1995		174945	100278	–	–	43	57			28	26	80	4	0	17	0	31.12.1998	96	67	5.7	
	ITALY, Latina	1983–1997	+	1413695	576820	–	36	33	30		Rb	152	90	91	<1	3	17	<1	31.12.1998	99	78	7.6	
	ITALY, Liguria	1988–1995		565441	303677	–	–	66	34	*		90	71	81	<1	0	7	<1	15.4.2000	99	89	8.2	
	ITALY, Lombardy	1978–1997	+	2667855	1143476	30	27	23	20		Wt	405	238	94	<1	0	4	<1	23.9.1999	99	66	7.1	
	ITALY, Macerata	1991–1997		271141	115992	–	–	29	71			38	27	89	–	8	6	0	30.9.2000	100	64	6	o3
	ITALY, Parma	1978–1995	+	962924	442951	33	29	25	13	*		139	81	93	0	0	6	0	1.4.1999	100	90	12	
	ITALY, Piedmont general	1988–1997		1097222	545600	–	–	56	44			186	109	97	<1	0	4	<1	31.5.2001	99	80	8.3	o2
	ITALY, Ragusa	1983–1997	+	883057	346031	–	35	33	31			112	65	95	0	<1	11	0	30.3.2000	100	84	9.1	
	ITALY, Sassari	1992–1995		304735	143235	–	–	26	74		Rb, Wt	41	30	90	0	4	8	0	30.12.1999	100	77	5.4	
	ITALY, Tuscany	1988–1997		1376966	671048	–	–	54	46	*		223	169	63	<1	0	13	<1	31.12.1998	99	56	5.5	
	ITALY, Umbria	1994–1996		315902	140191	–	–	–	100		Wt	59	36	87	0	0	9	2	31.12.1999	100	31	4.5	
	ITALY, Veneto	1990–1996		1730175	816316	–	–	45	55		Rb, Wt	288	199	95	<1	0	8	<1	31.12.1998	99	54	5.2	
	MALTA, National	1991–1997		570071	197534	–	–	29	71	*	Rb	78	27	96	0	<1	3	0	31.12.1999	98	69	6	
	SLOVENIA, National	1978–1997	+	8220264	2919236	26	26	25	23	*	Rb, Wt	990	400	98	0	0	5	0	31.12.1999	99	76	9.9	
	SPAIN, National	1990–1995		10377774	–	–	–	53	47	*	Rb, Wt	1371	–	92	0	2	4	0	31.12.2000	98	91	6.1	P o4 Z
	SPAIN, Albacete	1991–1997		473835	199238	–	–	30	70		Wt	57	40	92	1	0	8	0	15.9.2000	99	65	6.1	
	SPAIN, Asturias	1983–1997	+	2768535	1235271	–	38	34	28	*		374	208	94	2	<1	12	<1	31.12.1997	96	63	6.8	
	SPAIN, Basque Country	1988–1994		2522128	1234417	–	–	74	26			359	210	95	1	0	10	<1	31.12.2000	97	100	9.5	o4
	SPAIN, Canary Islands	1993–1996		1069190	479540	–	–	–	100			150	81	87	4	3	3	0	–	–	–	–	
	SPAIN, Girona	1994–1997		326767	155384	–	–	–	100			49	29	97	0	1	5	0	31.12.1997	99	0	2.4	o4
	SPAIN, Granada	1988–1997		1695848	–	–	–	53	47		Rb, Wt	208	–	98	0	<1	2	0	31.12.1999	98	68	6.6	G
	SPAIN, Mallorca	1988–1995		892125	369826	–	–	64	36		Rb	132	68	98	0	0	5	0	31.12.1998	95	82	7.2	o4

	SPAIN, Navarra	1978–1996	+	1942415	790001	30	28	25	17			272	144	95	2	0	7	0	31.12.1997	97	69	9.8	o4
	SPAIN, Tarragona	1983–1997	+	1572447	642620	–	36	33	31			209	124	94	<1	<1	9	<1	31.12.1998	97	66	7	o4
	SPAIN, Zaragoza	1978–1996	+	2954825	1219766	30	28	25	18	*		403	161	89	7	1	7	0	31.12.1996	93	69	8.4	o4
	TURKEY, Izmir	1993–1996		2931115	1084075	–	–	–	100		Rb, Wt	332	144	96	–	<1	4	0	–	–	–	–	
West	FRANCE, Brittany	1991–1997		3809039	–	–	–	29	71	*	Rb, Wt	527	–	98	–	2	2	0	1.1.2000	99	44	4.6	P
	FRANCE, Lorraine	1983–1997	+	7357727	–	–	35	33	32	*	Rb, Wt	971	–	93	–	<1	2	0	1.1.1999	100	61	6	P
	FRANCE, PACA & Corsica	1984–1996	+	10876853	–	–	30	38	32	*	Rb, Wt	1473	–	98	–	0	1	<1	31.3.1998	92	48	3.9	P
	FRANCE, Rhone Alpes	1988–1997		11178532	–	–	–	50	50	*	Rb, Wt	1376	–	97	–	<1	2	0	1.6.2000	93	52	4.7	P Nb o1
	FRANCE, Doubs	1978–1996	+	2109443	765760	28	27	25	19		Wt	262	125	45	–	4	7	<1	1.6.2001	91	31	1.9	
	FRANCE, Herault	1988–1997		1499508	581332	–	–	49	51			211	100	94	–	0	2	<1	–	–	–	–	
	FRANCE, Isere	1979–1997	+	4149282	1489370	21	26	26	26	*	Rb	628	231	96	–	3	4	<1	–	–	–	–	Nb o1
	FRANCE, Manche	1994–1996		292671	96325	–	–	–	100		Rb, Wt	40	14	91	–	0	2	0	31.5.2000	59	33	4.2	S
	FRANCE, Bas-Rhin	1978–1996	+	3725275	1436570	27	27	26	20			498	228	97	–	0	7	<1	31.12.1997	100	72	8.7	
	FRANCE, Haut-Rhin	1988–1997		1403085	468970	–	–	50	50			190	77	95	–	<1	4	0	31.12.1995	41	82	7.2	S
	FRANCE, Somme	1983–1996	+	1678648	629396	–	38	36	27			184	79	97	–	<1	5	<1	15.8.2000	99	49	4.9	
	FRANCE, Tarn	1983–1997	+	915738	342810	–	35	33	31		Rb	117	47	98	–	0	4	4	–	–	–	–	
	GERMANY, GCCR (East and West)	1991–1997	+	93284500	–	–	–	29	71	*	Rb, Wt	12153	–	99	–	0	2	0	31.12.1998	88	33	3.4	P Nb
	GERMANY, GCCR (only former West)	1983–1990	+	74685000	–	–	61	39	–	*		9124	–	100	–	0	2	0	31.12.1998	97	87	9.3	P
	NETHERLANDS, National	1989–1995		19372876	7130225	–	–	58	42		Wt	2665	1360	97	–	0	4	3	31.12.1998	65	64	5.8	S o5
	NETHERLANDS, Eindhoven	1978–1997	+	3909153	1569267	29	26	22	22		Wt	478	251	94	–	2	5	5	1.7.1999	99	70	8.3	o5
	NETHERLANDS, DCOG	1978–1997	+	57636767	–	27	24	24	25			2199	–	99	–	0	0	0	1.1.2000	99	81	8.8	P o5
	SWITZERLAND, Basel	1983–1997	+	938187	370892	–	35	32	33			144	84	99	–	0	5	<1	30.6.2000	100	80	8.6	
	SWITZERLAND, Geneva	1978–1997	+	1192884	465088	25	25	24	26			177	105	98	0	0	2	0	31.12.1999	100	73	8.1	
	SWITZERLAND, Graubunden & Glarus	1989–1997		367257	124578	–	–	44	56		Wt	48	30	94	0	3	5	0	25.5.2000	100	56	5.1	
	SWITZERLAND, St. Gallen Appenzell	1983–1997	+	1450053	517611	–	33	33	34	*	Rb, Wt	202	101	97	<1	0	5	0	1.2.2001	99	47	2.5	
	SWITZERLAND, Valais	1989–1997		452140	156055	–	–	44	56		Wt	67	31	99	0	0	3	0	1.12.1998	46	97	8.5	S

–	Not applicable
*	Systematic registration of non-malignant (Non-mal.) tumours
+	Included in time trend analyses
1+ days	Cases followed-up for 1 or more days, as a percentage of all cases in the registries with follow-up
5+ years	Cases followed-up for 5 or more years, as a percentage of all those not deceased by the closing date
C.a.	Carcinoid of appendix (C18.1, M-8240)
DCO	Registrations from death certificate only
DCOG	Dutch Childhood Oncology Group
G	General cancer registry, which has only contributed data for age-range 0–14
GCCR	National German Childhood Cancer Registry (until 1990 covering only West and since 1991 the reunified Germany)
MV	Microscopically verified cases
n	Number of cases
Nb	Systematic screening for neuroblastoma within (part of) registration area (see Table 1)
NCR	National Cancer Registry of the former German Democratic Republic. Data for 1978–87 contributed only to analyses of time trends for Europe as a whole. Data on children for 1988–89 were pooled with GCCR and included in West. For explanation, see text and footnote 1).
NOS	Cases with unspecified histology, including the ICCC categories Ie, IIe, IIIf, Vic, VIIc, VIIIe, IXe, XIIb, Xe (M-8000 to M-8004 only) and XIf (C76 to C80.9 only)
o1-o5	Overlapping registration areas: for the overlapping years, data from the registry with larger coverage are included in each analysis, according to availability (see Table 1 and text)
P	Paediatric cancer registry; age range for all registrations is 0–14
PACA	Provence, Alps, Côte d'Azur
Rb	Cancer registry with at least 90% of retinoblastoma cases with known laterality
S	Survival analyses were possible only for a restricted dataset (see Table 1)
Unknown	Registrations with unknown basis of diagnosis
Wt	Cancer registry with at least 90% of Wilms' tumour cases with known laterality
Z	Covers only selected areas (see Table 1)

excluded because it was not possible to verify compatibility of the local classification system of tumours with international standards.[12] Compared with the complete ACCIS database, application of the data quality and comparability requirements resulted in a selection of 80% of the total person-years available in children and 51% in adolescents, for the analyses related to the period 1988–1997. For the analyses of time trends (1978–1997), the selected person-years represented 89% for children and 71% for adolescents.

2.3. *Overview of the datasets selected for analyses*

Sixty-two cancer registries were qualified for inclusion in the analyses of incidence and 57 in the analyses of survival (Table 2). Their geographical coverage is illustrated in Fig. 1, separately for childhood and adolescent populations. Table 1 shows the basic characteristics of the registries. The year of start of registration is an indicator of likely stability of the incidence rates. Country coverage is the percentage of the national population at risk served by the cancer registry.

Deviation from the ICD-O classification of topography and morphology potentially introduces artificial differences in incidence and survival between registries for specific tumour groups. The most striking example was seen for Finnish data (Table 1), where dissimilar coding system has resulted in a large proportion of unspecified lymphomas (ICCC subgroup IIe) [Izarzugaza and colleagues, this issue] and no distinction between astrocytoma (IIIb) and other gliomas (IIId).[13] But even the different editions of the ICD-O were not directly compara-

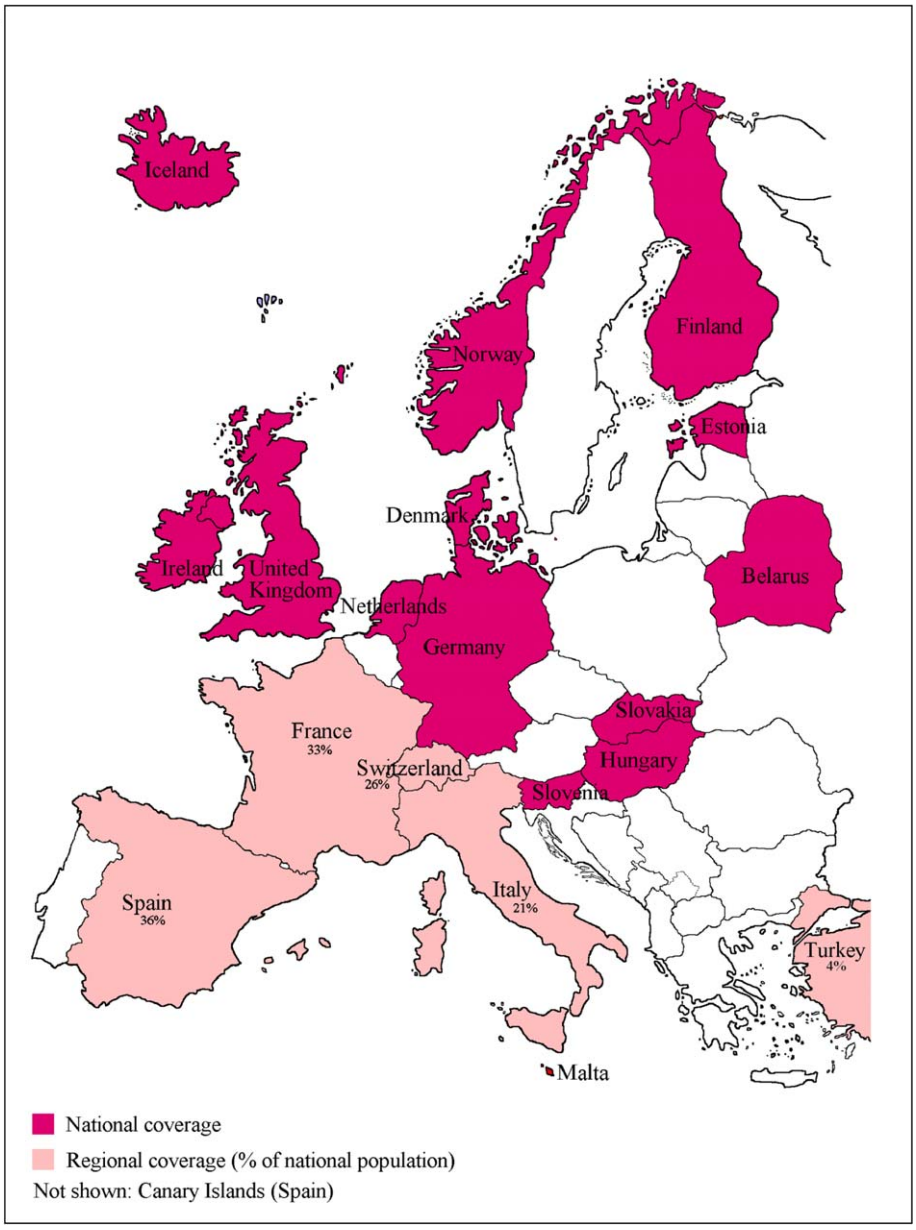

Fig. 1 – Europe, showing the countries represented in the ACCIS database and included in various analyses presented in this volume. (a) For children aged 0–14 years and (b) for adolescents aged 15–19 years. The percentages give an approximate coverage of the population at risk in the countries without national cancer registration in the 1990s. Source: ACCIS.

