EUROPEAN JOURNAL OF CANCER 45 (2009) 992–1005

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Survival of European children and young adults with cancer diagnosed 1995–2002

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ARTICLE INFO

Article history:
Received 4 June 2008
Received in revised form 25 September 2008
Accepted 4 November 2008
Available online 21 February 2009

Keywords:
Children
Adolescents
Young adults
Cancer survival
Population-based cancer registries
Rare tumours
Europe

ABSTRACT

This study analyses survival in 40,392 children (age 0–14 years) and 30,187 adolescents/young adults (age 15–24 years) diagnosed with cancer between 1995 and 2002. The cases were from 83 European population-based cancer registries in 23 countries participating in EUROCARE-4. Five-year survival in countries and in regional groupings of countries was compared for all cancers combined and for major cancers. Survival for 15 rare cancers in children was also analysed.

Five-year survival for all cancers combined was 81% in children and 87% in adolescents/young adults. Between-country survival differences narrowed for both children and adolescents/young adults. Relative risk of death reduced significantly, by 8% in children and by 13% in adolescents/young adults, from 1995–1999 to 2000–2002. Survival improved significantly over time for acute lymphoid leukaemia and primitive neuroectodermal tumours in children and for non-Hodgkin lymphoma in adolescents/young adults.

Cancer survival in patients <25 years is poorly documented in Eastern European countries. Complete cancer registration should be a priority for these countries as an essential part of a policy for effective cancer control in Europe.

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0959-8049/$ - see front matter
doi:10.1016/j.ejca.2008.11.042

1. Introduction

About 15,000 children (age 0–14 years) and 20,000 adolescents/young adults (age 15–24 years) are diagnosed with cancer each year in Europe.[1] Although only 1% of all cancers are diagnosed in these age groups, they have a number of characteristics that increase their impact on society:

- The prevalence of adults diagnosed with cancer before age 25 is increasing due to improving survival, and to a lesser extent, increasing cancer incidence.[2]
- The risk of second cancers is high in adults surviving cancer diagnosed before age 25.
- Many cancer survivors diagnosed before age 25 experience sequelae in later life that require medical treatment.
- European populations differ markedly in cancer survival, implying inequality of access to treatment for diseases in young people which are typically highly curable.
- Survival in adolescents/young adults is worse than in children with biologically similar cancers, probably because intensive treatment protocols have been mainly developed for children.

Survival data for young Europeans (below age 25) diagnosed with cancer between 1978 and 1994 are available in various EUROCARE publications.[3,4] The ACCIS project[5] produced survival figures for European children and adolescents <20 up to diagnosis year 1997, and substantiated the disparities in survival across Europe brought to light by EUROCARE. The present EUROCARE-4 study analyses survival and survival time trends in young Europeans diagnosed with cancer between 1995 and 2002, and also examines trends in survival differences between different European populations.

2. Materials and methods

Survival was analysed for 40,392 European children (age 0–14 years) and 30,187 adolescents/young adults (age 15–24 years) diagnosed with cancer during the period 1995–2002 and followed-up at least until December 31, 2003. All cases with a malignant neoplasm, as defined by ICD for Oncology (ICD-O-3)[6] behaviour code 3 or higher, were included. Only first tumours were analysed; 771 cases were excluded from the analysis as they were second or later primary tumours.

The cases were contributed by 83 population-based cancer registries in 23 countries participating in EUROCARE-4. The countries were Denmark, Finland, Iceland, Norway and Sweden (grouped as Northern Europe); the Czech Republic and Poland (Eastern Europe); Austria, Belgium, France, Germany, the Netherlands and Switzerland (Central Europe); Italy, Malta, Portugal, Slovenia and Spain (Southern Europe); and England, Ireland, Northern Ireland, Scotland and Wales (United Kingdom (UK) and Ireland).