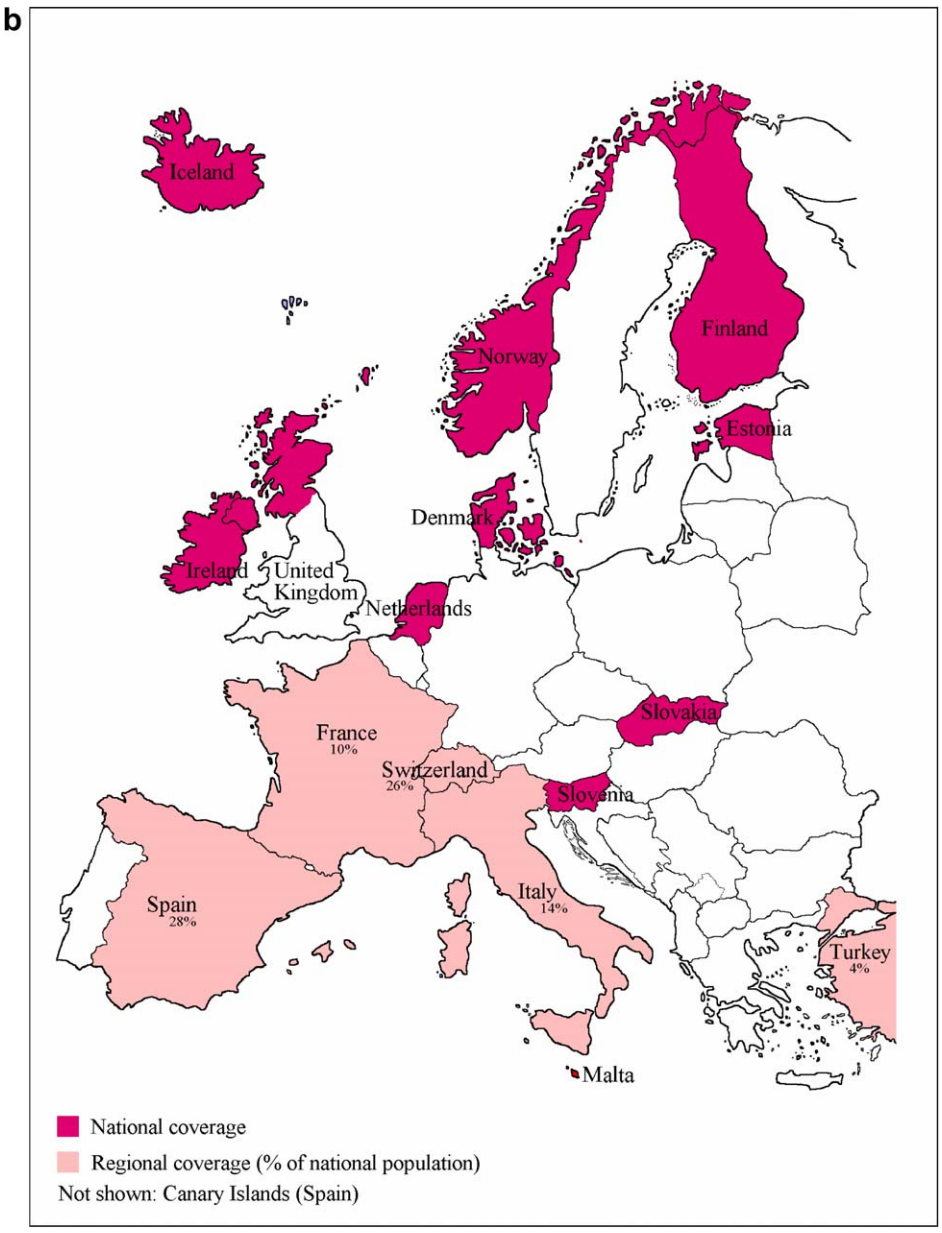

Fig. 1 – *continued*

ble for some tumour types. For example, the ICD-O-1 codes are insufficient to define optic nerve glioma (topography code C72.3 in ICD-O-2), rhabdoid sarcoma (M-8963 in ICD-O-2) and some other tumour types. Unless the original records contain the necessary information, the direct conversion is impossible for these tumour types.

The nature of the follow-up procedures indicates the reliability of survival statistics for a given period and area. The degree of completeness and accuracy of follow-up depend to some extent on systems of data collection. Direct access to a national source of identifiable death certificates would probably yield the most complete follow-up.

Table 2 provides details of the individual datasets included in the analyses. The datasets differed by size (ranging from 300,000 to 177 million person-years) and type of registry (paediatric or general), administrative area covered (national or regional), calendar period and number of years of registration (3–28 years), availability of follow-up data, etc.

2.4. *Constitution of dataset for analysis of time trends (1978–1997)*

All registries with at least 15 years of registration during 1978–1997 were included in the analyses of temporal trends for this 20-year period (Table 2). Two other registries were also included: Somme, and PACA (Provence, Alps, Côte d'Azur and Corsica), because of their substantial contribution to the French data, despite the slightly shorter period covered. All three datasets from German cancer registries were also included in the analyses of trends in children, since between them, they did cover the required 15-year period. To study trends in adolescents, data from the cancer registry of the former German Democratic Republic were included for the

period 1978–1987 in the analyses of time trends for Europe as a whole. Counting the German Childhood Cancer Registry (GCCR) only once, 33 and 31 registries with sufficiently long registration period thus contributed to the analyses of time trends of incidence and survival in children, respectively (Table 2). Slightly fewer registries were included in time trends analyses of incidence (26) and survival (24) for adolescents. The study period was divided into four successive 5-year periods, 1978–1982, 1983–1987, 1988–1992 and 1993–1997. Registries included in the time trend analyses contributed at least 3 years' data to any of these time periods. If only 1 or 2 years were contributed to any of the 5-year period, those years were excluded from analyses. The distribution of person-years over the four calendar periods is given in Table 2 for each registry.

2.5. *Definition of geographical regions*

All 62 datasets were used to describe the geographical, age and sex-specific patterns of incidence and survival in Europe for the most recent 10-year period (1988–1997). Participating countries were grouped into five regions, as shown in Table 2, and defined according to the United Nations (UN) definition of the European regions,[20] with four exceptions:

The United Kingdom (UK) and Ireland constituted a separate region labelled the British Isles, given the large number of cases available for the UK. These two countries were withdrawn from Northern Europe in the UN classification.

Estonia, one of the Baltic republics, was grouped with Eastern Europe (instead of Northern Europe in the UN classification), because of similar socio-economic determinants with those in the other countries grouped in East. This also helped to increase the number of cases available for this region.

Turkey, represented by the western city of Izmir (Western Asia by the UN categorisation), was grouped with other Mediterranean countries into Southern Europe. The Turkish data contributed only to the analyses of incidence.

The dataset for the national registry of the former German Democratic Republic (GDR) was split as follows: the years 1978–1987 were used in the analysis of trends of incidence and survival for Europe as a whole in children and adolescents. The remaining 2 years covered by the registry of the former GDR (1988–1989) were pooled with the childhood cancer datasets from the former Federal Republic of Germany (FRG), and this pool contributed to the West, while the same 2 years were excluded from all analyses for adolescents[j].

Table 2 shows that some areas overlap partially, for example, when a particular geographical area was covered both by a general and a paediatric cancer registry. To avoid including such overlapping areas twice in the analysis, only one of the relevant registries was selected for each particular analysis. As a rule, paediatric registries covered a larger population at risk than the overlapping general registries, and were thus included preferentially in the analyses concerning the age range 0–14 years. However, if a paediatric registry could not contribute to the time trend analyses, the related general registry was included instead. Since paediatric cancer registries do not provide data on adolescents, results for this age group (15–19 years) are based exclusively on information from general cancer registries. A triple overlap can be observed in Table 2 for the Netherlands. The three registries are the National Cancer Registry (since 1989), the regional cancer registry South based in Eindhoven (covering the entire study period 1978–1997), and the Dutch Childhood Oncology Group (DCOG), the latter providing national data for childhood leukaemia for the entire study period. All three were used, according to data availability: DCOG contributed to all analyses of childhood leukaemias, data from the National Cancer Registry were used for geographical analyses (period 1988–1997) of all tumours of childhood (except leukaemia-specific analyses) and incidence analyses of all tumours of adolescents. Eindhoven data were used in time-trend analyses of incidence and survival in childhood (except leukaemia-specific analyses) and adolescents, as well as in the analysis of survival in adolescents for the period 1988–1997, because survival data from the National Cancer Registry were available only for the childhood age-range (Table 1).

2.6. *Variations in registration practices*

The registries systematically recording data on non-malignant CNS tumours are flagged in Table 2. This information is based on the affirmation of this practice by the registry and the presence of a reasonable proportion of non-malignant tumours in the contributed dataset. The majority of registries were able to provide data on laterality of retinoblastoma and Wilms' tumour. Datasets in which this information was available for at least 90% of cases were included in the analyses by laterality (Table 2).

To calculate the proportion of unspecified tumours in each contributory dataset, the following tumour types were included: the complete ICCC subgroups Ie, IIe, IIIf, VIc, VIIc, VIIIe, IXe, XIIb, the unspecified histologies M-8000 to M-8004 in Xe, and the ill-defined and unspecified sites (C76 to C80.9 only) in the subgroup XIf (c.f. Annex).

According to ICD-O-2,[12] carcinoid of appendix (C18.1) should be coded to M-8240/1, i.e. 'uncertain' behaviour and would be, therefore, excluded from the ACCIS database. However, in some registries the behaviour code /3 (malignant) was reported for this tumour type. The percentage of the cases diagnosed with a 'malignant' carcinoid of appendix (C18.1, M-8240) is shown in Table 2.

Table 2 also permits evaluation of the length and completeness of follow-up in those registries following up patients for vital status. Some registries contributed a shorter time period to analyses of survival than to analyses of incidence (Manche and Haut-Rhine (France), the registry of the former German Democratic Republic, Valais (Switzerland) and the national cancer registry of the Netherlands, Tables 1 and 2). Legislation in some countries (e.g. Germany, France,

[j] This exceptional treatment of the registry of the former GDR was motivated by three simultaneous facts. Given the geopolitical situation of the former GDR considered in the above point (2), it would belong to the East region. However, data for the former GDR as a distinct registration area were only made available within ACCIS until 1989. Since during the relevant period the former GDR represented about 50% of the population at risk of the East region, the discontinuation of the data series after 1989 would have had a disproportionate effect on the time trends of incidence and survival of the East.

the Netherlands, Italy and Spain) does not allow access to the nation-wide mortality database of identifiable deceased individuals, which greatly reduces the opportunity for a cancer death being registered in patients who had escaped registration during their life-time. This lack of information is partly substituted in some registries of Italy and Spain through an access to regional deaths records, which permit registration of cancer deaths as DCO cases at least in a selected resident population.

2.7. Screening practices

According to the information received from the cancer registries, systematic population-based screening for neuroblastoma in very young children was limited to a few registration areas. In the West, children were screened in the region Rhone-Alps in France, during 1990–1996[21] and in Germany, screening was offered to about 50% of eligible children during 1995–2001.[22] In the British Isles, neuroblastoma screening was conducted among children aged less than 1 year in two small areas of the UK.[23] The possible impact on the incidence rates and survival and comparison between the regions is discussed in full in a paper on neuroblastoma [Spix and colleagues, this issue].

2.8. Statistical analysis of incidence

Incidence rates were calculated as the average annual number of cases per million person-years.[24] The age-standardised incidence rate (ASR) for the age-range 0–14 years is the weighted average of the age-specific incidence rates using the weights of the World standard population[25] for the age groups 0, 1–4, 5–9 and 10–14[k]. 95% confidence intervals (95% CI) were calculated using the Poisson approximation, or exactly, if less than 30 cases were observed.[26]

Pairs of age-specific and ASRs were compared using rate ratio and standardised rate ratio (SRR), respectively and their 95% CIs.[24] Differences between several incidence rates were evaluated using Poisson regression models and expressed as incidence rate ratio (IRR), adjusted for sex, age group and region, as applicable. The reported *P*-values test the null hypothesis of no difference in the relevant populations, compared with the reference.

Change of incidence rates over time was evaluated using Poisson regression models, adjusted for sex, age group and region and expressed as an average annual percent change (AAPC). The related *P*-values report the probability of the slope of the regression line of incidence rate over time being consistent with zero, i.e. no change over the years.

2.9. Statistical analysis of survival

The actuarial life-table method[15,27] was used to analyse survival of groups of cases defined by period of diagnosis and possibly other variables, such as age, sex, region of residence, diagnostic group, etc. Only cases with non-zero survival time were included in survival analyses. Five-year observed survival is the cumulative actuarial probability of surviving to the 5th anniversary of the incidence date. The 95 % CIs of the cumulative survival were calculated according to Kalbfleisch and Prentice.[28]

Differences in survival of two or more groups of patients were compared for the entire survivorship curves using the log-rank χ^2 test.[26] A log-rank test for trend was used to test a gradual change in survival curves over the successive time periods.[29]

3. Results

3.1. Study size

Overall, 88,465 tumours in children and 15,369 in adolescents were included in various analyses (excluding the overlapping registrations). In addition, 2199 childhood leukaemia cases from DCOG were included in leukaemia-specific analyses in replacement of 863 leukaemia cases of the two other Dutch registries [Coebergh and colleagues, leukaemias, this issue]. The precise sample size varied between the different analyses.

The underlying person years at risk included in the analyses of time trends are illustrated in Fig. 2. The person-years of observation for children were some 6–12-times more than for adolescents. This was due to the wider age-range and more complete geographical coverage of the childhood population, especially via the large paediatric cancer registries. On the other hand, distribution of person-years across regions and over time was much more homogeneous in adolescents than in children. The drop in person-years for Europe seen in Fig. 2(b) at the late 1980s represents the end of the contribution of data for adolescents by the cancer registry of the former GDR. In Fig. 2(a), the withdrawal of this registry from childhood person-years is evident as the dip at 1990 in the curve for Europe. In fact, case ascertainment in the territory of the former GDR was incomplete for the year 1990 and it is thus missing from the ACCIS database. The same area was covered since 1991 (for children only) by the national German Childhood Cancer Registry (GCCR) (Table 1). Inclusion of the area of the former GDR registry explains the increase in person-years for the West since 1991 seen in Fig. 2(a). Other minor irregularities to the curves for the West and South represent entries to and exits from the time trends dataset of some smaller registries. The European curve for children thus reflects the late arrival of the West, the early departure of England and Wales and the temporary lack of data from GDR in 1990.