The registries of Denmark, Finland, Iceland, Norway, Sweden, Austria, Germany (0–14 only), Malta, Slovenia, Ireland, Northern Ireland, Scotland, Wales and England cover the national entire populations. The other countries are represented by one or more local or regional registries. The general cancer registries of Saarland (Germany), Macerata, Biella and Torino (Italy), and England and Wales (UK) only contributed cases aged 15–24 years, since data from children were provided by childhood cancer registries covering the same territories. In fact eight childhood cancer registries contributed data: England and Wales; Germany; Piedmont and Marche in Italy; the Spanish Childhood Cancer Registry (Barcelona only) and Comunitat Valenciana (Castellón and Valencia); and Bretagne and Lorraine in France. Two specialised adult French cancer registries (Côte d'Or Haematologique and Marne-Ardennes (thyroid)) also contributed data.

Childhood cancers were classified into 12 main categories and their subgroups in the International Classification of Childhood Cancers (ICCCs) third edition.[7] However, in line with the EUROCARE protocol, skin cancers (ICCC XIe) were excluded, and only malignant cancers within the categories of intracranial and intraspinal neoplasms (III and Xa) were included. As in the previous EUROCARE studies, this meant that cases of non-malignant neoplasms such as craniopharyngioma, meningioma, ganglioglioma and teratoma were excluded. For the first time, however, pilocytic astrocytoma – the most frequent CNS cancer in children and young people – was also excluded because it has borderline behaviour code in ICD-O-3, whereas in the previous editions of ICD-O this cancer was considered malignant. Since pilocytic astrocytoma, which has a very good prognosis, was included in the earlier studies and the proportions of astrocytoma cases of unspecified subtype, which still have a malignant behaviour code, were expected to vary between European regions and registries, survival for an expanded category of astrocytoma including the 2103 children and 333 adolescents and young adults with pilocytic tumours was also analysed, so as to retain comparability between regions and earlier time periods (Tables 3 and 5 only).

In the data from the Finnish registry, astrocytomas and gliomas not otherwise specified (NOS) shared the same morphology code, and thus could not be distinguished. Therefore, Finland was excluded from the analysis of astrocytoma survival.

The registries of Denmark and Thames did not furnish ICD-O morphology codes but only ICD10 data,[8] thus for these registries it was not possible to apply the ICCC completely, and only cancers (all cancers combined, leukaemias, lymphomas and all CNS cancer combined) for which ICCC and ICD10 codes were similar were included.

Cancers in adolescents/young adults were classified using both the ICCC and the ICD-O-3 classifications, because the spectrum of cancers typical of these age groups differs from that in children. The following cancers, characteristic of adolescents and young adults, were classified according to ICD-O: skin melanoma (ICD-O topography = C44, ICD-O morphology = 872-879), cervix uteri (ICD-O = C53), thyroid (ICD-O = C73.9), colon (ICD-O = C18), lung (ICD-O = C34), bone (ICD-O = C40–41) and breast (ICD-O = C50) cancers.

Table 1 presents the cases by country, cancer registry, age and year of diagnosis, with main data quality indicators. The specialised registries of Calvados (digestive), Côte d'Or (digestive), Castellón (breast), Zurich (colon and rectum), Albacete (breast) and Palermo (breast) are not included in Table 1 as together they contributed only 10 cases. Sixty-six percent of cases were diagnosed from 1995 to 1999; 52 registries also contributed cases diagnosed from 2000 to 2002.

Table 1 – Cancer cases in young Europeans (0–24 years) diagnosed in 1995–2002, by registry, with data quality indicators.