3.2. Quality indicators

Table 3 documents overall quality of the dataset used for time trends analyses of incidence and survival. The proportion of microscopically verified cases varied between 90% and 99% for all periods, regions and age-ranges. The lowest proportion was observed in the British Isles and highest in the West (since 1983). The proportion of DCO cases was usually lower then 1% (Table 3), although only the registries where registration of cases from death certificates is possible contributed to this percentage. The proportion of cases with unknown method of diagnosis was also very low, with a maximum of

[k] Weights being 2.4, 9.6, 10 and 9, respectively.

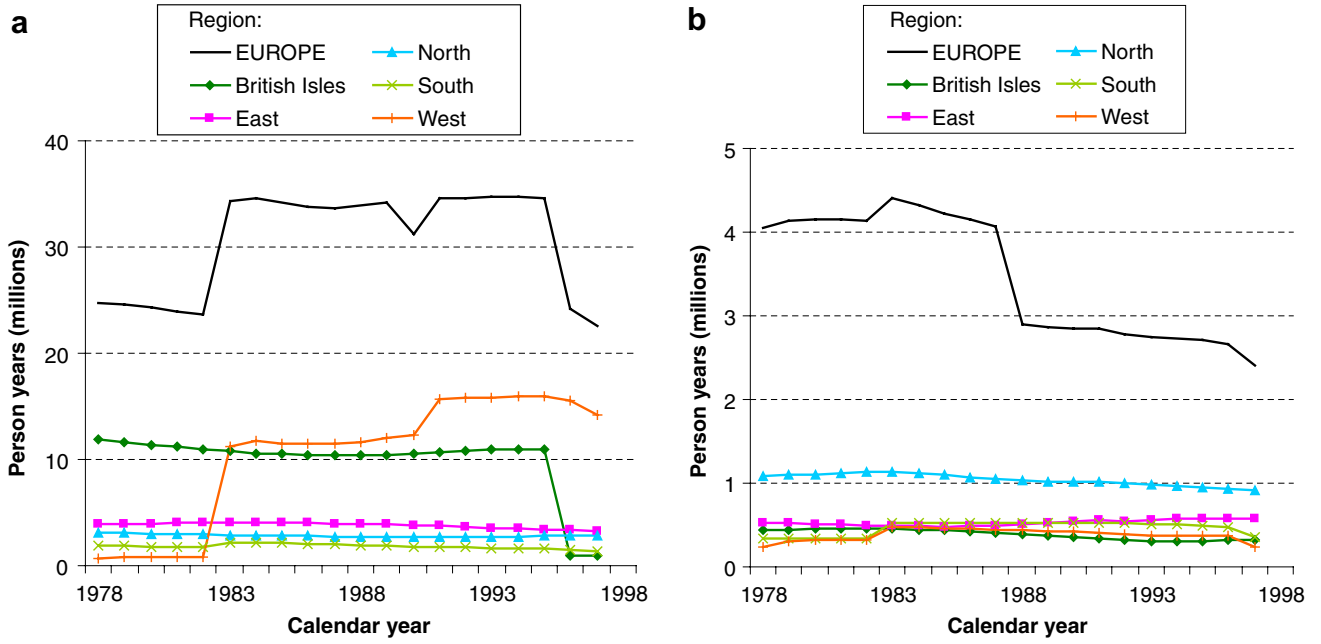

Fig. 2 – Distribution of person-years at risk included in the analyses of incidence time trends presented in this volume over calendar years. (a) Children (age 0–14 years), (b) adolescents (age 15–19 years). Europe includes the person-years contributed by the former GDR for the period 1978–1989, which are not included in any of the shown European regions. Source: ACCIS.

5% in early 1990s in the British Isles. There were no substantial differences in these quality indicators between children and adolescents, regions and 5-year periods.

Overall, 3.7% of cases included in the time-trends dataset for children were unspecified tumour types. Their proportion decreased from 6.1% in 1978–1982 to 2.9% in 1993–1997 (Table 3). In adolescents, the corresponding percentages were higher: 8.4% on average, decreasing from 8.9% to 7.1% between the first and the last period. The reduction in the proportion of unspecified tumours was fairly general (although the proportions were high and stable in the North and low and stable in the British Isles, Table 3).

Table 4 describes the size and the quality of the dataset used to examine geographical, sex- and age-specific patterns of incidence and survival for the 10-year period 1988–1997. The quality indicators and the follow-up data in this dataset are consistent with those observed in the time-trend dataset: the additional cancer registries (62 instead of 33) therefore did not markedly modify the data quality.

3.3. *Impact of the selection of registries on incidence time trends*

Eleven of the 33 registries included in the analyses of incidence trends contributed only to the final three 5-year periods (Table 2). The possible effect of these 'late' entries, and other deficiencies in complete coverage within the time-trends data set is examined in Table 5. Each pair of the adjacent datasets shown in Table 5 compares the 'long' study period (four quinquennia) with 'short' one (three quinquennia). Analyses were also carried out for the period ending in 1995 (datasets 5 to 8), because the last 2 years of the study period were covered less well (Fig. 2). The effect of the on-and-off contribution of the German datasets was examined by comparing the datasets 3, 4, 7 and 8 (excluding German data) to the corresponding ones (1, 2, 5 and 6, respectively). The analyses were carried out for both children and adolescents, although the scope for artefacts due to variable person-years contribution was much smaller in the time-trends dataset for adolescents.

The increase in incidence rates was consistent in all eight datasets, although formal statistical significance was not attained in children within the datasets 4 and 8, covering the period 1983–1997 and excluding the German datasets. This lack of significance is the result of the drastic reduction in the study power, since the overall incidence rates for the common period in datasets 4 and 8 were not lower than those in the other compared datasets. Formal comparison of the ASR for datasets 6 and 8 in children yielded non-significant result: SRR = 1.04, 95% CI = (0.96, 1.13). Dropping the last 2 years 1996 and 1997 (datasets 5 to 8) reduced the level of incidence rates slightly in both children and adolescents, which is consistent with the overall tendency of secular increase. Table 5 thus documents that the incidence trends are unlikely to be the result of the late addition of newer registries to those with long registration periods. On the contrary, the registries covering only the final three quinquennia may have slightly reduced, rather than increased, the rate of change in incidence rates, as seen from the comparison of ASR for the common periods in adolescents and in children with German data included.

3.4. *Effect of incomplete follow-up on survival results*

Table 3 shows the indicators of the completeness of follow-up for the subsets of data used for time trends analysis of survival. Overall, 96% of children registered in the registries

Table 3 – Numbers of cases and indicators of data quality by region and age group used for time trend analyses of incidence and survival in children (age 0–14 years) and adolescents (age 15–19 years) in Europe, 1978–1997 (Source: ACCIS)

Region	Period	Children (age 0–14 years)										Adolescents (age 15–19 years)									
		Person-years	Cases		NOS	Non-mal.	Basis of diagnosis			Follow-up		Person-years	Cases		NOS	Non-mal.	Basis of diagnosis			Follow-up	
							MV	DCO	Unknown	1+ days	5+ years						MV	DCO	Unknown	1+ days	5+ years
			%	*n*	%	%	%	%	%	%	%		%	*n*	%	%	%	%	%	%	%
Europe[a]	1978–82	121284732	20	13907	6	3	94	<1	<1	96	98	20622735	30	3177	9	1	95	<1	<1	96	98
	1983–87	170572963	28	20890	4	3	95	<1	<1	97	87	21169170	31	3530	9	2	96	<1	<1	98	77
	1988–92	168426435	28	21906	3	3	95	<1	2	97	88	14240018	21	2541	8	2	96	<1	<1	98	95
	1993–97	150824389	25	20408	3	3	96	<1	<1	93	36	13246564	19	2641	7	3	96	<1	<1	98	23
British Isles	1978–82	57031152	29	6179	3	3	93	<1	1	98	99	2261447	29	315	8	0	92	<1	0	99	100
	1983–87	52615567	27	6189	3	3	92	<1	2	98	99	2171285	28	344	8	0	94	0	0	99	100
	1988–92	52790201	27	6632	3	3	90	<1	5	98	99	1791372	23	320	5	0	94	0	0	100	100
	1993–97	34764851	18	4548	4	4	92	<1	3	99	90	1569618	20	302	5	0	95	<1	0	99	45
East	1978–82	19725395	26	2129	9	2	93	<1	0	92	93	2561929	24	340	15	2	89	6	0	90	100
	1983–87	20006154	26	2327	6	3	94	<1	0	95	84	2437063	23	336	9	1	94	<1	0	94	99
	1988–92	18992858	25	2326	5	3	95	<1	0	96	89	2681816	25	441	7	2	97	<1	0	97	100
	1993–97	16910976	22	2192	4	3	96	<1	0	98	31	2862995	27	494	5	2	95	2	0	95	4
North	1978–82	15090315	27	1996	11	4	95	<1	1	97	99	5535837	27	932	10	3	97	<1	<1	97	99
	1983–87	14037183	25	2042	9	3	96	0	<1	98	100	5470333	26	984	12	4	96	<1	<1	99	99
	1988–92	13584110	24	2045	8	4	96	<1	<1	98	99	5063716	24	985	10	3	97	<1	<1	99	98
	1993–97	13925266	25	2238	11	5	94	<1	1	99	26	4745895	23	1072	8	4	97	0	<1	100	26
South	1978–82	9046622	25	1168	9	5	90	3	<1	97	98	1707033	18	220	8	1	92	3	0	97	93
	1983–87	10520563	29	1381	7	3	95	<1	<1	99	99	2629396	28	404	10	2	95	<1	1	97	99
	1988–92	9090335	25	1281	6	2	96	<1	<1	99	96	2623252	28	444	7	2	97	1	<1	99	94
	1993–97	7744451	21	1196	5	2	96	<1	<1	99	34	2356491	25	443	7	2	95	1	<1	99	18
West	1978–82	3941628	2	470	22	2	84	0	1	99	92	1496339	20	239	8	<1	86	0	1	98	87
	1983–87	57355305	28	6879	1	3	98	<1	<1	98	89	2298998	30	331	12	2	93	0	<1	100	81
	1988–92	67496965	33	8828	<1	3	99	0	<1	95	77	2079862	27	351	9	<1	92	0	<1	97	74
	1993–97	77478845	38	10234	<1	3	99	0	<1	87	16	1711565	23	330	9	<1	98	0	2	98	24

1+ days Cases followed-up for 1 or more days, as a percentage of all cases in the registries with follow-up.
5+ years Cases followed-up for 5 or more years, as a percentage of all those not deceased by the closing date.
DCO Cases registered from death certificate only.
MV Microscopically verified diagnosis.
n Number of cases.
Non-mal. Includes non-malignant tumours located in CNS and classified in the ICCC group III and subgroup Xa.
NOS Cases with unspecified histology, including ICCC subgroups Ie, IIe, IIIf, VIc, VIIc, VIIIe, IXe, XIIb, Xe (M-8000 to M-8004 only) and XIf (C76 to C80.9 only).
a Europe includes the data of the former German Democratic Republic, which are not included in any of the regions.

Table 4 – Numbers of cases and indicators of data quality by region and age group used for geographical analyses of incidence and survival in children (age 0–14 years) and adolescents (age 15–19 years) in Europe, 1988–1997 (Source: ACCIS)

Region	Age group	Person-years	Cases	Non-mal.	NOS	C.a.	Basis of diagnosis			Follow-up		
							MV	DCO	Unknown	1+ days	5+ years	Median
			%	*n*	%	%	%	%	%	%	%	Years
Europe	0–14	401843320	90	53717	3	4	0.2	97	0.3	1.1	95	62	5.8
	0	25662950	6	5073	3.2	5.5	0	96.8	0.6	1.2	92	62	5.7
	1–4	105450671	24	19379	1.7	3.2	0	98.3	0.2	0.7	96	63	5.9
	5–9	134925501	30	14677	3.7	4.1	0.1	96.3	0.2	1.1	95	62	5.8
	10–14	135804198	30	14588	3.9	4.2	0.5	96.1	0.2	1.5	96	61	5.7
	15–19	44479551	10	8272	1.9	6.7	1.9	98.1	0.4	0.4	99	56	5.5
British Isles	0–14	92540901	95	11837	3.5	3.8	0	96.5	0.9	3.9	99	89	8.2
	0	6366126	7	1079	4.7	6.8	0	95.3	2.4	4.5	95	91	8.4
	1–4	25510910	26	4584	1.9	2.4	0	98.1	0.5	2.3	99	90	8.4
	5–9	30981391	32	3136	4.2	3.8	0	95.8	0.8	3.9	99	89	8.0
	10–14	29682474	30	3038	4.9	4.7	0	95.1	0.9	6.2	99	88	8.0
	15–19	5240123	5	968	1.3	8.5	0.6	98.7	0.1	0	100	49	4.9
East	0–14	56614254	91	7718	2.7	5.1	0	97.3	0.2	0	98	64	6.2
	0	3220674	5	570	2.6	10.2	0	97.4	0.5	0	91	62	6.3
	1–4	14033863	23	2468	1.9	5.8	0	98.1	0.2	0	98	65	6.4
	5–9	19130650	31	2216	3.1	4.6	0	96.9	0.2	0	98	66	6.5
	10–14	20229067	33	2464	3.1	3.7	0	96.9	0.1	0	99	61	5.9
	15–19	5544811	9	935	2.2	5.9	0.7	97.8	1.2	0	96	42	4.4
North	0–14	27509376	74	4283	4.4	9.3	0.7	95.6	0.3	0.9	98	59	5.8
	0	1919279	5	436	4.8	12.6	0	95.2	0.5	1.1	95	58	5.9
	1–4	7492182	20	1653	2.3	7.1	0	97.7	0.4	0.7	98	59	5.8
	5–9	8959113	24	1069	6	11.5	0.8	94	0.2	1.2	99	59	5.9
	10–14	9138802	24	1125	5.9	9.2	2	94.1	0.1	0.6	100	60	5.9
	15–19	9809611	26	2057	3.7	8.9	2.2	96.3	0.1	0.5	99	58	5.7
South	0–14	39317250	77	5534	1.8	5.4	0.1	98.2	0.3	1.1	99	72	6.1
	0	2238515	4	453	1.3	5.7	0	98.7	0.2	1.5	97	72	6.2
	1–4	9210623	18	1824	0.9	3.8	0	99.1	0.3	1	99	71	6.0
	5–9	12714912	25	1460	2.3	6.3	0	97.7	0.3	1	99	71	6.1
	10–14	15153200	30	1797	2.4	6.1	0.2	97.6	0.3	1.1	99	72	6.1
	15–19	11536094	23	2153	1.7	7.8	0.3	98.3	0.9	0.5	99	63	6.1
West	0–14	185861539	94	24345	2.9	2.4	0.2	97.1	0	0.1	92	47	4.4
	0	11918356	6	2535	2.7	2.7	0	97.3	0	0	89	49	4.5
	1–4	49203093	25	8850	1.6	2.1	0	98.4	0	0.1	93	48	4.5
	5–9	63139435	32	6796	3.7	2.6	0.1	96.3	0	0.1	91	47	4.2
	10–14	61600655	31	6164	3.7	2.6	0.7	96.3	0	0.1	92	45	4.2
	15–19	12348912	6	2159	0.4	3.1	4.4	99.6	0	0.4	98	52	5.0

1+ days Cases followed-up for 1 or more days, as a percentage of all cases in the registries with follow-up.
5+ years Cases followed-up for 5 or more years, as a percentage of all those not deceased by the closing date.
C.a. Carcinoid of the appendix (C18.1, M-8240).
DCO Cases registered from death certificate only.
MV Microscopically verified diagnosis.
n Number of cases.
Non-mal. Includes non-malignant tumours located in CNS and classified in the ICCC group III and subgroup Xa.
NOS Cases with unspecified histology, including ICCC subgroups Ie, IIe, IIIf, VIc, VIIc, VIIIe, IXe, XIIb, Xe (M-8000 to M-8004 only) and XIf (C76 to C80.9 only).

conducting follow-up were included in survival analyses. In adolescents, the start of follow-up was even more complete (98%), although at the end of 5 years, fewer cases were still tracked in adolescents (71%) than in children (74%). Follow-up was most complete in the British Isles and least complete in the West. The proportion of followed-up patients in the first three 5-year periods was largely complete and did not vary much, while large differences were observed between the regions in the last period. Besides the efficiency of the tracing procedures, the completeness of the follow-up at 5 years obviously depended on the length of the registration period (if it was shorter than 5 years), and the timing of the closing date of the study (Table 2).

The proportion of patients followed-up for 5 years or more was far from 100% for some cancer registries (Table 2), which reduced comparability between the regions (Table 3). This was mostly caused by the early closing date of the study, so that many cases were withdrawn alive (censored) before the 5-

Table 5 – Simulation of incidence time trends with various subsets of data (Source: ACCIS)

Dataset	Period	Modifications	Children (age 0–14 years)						Adolescents (age15–19 years)					
			Registries	Person-years	Cases	Common period	Total period		Registries	Person-years	Cases	Common period	Total period	
			n	Millions	*n*	ASR	AAPC	P > |z|	*n*	Millions	*n*	Rate	AAPC	P > |z|
1	1978–1997		22	413	51,896	134.6	1.2	<0.0001	18	44	7914	179.9	2.0	<0.0001
2	1983–1997		11	198	25,215	132.7	1.2	<0.0001	8	5	798	171.2	2.6	0.002
3	1978–1997	Germany excluded	21	374	47,065	135.1	1.2	<0.0001	17	38	6783	179.3	2.0	<0.0001
4	1983–1997	Germany excluded	10	30	3938	136.8	0.7	0.14	7	5	798	171.2	2.6	0.002
5	1978–1995		22	396	49,348	133.6	1.2	<0.0001	18	39	6985	177.0	2.0	<0.0001
6	1983–1995		11	169	21,210	130.6	1.0	<0.0001	8	4	690	167.5	2.7	0.01
7	1978–1995	Germany excluded	21	357	44,517	134.0	1.2	<0.0001	17	33	5854	175.8	1.9	<0.0001
8	1983–1995	Germany excluded	10	27	3521	136.2	0.6	0.095	7	4	690	167.5	2.7	0.01

Common period includes the overlapping years of both compared datasets. Total period refers to all years shown in Period column. Average annual percentage change (AAPC) was calculated from Poisson regression model, with year as explanatory variable, adjusted for sex, region and, for children only, age group. The registries included can be found in Table 2.
n, number; ASR, age-standardised incidence rate (World standard); Rate, age-specific incidence rate.

Table 6 – Example of modification of 5-year survival estimate in relation to the proportion of withdrawals and their eventual trace-back in a fictitious study of 10,000 subjects (Source: ACCIS)

	Cohort A: 10,000 cases				Cohort B: 10,000 cases				Cohort C: 10,000 cases			
	Alive at the end of 5 years	Dead during 5 years	Withdrawn during 5 years	5-year OS	Alive at the end of 5 years	Dead during 5 years	Withdrawn during 5 years	5-year OS	Alive at the end of 5 years	Dead during 5 years	Withdrawn during 5 years	5-year OS
	n	*n*	*n*	%	*n*	*n*	*n*	%	*n*	*n*	*n*	%
Follow-up < 5 years	7.5% withdrawals				15% withdrawals. Number of deaths is the same as in cohort A.				15% withdrawals. Number of deaths is lower than in cohort A, proportionately to the number of withdrawals.			
No withdrawals traced	6000	3250	750	66.9	5250	3250	1500	66.3	5492	3008	1500	68.9
Follow-up ⩾ 5 years												
All withdrawals confirmed deceased	6000	4000	0	60.0	5250	4750	0	52.5	5250	4750	0	52.5
All withdrawals confirmed alive	6750	3250	0	67.5	6750	3250	0	67.5	6750	3250	0	67.5
1/2 withdrawals deceased, 1/2 alive	6375	3625	0	63.8	6000	4000	0	60.0	6000	4000	0	60.0

OS, observed survival, calculated from life table. Number of losses in each follow-up year for cohorts B and C were double those in cohort A.

year follow-up was completed. Early censoring may bias the results of survival analyses, as demonstrated in Table 6. The 5-year survival estimate of 66.3% for group B is based on a cohort of 10,000 cases followed-up incompletely, with 15% of cases censored at the closing date. Depending on the fate of the patients, the final 5-year survival (based on completed follow-up) may be as low as 52.5% or as high as 67.5%. With the same number of deaths, the corresponding range is narrower, 60.0% to 67.5% in the cohort A with only 7.5% of withdrawals. Assuming that the proportion of deaths among withdrawals is the same as in the cohort with completed follow-up, the 5-year actuarial probability will be overestimated at an early closing date, as seen for the cohort C in Table 6.

3.5. *Consequence of variable registration of non-malignant tumours*

About 97% of all childhood cancer cases were malignant tumours, the remaining 3% were non-malignant tumours occurring in the CNS. Due to a good representation of the registries with systematic registration of non-malignant tumours in the childhood datasets, the percentage of non-malignant tumours was only slightly higher in the restricted dataset (composed exclusively of the registries with systematic registration of non-malignant tumours, Table 7). In adolescents, the proportion of such registries was lower on average (except in the North), which resulted in less comparable proportions of non-malignant tumours between the full and the restricted datasets in Table 7. On the whole, there seem to be slightly fewer non-malignant tumours among adolescents than among children, which is consistent with the lower incidence rates of CNS tumours in adolescents [Stiller, Desandes, Danon and colleagues, this issue] than in children [Peris-Bonnet and colleagues, this issue]. Table 8 shows that during the most recent 10-year period there were no differences in incidence rates of malignant tumours in children, whether all registries or only those with systematic registration of non-malignant tumours were included. Only a marginal difference (for Europe as a whole) was observed for the same comparison in adolescents, with higher rate in the dataset composed of selected registries. This was due to a larger weight of North, the region with highest incidence rates, among the selected (50% of the cases) than among all (24%) registries. Overall, the incidence rates of non-malignant tumours in children were higher by some 14% when only selected registries were included, compared with the unrestricted dataset. In adolescents the selection of the registries did not influence the rates of non-malignant tumours significantly (except in the East), although their rates also seemed to be considerably higher in the restricted than in the unrestricted dataset for British Isles, South and West (Table 8). Fig. 3 illustrates the increasing incidence of malignant and non-malignant tumours over the study period 1978–1997 in Europe as a whole (Fig. 3(a)), and in the individual regions (Fig. 3(b and c)). The differences between the regions were somewhat wider in the dataset destined for analysis of the most recent period 1988–1997 than in the dataset for time trends (Table 7), reflecting the larger representation of registries registering only malignant tumours, especially in the South and West, and for adolescents in the British Isles. Table 9 shows that the incidence of both malignant and non-malignant tumours was increasing, slightly faster for non-malignant tumours (non-significantly in adolescents). The rate of increase was slightly higher when only the registries with systematic collection of non-malignant tumours were included.

Selection of the registries according to the registration of non-malignant tumours did not seem to influence much the overall survival, as Fig. 4 shows for children. Similar results were seen in adolescents: a difference between the total and the restricted dataset was only seen for the British Isles, where five-year survival with malignant tumours was 72%,

Table 7 – Proportion of non-malignant tumours of the total registrations in the various datasets (Source: ACCIS)

	Geographical analyses (period 1988–1997)					Time trends analyses (period 1978–1997)				
	All registries		Selected registries			All registries		Selected registries		
	n	% non-malignant	% PY	*n*	% non-malignant	*n*	% non-malignant	% PY	*n*	% non-malignant
Children (age 0–14 years)										
Europe	53,717	3.0	86	46,033	3.4	77,111	3.3	92	70,855	3.5
British Isles	11,837	3.5	90	10,595	3.9	23,548	3.5	91	21,112	3.9
East	7718	2.7	94	7289	2.8	8974	2.7	89	8164	2.9
North	4283	4.4	100	4283	4.4	8321	3.9	100	8321	3.9
South	5534	1.8	63	3505	2.7	5026	3.0	77	3876	3.8
West	24,345	2.9	84	20,361	3.3	26,411	3.1	93	24,551	3.2
Adolescents (age 15–19 years)										
Europe	8272	1.9	48	4097	3.6	11,889	2.6	74	8698	3.4
British Isles	968	1.3	36	346	3.8	1281	0.0	0	0	–
East	935	2.2	81	751	2.8	1611	2.0	76	1281	2.5
North	2057	3.7	100	2057	3.7	3973	3.7	100	3973	3.7
South	2153	1.7	37	755	4.1	1511	1.7	64	850	2.7
West	2159	0.4	9	188	2.1	1251	1.0	26	332	1.8

Selected registries are those with systematic registration of non-malignant tumours (Table 2). *n*, total number of registrations, %PY, percent person-years covered by the selected registries.

Table 8 – Number (n) and incidence rate of the malignant and non-malignant tumours in the European regions in children and adolescents incident in the period 1988–1997 (Source: ACCIS)

	Malignant tumours						Non-malignant tumours					
	All registries		Selected registries		Comparison		All registries		Selected registries		Comparison	
	n	Rate	*n*	Rate	Rate ratio	95% CI	*n*	Rate	*n*	Rate	Rate ratio	95% CI
Children (age 0–14 years)												
Europe	52,109	129.7	44,453	128.7	0.99	0.98–1.00%	1,608	4.0	1580	4.6	1.14	1.13–1.15%
British Isles	11,419	123.4	10,177	122.7	0.99	0.96–1.03%	418	4.5	418	5.0	1.12	1.08–1.15%
East	7511	132.7	7084	132.7	1.00	0.95–1.05%	207	3.7	205	3.8	1.05	1.00–1.11%
North	4094	148.8	4094	148.8	1	–	189	6.9	189	6.9	1	–
South	5435	138.2	3411	138.7	1.00	0.90–1.12%	99	2.5	94	3.8	1.52	1.35–1.71%
West	23,650	127.3	19,687	125.4	0.99	0.97–1.00%	695	3.7	674	4.3	1.15	1.13–1.17%
Adolescents (age 15–19 years)												
Europe	8117	182.5	3951	183.9	1.01	1.00–1.01%	155	3.5	146	6.8	1.95	0.52–7.36%
British Isles	955	182.3	333	177.2	0.97	0.95–1.00%	13	2.5	13	6.9	2.79	0.17–45.20%
East	914	164.8	730	163.3	0.99	0.99–0.99%	21	3.8	21	4.7	1.24	1.09–1.41%
North	1980	201.8	1980	201.8	1	–	77	7.9	77	7.9	1	–
South	2117	183.5	724	171.7	0.94	0.76–1.15%	36	3.1	31	7.4	2.36	0.28–19.80%
West	2151	174.2	184	166.8	0.96	0.91–1.00%	8	0.7	4	3.6	5.60	0.08–417.27%

Selected registries are those with systematic registration of non-malignant tumours (Table 2). Rate is age-standardised (World standard) incidence rate for children and age-specific rate for adolescents. Rate ratio is standardised incidence ratio for children and simple rate ratio for adolescents.

95% CI = (69, 75) in the complete data set and 63%, 95% CI = (57, 69) in the restricted dataset, reflecting the absence of Scotland in the latter. The next largest difference concerned the survival of children with non-malignant tumours in the South, with the corresponding survival of 89%, 95% CI = (68, 96) in the complete, compared with 92%, 95% CI = (68, 98) in the restricted dataset.

3.6. *Influence of the registration of multiple primary tumours*

A half percentage of the tumours in children and about 1% in adolescents were multiple primaries: second, third, fourth or fifth malignancies in a single individual. This percentage varied slightly between the regions and with age at diagnosis (Table 10). Information on second and higher primary tumours was not provided from the large paediatric registry of England and Wales (Table 1), which represented a substantial component of the British Isles. Assuming the odds of multiple to first primaries in each age group being the same as in the other European regions, the ASR of the multiple primaries for British Isles in 1988–1997 would be 0.76 per million and the corresponding European ASR would be 0.81 per million: only slightly higher than those shown in Table 10. In the 1988–1997 dataset, multiple primaries accounted for less than 1 per million in children and about 3 per million in adolescents (Table 10). The highest incidence rates of second and higher primary tumours were observed in North. Incidence of multiple tumours increased between the first and the last 5-year period almost five-fold both in children and adolescents (Table 10). However, the incidence rates of first primary tumours were also increasing significantly (Table 10).

Multiple primary tumours were included in survival analyses, but their inclusion did not affect survival markedly, as shown in Fig. 5, because their proportion was very small. For example, 5-year survival of 49,651 European children incident in 1988–1997 was 71.89%, 95% CI = (71.56, 72.36), while 5-year survival of 49,407 children with first primaries only was 72.12%, 95% CI = (71.70, 72.53). In the North and West, the regions with highest proportion of multiple primaries, the 5-year survival differed by 0.24 and 0.27 percentage points, respectively. Nevertheless, survival of children with multiple primaries was considerably lower than that of children with first primary tumours. This disparity was observed in each period except the first (Fig. 5(a)) and in each region except the British Isles (Fig. 5(b)), due to a deficiency of multiple primaries. While survival of children with first primaries has improved significantly over the 20 years ($P < 0.0001$), survival of children with multiple primaries did not change ($P = 0.76$).

The most common groups of tumours occurring as second or higher primary tumours were the CNS tumours (26%), followed by leukaemias (20%), carcinomas (15%) and lymphomas (13%). At the level of ICCC subgroups, more than 10% each were contributed by ANLL and astrocytoma. Since the reporting of multiple primary tumours was incomplete and non-comparable within ACCIS, further detail is not presented.

3.7. *Scale of registration of carcinoid of appendix as malignant tumour*

An additional potential source of artefact is the recording of carcinoid of the appendix as a malignant tumour by some registries. There were 341 'malignant' cases of carcinoid of the appendix in the data used for analyses, none occurring before the age of 5 years and the majority occurring in adolescents. Since only 5 carcinoids of the appendix were reported from two paediatric cancer registries, the results reported below are based on the dataset composed of the general cancer registries only. Incidence rates of this tumour increased with age and with period of diagnosis (Fig. 6(a)). Differences were observed between the regions, with especially high incidence

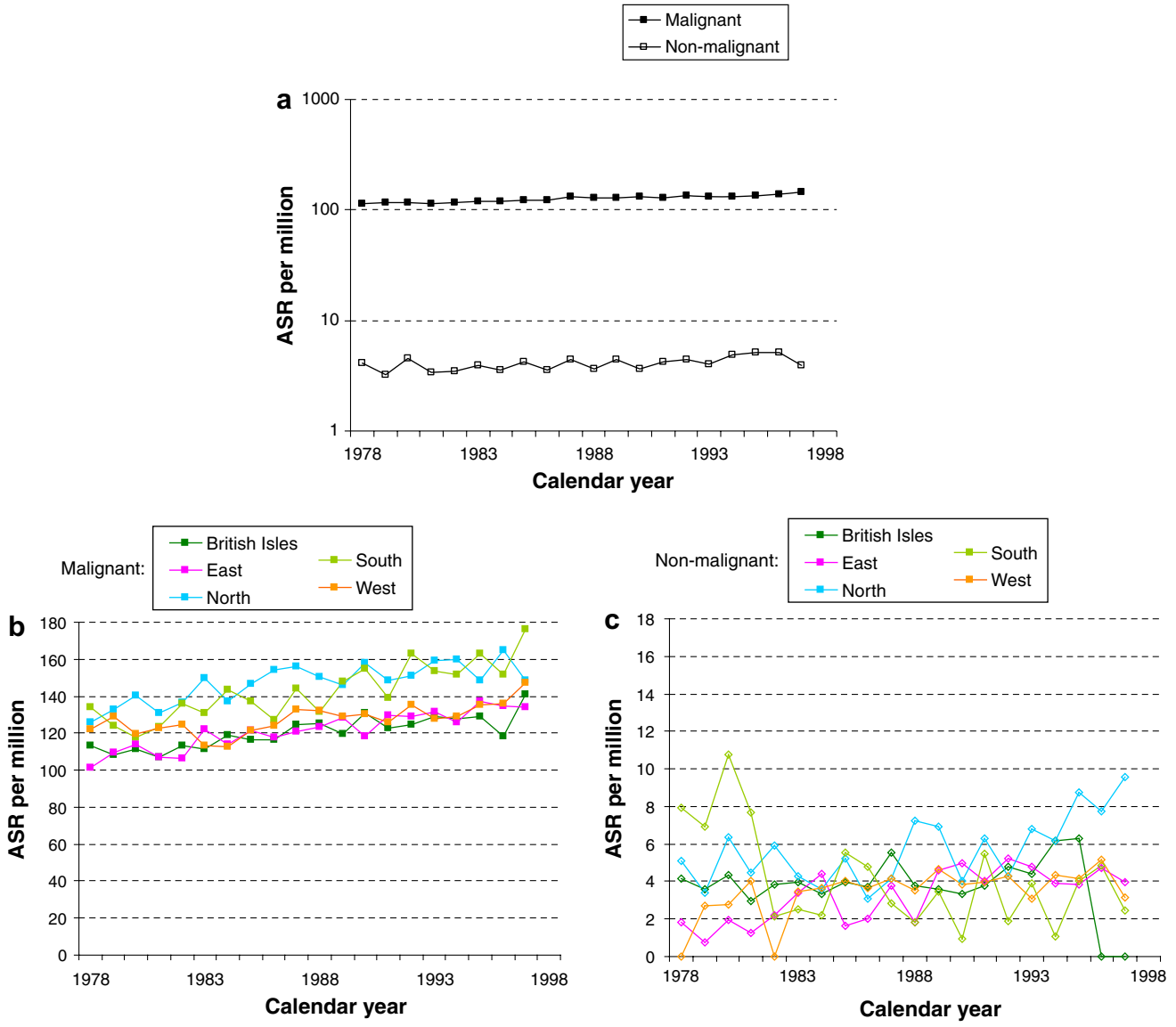

Fig. 3 – Age-standardised incidence rates (ASR, world standard) of malignant and non-malignant tumours in European children (age 0–14 years) over time. Based on all registries included in the time trends dataset (1978–1997), *n* = 77,111. Europe includes data contributed by the former GDR, which are not included in any of the shown European regions. (a) Europe, (b) malignant tumours, (c) non-malignant tumours. Source: ACCIS.

Table 9 – Number (n) and average annual percent change (AAPC) in incidence rate of the malignant and non-malignant tumours in all cancer registries included in the time trends analyses in Europe, 1978–1997 (Source: ACCIS)

	All registries			Selected registries		
	n	AAPC	*P*	*n*	AAPC	*P*
Children (age 0–14 years)						
Malignant	74,592	1.10	<0.0001	68,363	1.30	<0.0001
Non-malignant	2519	1.66	<0.0001	2492	1.71	<0.0001
Adolescents (age 15–19 years)						
Malignant	11,584	2.00	<0.0001	8402	2.03	<0.0001
Non-malignant	305	2.02	0.087	296	2.24	0.062

AAPC was calculated from Poisson regression model with year as explanatory variable, adjusted for sex, region and, for children only, age group.

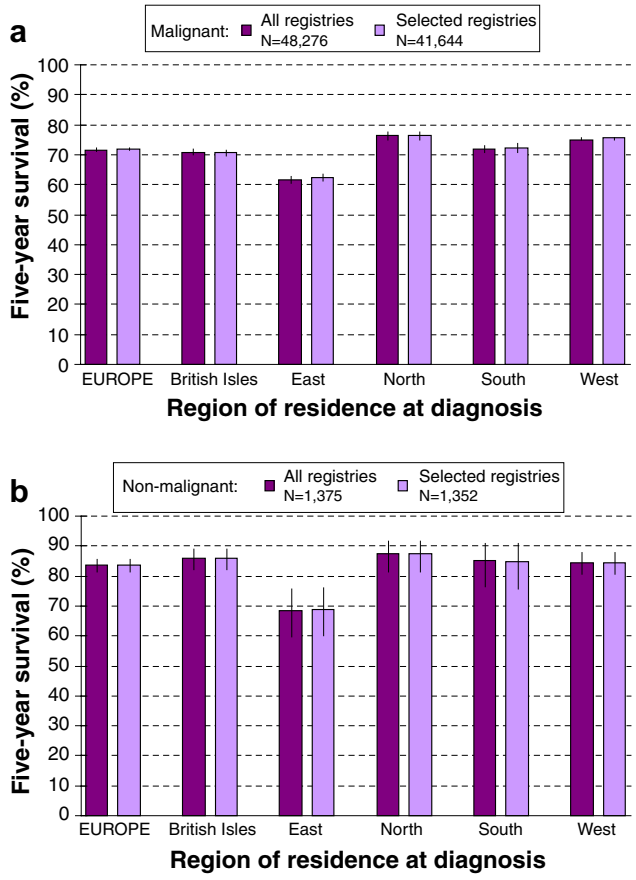

Fig. 4 – Five-year survival of children diagnosed in Europe in 1988–1997 with (a) malignant tumours and (b) non-malignant tumours. Data provided by all registries are compared with those with systematic registrations of non-mailgnant tumours (Selected registries). N, number of cases included in analysis. 95% confidence intervals are shown as line sections. Source: ACCIS.

rates in the North and West (Fig. 6(b)). The overall age-specific rates of cancer in adolescents reported from these two regions were therefore inflated by about 3 per million in the North and 8 per million in the West. The effect on the age-standardised incidence rate in the age-range 0–14 years in the West is diluted by the contribution of the large German registry and other paediatric cancer registries, with no or exceptional registrations of 'malignant' carcinoid of the appendix. In the North, the inclusion of the carcinoid of the appendix diagnosed before the age of 15 years increased the rates by at most one per million, that is from 162.8 to 163.9 in 1993–1997, the period with highest incidence of these tumours.

Survival of patients with carcinoid of the appendix is excellent: only 2 of all 243 patients followed up have died, possibly of other causes. The variable proportion of these tumours in the region-specific datasets was therefore thought to contribute to differences in survival by time period or region. However, in adolescents of the North the overall 5-year observed survival (OS) was actually slightly higher for the complete cohort (OS = 78.6%, 95% CI = (77.0, 80.0), $n = 3085$) than for the cohort free from these cases (OS = 78.3%, 95% CI = (76.7, 79.8), $n = 3040$). The corresponding figures in the West for the total dataset of 660 cases were OS = 74.2%, 95% CI = (70.3, 77.6) and for the dataset free of carcinoid of the appendix ($n = 647$) it was OS = 73.6% 95% CI = (69.7, 77.1). This is because in the smaller cohorts there were fewer patients at risk of dying for the same number of deaths. Unequal presence of carcinoid of the appendix in different regions did not enhance regional differences in survival.

3.8. *Systematic differences between paediatric and general cancer registries*

Paediatric cancer registries (Table 2) contributed a substantial proportion of person-years during the most recent 10-year period 1988–1997, as seen in Fig. 7. However, their representation

Table 10 – Numbers (n) and incidence rates by tumour multiplicity in Europe (Source: ACCIS)

		Children (age 0–14 years)					Adolescents (age 15–19 years)				
		First primary		Multiple primaries			First primary		Multiple primaries		
		n	ASR	% of total	n	ASR	n	Age-specific rate	% of total	n	Age-specific rate
1988–1997	Europe	53,447	137.8	0.5	270	0.65	8,192	128.2	1.0	80	1.80
	British Isles	11,831	131.1	0.1	6	0.06	961	183.4	0.7	7	1.34
	East	7704	140.7	0.2	14	0.22	929	167.5	0.6	6	1.08
	North	4247	158.9	0.8	36	1.27	2022	206.1	1.7	35	3.57
	South	5512	148.0	0.4	22	0.46	2145	185.9	0.4	8	0.69
	West	24,153	134.9	0.8	192	1.01	2135	172.9	1.1	24	1.94
1978–1982		13,885	119.3	0.2	22	0.18	3167	153.6	0.3	10	0.49
1983–1987		20,838	126.9	0.2	52	0.30	3510	165.8	0.6	20	0.95
1988–1992		21,812	133.8	0.4	94	0.53	2508	176.1	1.3	33	2.32
1993–1997		20,277	140.1	0.6	131	0.81	2609	197.0	1.2	32	2.42
AAPC (1978–1997)		1.1061		4.2478			1.9694		2.087		
P		<0.0001		<0.0001			<0.0001		0.352		

Multiple primaries are second, or higher order tumours occurring in a single individual. They are underrepresented in ACCIS for children of the British Isles (see text). ASR, age-standardised rate (world standard); AAPC, average annual percent change in incidence rate, derived from a Poisson regression model with year as explanatory variable, adjusted for sex, region and, for children only, age group.

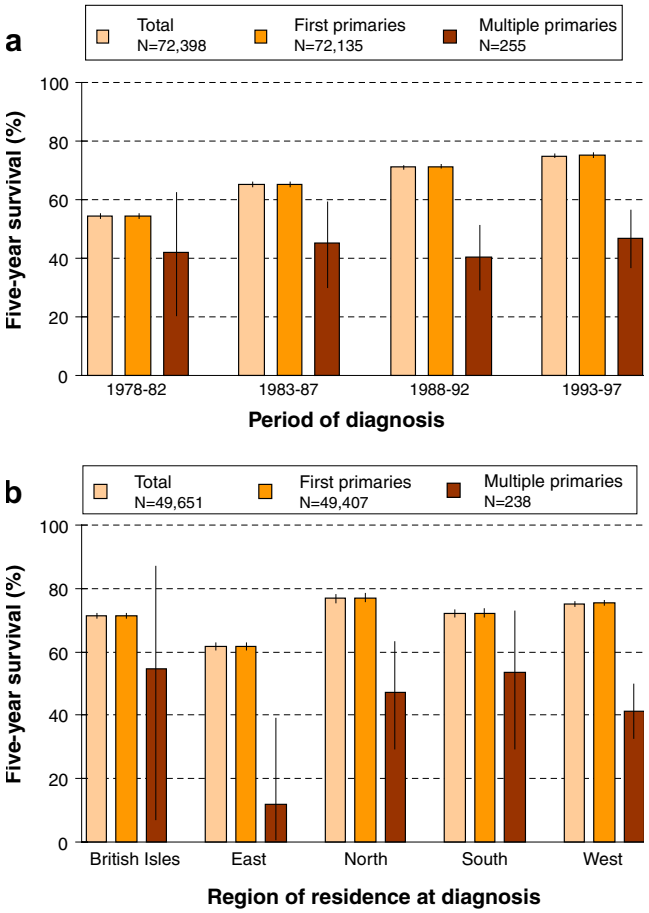

Fig. 5 – Five-year survival of children (age 0–14 years) in Europe according to tumour multiplicity. (a) Europe, dataset 1978–1997; (b) Europe, dataset 1988–1997. Multiple primaries are second, or subsequent tumours occurring in a single individual. They are underrepresented in ACCIS for children of British Isles (see text). N, number of cases included in analyses. 95% confidence intervals are shown as line sections. Source: ACCIS.

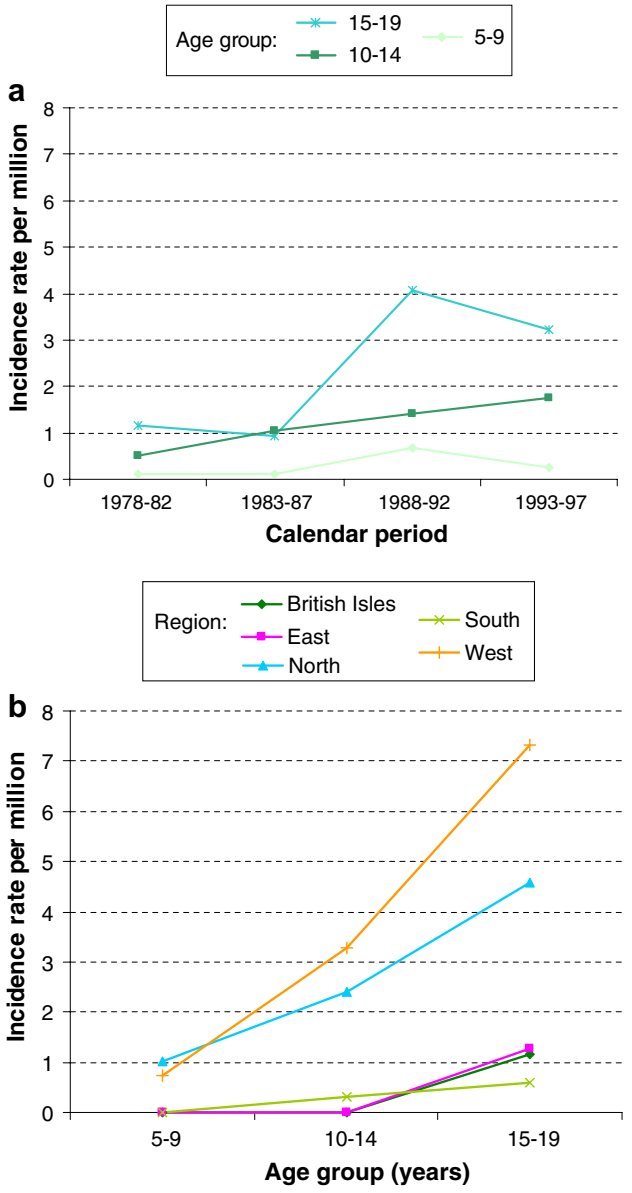

Fig. 6 – Age-specific incidence rates of carcinoid of appendix (M8240, C181) in children and adolescents in Europe. (a) Dataset 1978–1997 (number of cases = 215), (b) dataset 1988–1997 (number of cases = 171). The total Europe includes data contributed by the former GDR for the period 1978–1987, which are not included in any of the shown European regions. Source: ACCIS.

differed greatly by region, and in the North all the contributing cancer registries were general. Incidence rates recorded by the two types of registries within the age-range 0–14 years are compared in Fig. 8. While the age-specific incidence rates of all specified tumours are very similar, at least up to the age of 11 years, there is a constant excess of unspecified tumours recorded by the general cancer registries. The overall age-standardised rate (ASR) was higher in general than in the paediatric registries; but this was largely due to the higher rates of unspecified tumour types (Table 11). This pattern was also observed when the North (with no paediatric cancer registry) was excluded from the dataset of the general cancer registries (Table 11). Overall survival was slightly higher in paediatric than in general cancer registries. Survival of children with unspecified tumour types was markedly inferior to survival of children with specified tumour types and this was observed to a larger extent in the paediatric than in the general cancer registries. However, since the proportion of unspecified tumours in the paediatric datasets was about half of that in the general ones, the overall survival was higher in paediatric than in the general cancer registries (Table 11). With the North excluded, survival of patients with unspecified tumours was similar in general and paediatric cancer registries (Table 11): which implies that patients with 'unspecified' tumours have better prognosis in the North than in the other regions.

3.9. *Systematic differences between national and regional cancer registries*

Despite the large number of regional cancer registries contributing to the ACCIS database (44 of 62), cancer registries cover-

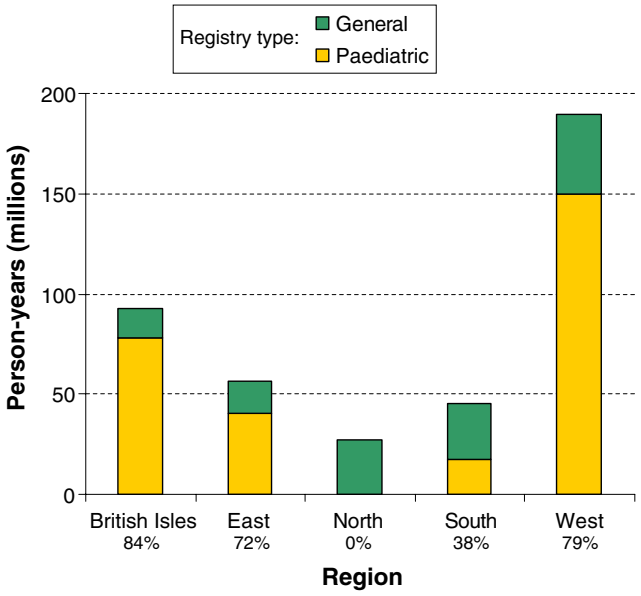

Fig. 7 – Distribution of person-years at risk for the period 1988–1997 in the age-range 0–14 years by the five European regions, according to the type of reporting cancer registry. Percentages show coverage by the paediatric cancer registries in each region. Source: ACCIS.

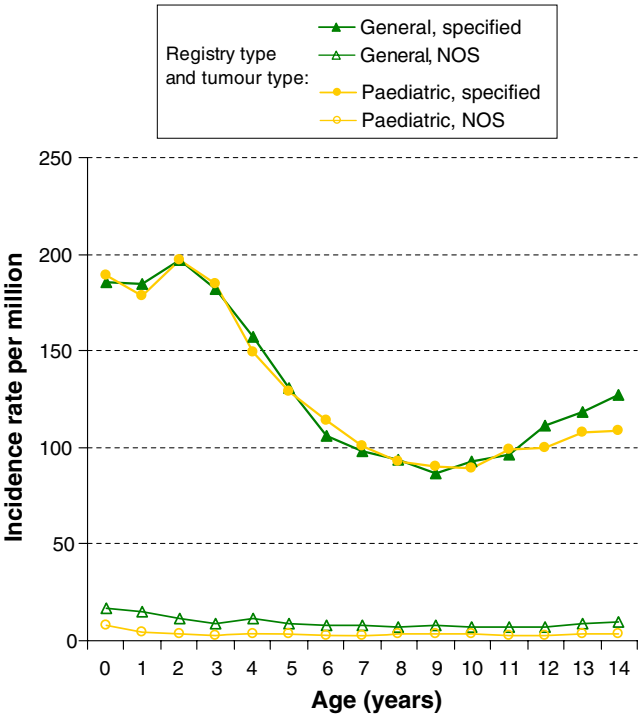

Fig. 8 – Age-specific incidence rates of childhood cancer in Europe 1988–1997, as registered by the paediatric and general cancer registries (number of cases = 55,227). The following tumour groups were included among unspecified (NOS): the ICCC categories Ie, IIe, IIIf, VIc, VIIc, VIIIe, IXe, XIIb, the morphology codes M-8000 to M-8004 in Xe and topography codes C76 to C80 in XIf. Source: ACCIS.

ing a whole country contributed a large proportion of person-years (54%). Contrary to the information shown in Table 2, all regional registries covering jointly the whole country were considered as being national in this comparison. All regional cancer registries are thus found in only two of the five regions, South and West (Fig. 9). As shown in Table 12, the incidence rates reported by the regional cancer registries were significantly higher than those reported by the national cancer registries, irrespective of the tumours specificity (the difference was larger for unspecified tumours). The difference persisted virtually unchanged in all ages, with additional excess in infants (Fig. 10). This was due mainly to more numerous lymphomas (O/E = 29/15, OR = 2.4, 95% CI = (1.9, 7.1)) and neuroblastoma (O/E = 350/296, OR = 1.3, 95% CI = (1.2, 4.0)) among the specified tumour types. Part of this discrepancy in age 0 may be due to earlier diagnosis (or reporting) in the areas covered by regional registries, since the excess incidence is not observed at age 1 year (Fig. 10).

Survival of children with unspecified tumour types was similar whether they were followed-up by a national or regional cancer registry, while the pattern was more complicated for the specified tumours. Within Europe as a whole, slightly higher survival was observed in the regional cancer registries. However, this was lower than the survival observed in the national registries of the two combined regions, South and West (including Germany, Malta, Netherlands and Slovenia), by some three percentage points. Of note is the lower completeness of the follow-up in the dataset for the combined region (Table 12).

4. Discussion

Sixty-two population-based cancer registries contributed to the analyses. They differed by size, geographical location, administrative area, age-range and other criteria for registration, time period available, methods of registration and follow-up of the patients, data management systems, availability of data sources, data protection legislation, etc. These different settings contributed to the complexity of the ACCIS database, its exploitation and interpretation of results. We have chosen to include a maximum of cancer registries, to reach a maximum sample size and preserve the heterogeneity within each analysis. The possibility that some of the differences in incidence and survival represent artefacts, caused by the registration process, must therefore be considered.

Only the datasets judged to be of high quality and completeness were selected for the analyses, with a considerable loss of the person-years available within ACCIS. A high percentage of microscopically verified cases indicated high precision of diagnoses. Cases detected through death certificate only (DCO cases) were rare in the registries with access to information that allows registration of DCO cases. While lack of access to national mortality database may seriously alter incidence rates in patients of all ages due to missed DCO cases, it would cause much less of a problem in childhood populations, for several reasons. First, the probability of cancer remaining undiagnosed in a child is much lower than in an elderly person. Secondly, due to the rarity of childhood cancers, diagnostic and treatment centres for children with cancer are organised into networks and usually work with

Table 11 – Numbers of cases, data quality indicators, incidence rates and population-based survival as recorded by general and paediatric cancer registries in Europe for the period 1988–1997 (Source: ACCIS)

	All tumours			Specified tumours			Unspecified tumours		
	General	G (excl. North)	Paediatric	General	G (excl. North)	Paediatric	General	G (excl. North)	Paediatric
Incidence									
n	17,640	13,357	37,587	16,441	12,558	36,566	1,199	799	1,021
MV (%)	94	94	96	97	97	97	53	49	56
DCO (%)	0.3	0.3	0.3	0.2	0.2	0.2	2.2	3.4	3.3
Unknown (%)	0.4	0.3	1.4	0.2	0.2	1.0	3.2	2.4	14.9
ASR	144.9	140.4	136.5	135.0	132.0	132.8	9.8	8.4	3.7
95% CI(ASR)	(142.5, 147.2)	(137.4, 143.4)	(135.5, 137.4)	(132.8, 137.2)	(129.2, 134.8)	(131.8, 133.8)	(9.7, 10)	(8.2, 8.6)	(3.6, 3.7)
SRR	1.06	1.03		1.02	1.00		2.68	2.29	
95% CI(SRR)	(1.04, 1.08)	(1.01, 1.05)		(0.999, 1.04)	(0.97, 1.02)		(2.61, 2.75)	(2.22, 2.36)	
Survival									
n	15,003	10,785	36,833	13,980	10,146	35,939	1,023	639	894
Follow-up (%)	85	81	98	85	81	98	85	80	88
w1–5 (%)	31	31	26	31	31	26	28	24	15
w1–10 (%)	66	65	63	66	66	63	56	50	45
5+years (%)	57	56	65	57	56	64	54	56	73
Median (years)	5.6	5.5	5.9	5.6	5.5	5.9	5.3	5.4	6.2
5-year OS	71	69	72	72	70	73	60	53	53
95% CI (OS)	(71, 72)	(68, 70)	(72, 73)	(71, 73)	(69, 71)	(72, 73)	(57, 63)	(48, 57)	(50, 57)
χ^2	7.8	52.4		3.3	34.1		9.1	0.15	

Unspecified tumours: includes ICCC categories Ie, IIe, IIIf, VIc, VIIc, VIIIe, IXe, XIIb, the morphology codes M-8000 to M-8004 in Xe and topography codes C76 to C80 in XIf.

G (excl. North), general cancer registries outside Northern region; *n*, number of cases included in analyses; MV (%), percentage of cases with microscopic verification of diagnosis; DCO (%), percentage of cases registered from death certificate only; Unknown (%); percentage of cases with unknown basis of diagnosis; ASR, age standardised rate (World standard); SRR, standardised rate ratio comparing ASR in general with ASR in paediatric cancer registries; 95% CI, 95% confidence interval; Follow-up (%), percentage of cases included in survival analyses of the total registered; w1–5 (%), percentage of cases withdrawn from survival analysis during the first 5 years of follow-up; w1–10 (%), percentage of cases withdrawn from survival analysis during the first 10 years of follow-up; 5+ years (%), percentage of cases followed-up for at least 5 years in the registries with follow-up, among those who did not deceased by the closing date of the study; median (years), median follow-up time in years of the cases included in survival analyses, among those who did not deceased by the closing date of the study; 5-year OS, 5-year observed survival (cumulative actuarial survival probability at 5 years since diagnosis); χ^2, statistic of the log-rank test of equality of survival in general and paediatric cancer registries; *P*, associated *P*-value.

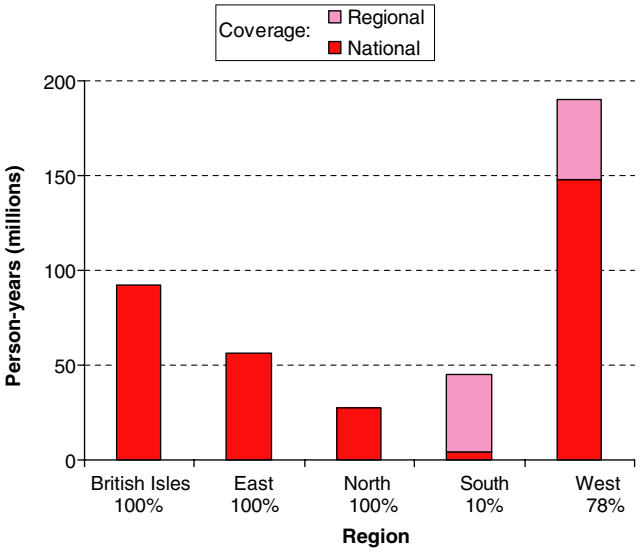

Fig. 9 – Distribution of person-years at risk contributed for the period 1988–1997 and the age-range 0–14 years by the five European regions, according to the country coverage of reporting cancer registry. Percentages show coverage by the national cancer registries in each region. Source: ACCIS.

cancer registries. Thirdly, favourable prognosis reduces the proportion of potential deaths in the childhood population. On the other hand, late deaths do occur in childhood cancer cases and access to the relevant information may increase incidence rates slightly and improve the completeness of the follow-up. Access to nominative death certificates, centralised nationally, would help to improve data quality and completeness and their evaluation. Alternatively, anonymous death records may be used to compare incidence, survival and mortality from cancer in the relevant childhood population and possibly to estimate the extent of potential loss of cases. In our database, the decreasing proportion of DCO cases during the 1980s may be explained by a reduced proportion of registries having access to mortality databases, by improved ascertainment of cases from primary sources, or possibly by more efficient retrospective finding of cases first notified via a death certificate (DCN)[1]. It was not possible to evaluate the proportion of DCN cases in the present data. The proportion of cases with unknown source of diagnosis

[1] These are the cases first notified from death certificate, which are then traced back to find further information of the case in medical records.

Table 12 – Numbers of cases, data quality indicators, incidence rates and population-based survival as recorded by national and regional cancer registries in Europe for the period 1988–1997, with the indicators of data quality (Source: ACCIS)

	All tumours			Specified tumours			Unspecified tumours		
	National	National (S&W)	Regional	National	National (S&W)	Regional	National	National (S&W)	Regional
Incidence									
n	43,690	19,852	11,537	41,981	19,381	11,026	1709	471	511
MV (%)	96	99	94	97	99	95	54	21	57
DCO (%)	0.3	0.0	0.3	0.2	0.0	0.2	3.2	0.0	2.2
Unknown (%)	1.1	0.0	0.8	0.8	0.0	0.6	9.5	0.0	5.3
ASR	137.3	135.4	145.9	132.0	132.2	139.7	5.4	3.2	6.3
95% CI(ASR)	(136.4, 138.2)	(134.5, 136.2)	(142.2, 149.7)	(131.1, 132.8)	(129.3, 135.1)	(136.1, 143.3)	(5.3, 5.4)	(3.2, 3.2)	(6.1, 6.5)
SRR	0.94	0.93		0.94	0.95		0.86	0.51	
95% CI(SRR)	(0.92, 0.97)	(0.9, 0.95)		(0.92, 0.97)	(0.91, 0.98)		(0.83, 0.89)	(0.49, 0.53)	
Survival									
n	40,852	17,422	10,984	39,374	17,052	10,545	1478	370	439
Follow-up (%)	94	88	95	94	88	96	70	22	13
5+yrs (%)	63	48	60	63	47	60	63	58	63
w1–5 (%)	27	41	29	27	41	29	26	24	26
w1–10 (%)	63	75	67	63	75	68	49	54	56
Median (years)	5.9	4.5	5.6	5.9	4.5	5.6	5.7	4.4	5.9
5-year OS	72	76	73	72	76	73	58	53	55
95% CI (OS)	(71, 72)	(75, 76)	(72, 74)	(72, 73)	(75, 77)	(72, 74)	(55, 60)	(47, 58)	(50, 60)
χ^2	4.1	25.71		6.09	19.84		1.01	0.02	
P	0.0429	<0.0001		0.0136	<0.0001		0.3145	0.8776	

Unspecified tumours, includes ICCC categories Ie, IIe, IIIf, VIc, VIIc, VIIIe, IXe, XIIb, the morphology codes M-8000 to M-8004 in Xe and topography codes C76 to C80 in XIf. National (S& W), national cancer registries of the South and West regions only; *n*, number of cases included in analyses; MV (%), percentage of cases with microscopic verification of diagnosis; DCO (%), percentage of cases registered from death certificate only; Unknown (%), percentage of cases with unknown basis of diagnosis; ASR, age standardised rate (World standard); SRR, standardised rate ratio comparing ASR in national with ASR in regional cancer registries; 95% CI, 95% confidence interval; Follow-up (%), percentage of cases included in survival analyses of the total registered; w1–5 (%), percentage of cases withdrawn from survival analysis during the first 5 years of follow-up; w1–10 (%), percentage of cases withdrawn from survival analysis during the first 10 years of follow-up; 5+ years (%), percentage of cases followed-up for at least 5 years in the registries with follow-up, among those who did not deceased by the closing date of the study; Median (years), median follow-up time in years of the cases included in survival analyses, among those who did not deceased by the closing date of the study; 5-year OS, 5-year observed survival (cumulative actuarial survival probability); χ^2, statistic of the log-rank test of equality of survivor curves in national versus regional cancer registries; *P*, associated *P*-value.

describes the level of difficulties in finding information about eligible cases, but more detailed enquiry in each registry would be necessary to understand why the source of information was not identified. In any case, the values of indicators derived from the variable 'basis of diagnosis' do not suggest that variations in quality and comparability of data between the regions and over time contributed significantly to observed differences in incidence or survival.

In the future, registration completeness should be evaluated more formally, for example by reporting number of sources per case,[19] if this information is available in the collaborating registries and by reporting DCN cases. Registration flow[30] might be available from those registries, which distinguish date of incidence and date of registration and can determine for their area the probability that cancer is mentioned on the death certificates of cancer patients who die. Other methods of evaluation of completeness, such as capture-recapture[31] may be applicable at registry level and evaluated qualitatively within ACCIS. Mortality to incidence ratio (M/I ratio),[19] the usual measure of registration completeness is difficult to apply to childhood cancer data, because the cause of death data may not be specific enough and mortality is postponed markedly to older ages.

Multiple primaries were incompletely represented within ACCIS, but their variable registration did not materially influence the comparison between the regions and periods. More emphasis will be devoted to this topic after the completion of records.

Differences in coding of tumours resulting in artificial differences for some diagnostic subgroups were of special concern in the North [Stiller, Marcos-Gragera, Ardanaz and colleagues; and Stiller, Desandes, Danon and colleagues, this issue]. These differences persist despite some 15 years of coordination and common recommendations for data definition, classification, coding and management, within Europe.[11] This study shows in particular the need for homogenous coding of carcinoid of the appendix. Adherence to the latest edition of ICD-O across the registries would facilitate international comparison, which in turn helps further data standardisation.

We have shown that the increase of incidence previously reported from the ACCIS study[7] is unlikely to be due to different registries contributing to different periods. Neither can the inclusion of non-malignant tumours and multiple primaries explain the observed increase, since we have seen that the incidence increased significantly irrespective of behaviour or multiplicity of tumour. The incidence trends are further

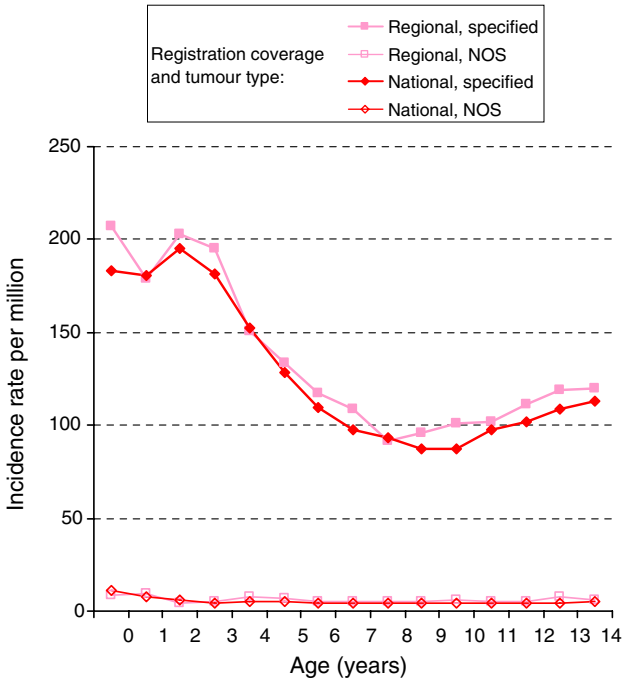

Fig. 10 – Age-specific incidence rates of childhood cancer in Europe 1988–1997, as registered by the national and regional cancer registries (number of cases = 55,227). The following tumour groups were included among unspecified (NOS): the ICCC categories Ie, IIe, IIIf, VIc, VIIc, VIIIe, IXe, XIIb, the morphology codes M-8000 to M-8004 in Xe and topography codes C76 to C80 in XIf. Source: ACCIS.

discussed elsewhere[7,32] [Kaatsch and colleagues; and Stiller, Desandes, Danon and colleagues, this issue].

Some of the differences in observed survival between the regions (and over time) might be explained by unequal completeness of follow-up in different data sets, since incomplete follow-up may bias survival estimates.[33] Therefore, proportion of cases lost to follow-up (or, more generally, withdrawals) should be kept to a minimum. Losses to follow-up are especially of concern in the registries without an access to official (national) mortality data. However, in our data the follow-up indicators did not differ systematically between national and regional cancer registries. Rather, the difference depended on geographical region, with access restricted more in South and West than in other regions. Paediatric cancer registries, which have to invest extra efforts to ensure follow-up of their cases after they quit the childhood age-range, had actually a slightly more complete follow-up than the general cancer registries (although this advantage is likely to diminish with lengthening of follow-up).

We have identified systematic differences between the data provided by general and paediatric cancer registries. The observed incidence patterns suggest a more careful recording of tumours in the paediatric registries, accompanied perhaps by a lack of access to some data generated outside the paediatric healthcare structures, especially for older children. Simultaneously, the higher rates of unspecified tumours observed in general cancer registries may reflect either more complete registration or less efficient checking procedures (due to large total number of cases) and higher probability of random errors, which may go unnoticed in childhood age-range. Overall, however, the observed differences do not preclude pooling the data, and are rather beneficial for overall comparison, at least until the potential problems could be identified.

Our attempt to compare quality of data provided by national as opposed to regional cancer registries was only partially fulfilled, since the two categories also differed in other aspects (geographic coverage, type of registry, etc.). In any case, the observed patterns, notably higher incidence rates in regional than national cancer registries document the need for further standardisation of cancer registration techniques.

Geographical grouping of countries was justified by a combination of factors, such as previous observations of similar incidence and survival patterns[3,5] and balanced numerical representation of each region in analyses. Although there are differences in incidence and survival between countries within each region [Stiller, Marcos-Gragera, Ardanaz and colleagues; Sankila and colleagues; Stiller, Desandes, Danon and colleagues; and Pritchard-Jones and colleagues, this issue], the purpose of this study was, by comparing large geographical areas, to identify consistent patterns that might not have been obvious when comparing smaller geographical areas. The inter-regional comparison is certainly influenced by the definition of the geographical regions, which is somewhat arbitrary and susceptible to future modification, depending on data availability.

4.1. *The British Isles*

Two countries contributed data for the British Isles (UK and Ireland), but these provided a considerable proportion of person-years for the childhood age-range. The large specialised registry of England and Wales covered the childhood population for the entire study period (except the last 2 years), and so had a major influence on the results for the region as a whole. The incidence rates were at the lower end of the scale and would have been little higher (possibly up to 1 per million) had multiple primary tumours been included for England and Wales. The low incidence might be explained by efficient exclusion of non-eligible cases, e.g. non-malignant, non-childhood, unconfirmed, etc., considering the outstanding tradition of the UK's Childhood Cancer Research Group (CCRG), to which the cancer registry is affiliated.[35] Notification of cases is voluntary, so under-reporting cannot be excluded, although it is unlikely. The childhood cancer registry of England and Wales receives data from general registries, both regional and national, including the general registry of Scotland.[36] A link with the databases of clinical trials is also maintained.[36] This cancer registry was used as a gold standard in a study of completeness of childhood cancer registration and recorded 109% of the registrations made by the general cancer registries across the country during the period 1971–1984.[37] About 6% of the British population was represented by the ethnic minorities,[36] the majority being of south Asian or African origin, who typically have low incidence rates of childhood cancer.[38] However, it is unlikely that this small proportion of population would influence the overall rates markedly.

The high quality of follow-up data in the CCRG and Scotland[39] and the information available in ACCIS may be partly responsible for the average level of observed survival in the British Isles in children [Sankila and colleagues, this issue]. The complete follow-up in the British Isles may theoretically result in lower estimates of survival than in the other regions with a less complete follow-up, as shown in the above example in Table 6. However, for the earlier 5-year diagnostic periods, follow-up was fairly complete in all regions and the rank for the British Isles was the same [Magnani and colleagues, this issue]. This would suggest that the censored observations and the withdrawals in the other regions would mostly comprise patients with long-term survival, as seen recently for the German childhood cancer registry.[34]

The dataset used to describe the adolescent population of the British Isles was represented by Ireland, Northern Ireland and Scotland and excluded England and Wales, for which data on adolescents were not available. The incidence rates attained average levels [Stiller, Desandes, Danon and colleagues, this issue] and would have been slightly higher, should all the registries include non-malignant tumours. The follow-up of the adolescents incident in 1988–1997 in the British Isles was markedly lower than that for children, especially in the Irish registries. The level of bias due to incomplete follow-up is therefore comparable with other regions.

4.2. *The East*

The cancer registries grouped in the East region were all national, relying either upon compulsory notification (in the general registries of Estonia and Slovakia) or the largely active ascertainment of cases (in the paediatric cancer registries of Belarus and Hungary). Several other registries, operating in central and Eastern Europe were excluded from analyses because of lack of data comparability. The cancer registry of the former German Democratic Republic could have also been included in the East, had the data from the same registration area been available until the end of the study period. It will hopefully be possible in the future to study the impact of the socio-economic changes on cancer burden in the young population of this part of Germany, although dilution of such effects would be expected due to migration of the population between the two parts of Germany since the 1990s.

The East seemed to be the most perilous region, in terms of relatively high incidence rates [Stiller, Marcos-Gragera, Ardanaz and colleagues, this issue] and low survival [Sankila and colleagues, this issue]. The high incidence rates can be explained entirely by a rapid rise in the incidence of thyroid cancer in Belarus due to the Chernobyl accident [Steliarova-Foucher, Stiller, Pukkala and colleagues, this issue]. Exclusion of the thyroid cancer cases of Belarus from the East would result in an ASR of 132.4 (instead of 140.9), ranking the East second lowest, just above the British Isles. Incidence rate of childhood cancer in the East is low compared with the high incidence in adults, especially in males.[1] Under-registration is therefore unlikely, unless limited specifically to childhood ages.

Low survival in the East [Sankila and colleagues, this issue] is the likely consequence of specific socio-economic setting, as discussed in detail elsewhere [Pritchard-Jones and colleagues, this issue], since completeness of follow-up is similar to that of other regions. The recent political changes in this part of Europe will undoubtedly contribute to changes in the patterns of incidence[40] and survival, as can be judged from the differences in survival already seen between the countries grouped within this region [Pritchard-Jones and colleagues, this issue]. The first prerequisite for future comparative studies is the access to data. This seems to be threatened due to the new data protection constraints currently replacing the previous legislative vacuum in the countries grouped within the East.[41] Such restrictions will lead at best to underestimation of incidence rates, at worst to no data at all.

4.3. *The North*

The North was the most homogeneous region, with 100% national coverage by general cancer registries and coordinated registration practices.[42] As a result, the representation of the Northern region was almost unchanged in the various analyses (geographical, time trends, children, adolescents, survival, etc.). In addition, the cancer registries in Nordic countries have an access to other national databases (population registers), which is especially valuable for follow-up of cancer patients, using linkage via the unique personal identification number.

The Northern region was also outstanding in having the highest incidence rates [Stiller, Marcos-Gragera, Ardanaz and colleagues; and Stiller, Desandes, Danon and colleagues, this issue] and the most favourable survival [Sankila and colleagues; and Stiller, Desandes, Danon and colleagues, this issue]. These patterns may be explained partly by differences in diagnostic and registration routines, documented by the highest percentage of non-malignant tumours and multiple primaries, as well as the large number of the carcinoids of appendix (up to 3 per million in adolescents). Misleading results may have been obtained for some tumour groups due to the use of outdated classification systems, during the period under study. For example, the low rate of neuroblastoma [Spix et al., this issue] and high rate of soft tissue sarcomas [Pastore, Peris-Bonet, Carli and colleagues, this issue] are difficult to explain otherwise than by classification mismatch [Stiller, Marcos-Gragera, Ardanaz and colleagues, this issue]. Finally, the high proportion of unspecified tumours can result from high level of automation and possibly a lack of validation of individual records for children. The relatively high survival of patients with unspecified tumours in the North may suggest that this group may include some tumour types that would be classified among specified in other regions.

Case mix of the total incidence data may partly explain the high survival, especially if a larger proportion of tumours with a favourable prognosis were included in the analyses for the North than for the other regions. The Nordic cancer registration system based on fine cross-linkage of various registries may be especially prone to include all non-fatal tumours, which are not notified (or not subject to notification) in other regions. This system also ensures high completeness of follow-up. Coordinated management of childhood cancer patients through the Nordic Society of Paediatric Haematology and Oncology (NOPHO), as well as the high socio-economic level of the Scandinavian countries certainly also contribute to the superior outcome in the North [Sankila and colleagues, this issue].

4.4. *The South*

The South was the most heterogeneous of all regions, including national, regional, general and paediatric cancer registries in the Mediterranean area (Italy, Malta, Slovenia, Spain and, for incidence only, Turkey). Relatively high incidence rates (second rank after North) were observed [Stiller, Marcos-Gragera, Ardanaz and colleagues; and Stiller, Desandes, Danon and colleagues, this issue], despite the lowest proportion of non-malignant tumours. This is partly due to the high incidence of haematopoietic neoplasms, reported from Spain in the past and in this volume[2,3] [Coebergh, Reedijk, de Vries and colleagues; Clavel and colleagues; and Izarzugaza and colleagues, this issue], consistently with findings in Hispanic populations elsewhere in the world.[2,3,43] The South also has the largest proportion of person-years coming from regional cancer registries (which tend to record higher incidence rates than national ones). Rather high incidence rates were accompanied by average levels of survival [Sankila and colleagues; and Stiller, Desandes, Danon and colleagues, this issue]. The excess incident cases therefore did not have a better prognosis. Procedures for excluding cases occurring among non-residents should be examined in these registries, since the regional hospitals may attract non-residents with cancers that are difficult to treat.

4.5. *The West*

For children, the West region was dominated by the patterns of German Childhood Cancer Registry, which provided 80% of the data for trends analysis and 70% of that used for geographical comparison. It overshadowed the contributions from France, Netherlands and Switzerland. The incidence data for this region are therefore affected by underreporting of brain tumours in this registry.[44] Observed survival data might be influenced by less complete follow-up (92% of cases included in survival analyses compared with about 98% in other regions) and this may contribute to the West (together with the North) having relatively high survival. However, in a recent German study with the closing date of December 2004[34] it became evident that the follow-up considered in this study was more complete for deceased patients than for survivors, which largely invalidates the assumption of overestimation of survival in the West due to incomplete follow-up. A specific issue of the West is also the temporary implementation of systematic screening programme for neuroblastoma in some areas and years covered by this study, which might have contributed to the increased level of incidence rate of this tumour, although its effect is relatively moderate [Spix and colleagues, this issue].

Data on adolescents in the West were provided by the registries of France, Netherland and Switzerland. This dataset was marked by a low proportion of registries recording non-malignant tumours and high proportion of carcinoid of appendix (ASR of almost 8 per million).

The West was least well represented in the early years of the study period (especially in children), which might have introduced random fluctuations to the yearly rates and affect time trends. These problems are compounded by the varying constitution of the datasets for different analyses, notably due to the contributions of German and Dutch registries. However, these irregularities did not seem to much affect the overall European time trends. A better equilibrium of the West region (as defined for the purposes of this study) will be achieved in the future, when the contribution of the Dutch National Cancer registry has increased with the passing of time[45] and the two French national paediatric registries[46,47] have joined the study. Newer cancer registries from other countries in this region may also be able to contribute.

5. Conclusion

Despite common recommendations and standardisation of data, the subsets of the ACCIS database are not strictly comparable. However, we have identified a number of artefacts and quantified their possible impact on the comparisons. Geographical differences between the regions are relatively small and removal of the detected artefacts would reduce them to some extent. Further standardisation of data collection and processing is therefore necessary, especially in children and adolescents. Improvements have already been recorded in some registries, for example in the German Childhood Cancer Registry,[34] cancer registry of Doubs, France [A. Danzon, personal communication] and some Italian cancer registries [C. Magnani, personal communication], partly as a result of this international collaboration within ACCIS. The construction of the ACCIS database, data standardisation, evaluation, analyses and interpretation was a long process, and new data are now available within the collaborating registries, since the current version of the database was 'closed' at the end of 2002. Extension of the database and its further exploration is imminent and will help to answer many of the questions generated in this series of articles.

Conflict of interest statement

None declared.

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Appendix. International Classification of Childhood Cancer (ICCC)[14] (Reprinted with the permission from the International Journal of Cancer)

Diagnostic group	ICD-O-2 codes	
	Morphology	Topography
I LEUKAEMIA		
(a) Lymphoid leukaemia	9820–9827, 9850	
(b) Acute non-lymphocytic leukaemia	9840, 9841, 9861, 9864, 9866, 9867, 9891, 9894, 9910	
(c) Chronic myeloid leukaemia	9863, 9868	
(d) Other specified leukaemias	9830, 9842, 9860, 9862, 9870–9890, 9892, 9893, 9900, 9930–9941	
(e) Unspecified leukaemias	9800–9804	
II LYMPHOMAS AND RETICULOENDOTHELIAL NEOPLASMS		
(a) Hodgkin's disease	9650–9667	
(b) Non-Hodgkin lymphoma	9591–9595, 9670–9686, 9690–9714, 9723	
(c) Burkitt's lymphoma	9687	
(d) Miscellaneous lymphoreticular neoplasms	9720, 9731–9764	
(e) Unspecified lymphomas	9590	
III CNS AND MISCELLANEOUS INTRACRANIAL AND INTRASPINAL NEOPLASMS		
(a) Ependymoma[b]	9383, 9390–9394	
(b) Astrocytoma	9380	C72.3
	9381, 9400–9441	
(c) Primitive neuroectodermal tumours	9470–9473	
(d) Other gliomas	9380	C70.0–C72.0, C72.4–C72.9
	9382[a], 9384[a]	
	9442–9460, 9481	
(e) Other specified intracranial and intraspinal neoplasms[b]	8270–8281, 8300, 9350–9362, 9480, 9505, 9530–9539	
(f) Unspecified intracranial and intraspinal neoplasms[b]	8000–8004	C70.0–C72.9, C75.1–C75.3

(continued on next page)

Appendix – *continued*

Diagnostic group	ICD-O-2 codes	
	Morphology	Topography
IV SYMPATHETIC NERVOUS SYSTEM TUMOURS		
(a) Neuroblastoma and ganglioneuroblastoma	9490, 9500	
(b) Other sympathetic nervous system tumours	8680, 8693–8710, 9501–9504, 9520–9523	
V RETINOBLASTOMA		
	9510–9512	
VI RENAL TUMOURS		
(a) Wilms' tumour, rhabdoid and clear cell sarcoma	8960, 8964	
	8963	C64.9, C80.9
(b) Renal carcinoma	8010–8041, 8050–8075, 8082, 8120–8122, 8130–8141, 8143, 8155, 8190–8201, 8210, 8211, 8221–8231, 8240, 8241, 8244–8246, 8260–8263, 8290, 8310, 8320, 8323, 8401, 8430, 8440, 8480–8490, 8504, 8510, 8550, 8560–8573	C64.9
	8312	
(c) Unspecified malignant renal tumours	8000–8004	C64.9
VII HEPATIC TUMOURS		
(a) Hepatoblastoma	8970	
(b) Hepatic carcinoma	8010–8041, 8050–8075, 8082, 8120–8122, 8140, 8141, 8143, 8155, 8190–8201, 8210, 8211, 8230, 8231, 8240, 8241, 8244–8246, 8260–8263, 8310, 8320, 8323, 8401, 8430, 8440, 8480–8490, 8504, 8510, 8550, 8560–8573	C22.0, C22.1
	8160–8180	
(c) Unspecified malignant hepatic tumours	8000–8004	C22.0, C22.1
VIII MALIGNANT BONE TUMOURS		
(a) Osteosarcoma	9180–9200	
(b) Chondrosarcoma	9220–9230	
	9231, 9240	C40.0–C41.9
(c) Ewing's sarcoma	9260	C40.0–C41.9, C80.9
	9363, 9364	C40.0–C41.9
(d) Other specified malignant bone tumours	8812, 9250, 9261–9330, 9370	
(e) Unspecified malignant bone tumours	8000–8004, 8800, 8801, 8803, 8804	C40.0–C41.9
IX SOFT-TISSUE SARCOMAS		
(a) Rhabdomyosarcoma and embryonal sarcoma	8900–8920, 8991	
(b) Fibrosarcoma, neurofibrosarcoma and other fibromatous neoplasms	8810, 8811, 8813–8833, 9540–9561	
(c) Kaposi's sarcoma	9140	
(d) Other specified soft tissue sarcomas	8840–8896, 8982, 8990, 9040–9044, 9120–9134, 9150–9170, 9251, 9581	
	8963	C00.0–C63.9, C65.9–C76.8
	9231, 9240, 9363, 9364	C00.0–C39.9, C47.0–C80.9
	9260	C00.0–C39.9, C47.0–C76.8
(e) Unspecified soft tissue sarcomas	8800–8804	C00.0–C39.9, C44.0–C80.9

Appendix – *continued*

Diagnostic group	ICD-O-2 codes	
	Morphology	Topography
X GERM-CELL, TROPHOBLASTIC AND OTHER GONADAL NEOPLASMS		
(a) Intracranial and intraspinal germ cell tumours[b]	9060–9102	C70.0–C72.9, C75.1–C75.3
(b) Other and unspecified non-gonadal germ cell tumours	9060–9102	C00.0–C55.9, C57.0–C61.9, C63.0–C69.9, C73.9–C75.0, C75.4–C80.9
(c) Gonadal germ cell tumours	9060–9102	C56.9, C62.0–C62.9
(d) Gonadal carcinomas	8010–8041, 8050–8075, 8082, 8120–8122, 8130–8141, 8143, 8155, 8190–8201, 8210, 8211, 8221–8241, 8244–8246, 8260–8263, 8290, 8310, 8320, 8323, 8430, 8440, 8480–8490, 8504, 8510, 8550, 8560–8573, 8380, 8381, 8441–8473	C56.9, C62.0–C62.9
(e) Other and unspecified malignant gonadal tumours	8590–8670, 9000 8000–8004	C56.9, C62.0–C62.9
XI CARCINOMAS AND OTHER MALIGNANT EPITHELIAL NEOPLASMS		
(a) Adrenocortical carcinoma	8370–8375	
(b) Thyroid carcinoma	8010–8041, 8050–8075, 8082, 8120–8122, 8130–8141, 8155, 8190, 8200, 8201, 8211, 8230, 8231, 8244–8246, 8260–8263, 8290, 8310, 8320, 8323, 8430, 8440, 8480, 8481, 8500–8573 8330–8350	C73.9
(c) Nasopharyngeal carcinoma	8010–8041, 8050–8075, 8082, 8120–8122, 8130–8141, 8155, 8190, 8200, 8201, 8211, 8230, 8231, 8244–8246, 8260–8263, 8290, 8310, 8320, 8323, 8430, 8440, 8480, 8481, 8504, 8510, 8550, 8560–8573	C11.0–C11.9
(d) Malignant melanoma	8720–8780	
(e) Skin carcinoma	8010–8041, 8050–8075, 8082, 8090–8110, 8140, 8143, 8147, 8190, 8200, 8240, 8246, 8247, 8260, 8310, 8320, 8323, 8390–8420, 8430, 8480, 8542, 8560, 8570–8573, 8940	C44.0–C44.9
(f) Other and unspecified carcinomas	8010–8082, 8120–8155, 8190–8263, 8290, 8310, 8314–8323, 8430–8440, 8480–8580, 8940, 8941	C00.0–C10.9, C12.9–C21.8, C23.9–C39.9, C48.0–C48.8, C50.0–C55.9, C57.0–C61.9, C63.0–C63.9, C65.9–C72.9, C75.0–C80.9
XII OTHER AND UNSPECIFIED MALIGNANT NEOPLASMS		
(a) Other specified malignant tumours	8930, 8933, 8950, 8951, 8971–8981, 9020, 9050–9053, 9110, 9580	
(b) Other unspecified malignant tumours	8000–8004	C00.0–C21.8, C23.9–C39.9, C42.0–C55.9, C57.0–C61.9, C63.0–C63.9, C65.9–C69.9, C73.9–C75.0, C75.4–C80.9

a Behaviour code /1 is included.
b Behaviour codes /0 and /1 are included.

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