Registry	1995–2002 Number of cases	1995–1999 Number of cases	2000–2002 Number of cases	1995–2002								1995–1998
				0–4 Years (%)	5–9 Years (%)	10–14 Years (%)	15–19 Years (%)	20–24 Years (%)	DCO/ autopsy (%)	MV (%)	Unspecified cases[a] (%)	Alive with follow-up <5 years (%)
Northern Europe												
Denmark	1407	1407		18.6	10.9	11.3	19.0	40.2	0.2	95.2	41.0	0.9
Finland	2447	1532	915	22.5	10.8	12.9	23.3	30.4	0.3	99.2	2.6	0.1
Iceland	178	119	59	16.3	11.2	9.6	25.3	37.6	0.0	97.2	4.5	0.0
Norway	2087	1345	742	21.2	11.2	11.7	20.4	35.4	0.1	96.6	3.3	0.5
Sweden	3612	2287	1325	22.9	12.5	13.3	19.5	31.9	0.2	98.4	5.0	0.4
Eastern Europe												
Czech Republic												
West Bohemia	370	244	126	11.9	9.2	10.0	27.8	41.1	4.1	95.9	6.2	10.5
Poland												
Cracow	308	194	114	14.6	9.1	11.7	25.3	39.3	0.3	93.2	14.0	9.4
Kielce	543	325	218	14.9	12.0	14.0	26.7	32.4	0.0	89.3	14.5	0.0
Warsaw	580	385	195	13.8	9.8	13.8	25.9	36.7	0.7	89.1	10.9	0.7
Central Europe												
Austria	3211	2007	1204	19.7	11.8	13.8	22.3	32.3	1.8	95.5	5.6	10.5
Belgium												
Flanders	1639	947	692	20.2	11.0	13.4	21.5	34.0	0.1	96.9	5.2	0.0
France												
Bas Rhin	178	178		18.0	8.4	12.4	24.2	37.1	0.0	97.2	5.1	3.4
Bretagne	551	328	223	43.7	26.1	30.1			0.0	88.9	1.5	0.4
Calvados	87	87		10.3	6.9	19.5	31.0	32.2	0.0	98.9	1.1	2.3
Côte d'Or (Hematologique)	95	60	35	27.4	16.8	8.4	25.3	22.1	0.0	100.0	0.0	8.4
Doubs	91	91		18.7	7.7	18.7	20.9	34.1	0.0	97.8	0.0	3.3
Haut Rhin	131	131		16.8	14.5	13.7	19.8	35.1	0.0	97.7	1.5	13.7
Herault	180	180		25.0	10.6	8.9	20.0	35.6	0.0	n.a.	0.6	6.1
Isère	201	201		23.4	15.4	15.4	14.4	31.3	0.0	96.5	1.5	4.0
Lorraine	419	259	160	43.0	24.3	32.7			0.0	94.7	2.6	0.2
Manche	89	89		14.6	15.7	16.9	19.1	33.7	0.0	95.5	2.2	2.2
Marne and Ardennes	11	11					36.4	63.6	0.0	100.0	0.0	0.0
Somme	90	90		14.4	14.4	13.3	22.2	35.6	0.0	95.6	5.6	12.2
Tarn	51	51		19.6	11.8	13.7	17.6	37.3	0.0	98.0	2.0	2.0

Germany												
Germany (child)	13,098	8235	4863	46.3	27.0	26.8			0.0	100.0	0.9	7.4
Saarland	238	142	96				43.7	56.3	0.4	99.6	2.5	9.2
The Netherlands												
Amsterdam	1185	743	442	22.6	12.4	11.7	20.8	32.4	0.0	97.6	1.6	0.6
Eindhoven	374	262	112	18.2	9.1	16.8	16.6	39.3	0.0	98.7	1.6	0.0
North Netherlands	822	584	238	22.0	10.2	10.9	22.5	34.3	0.9	99.3	2.3	0.0
Switzerland												
Basel	149	117	32	17.4	8.1	9.4	28.2	36.9	0.0	98.7	4.7	8.7
Geneva	177	115	62	14.1	7.3	16.4	20.9	41.2	0.0	97.7	1.1	3.4
Grisons	7	7					14.3	85.7	0.0	100.0	0.0	14.3
St Gallen	246	143	103	12.6	12.2	11.8	21.5	41.9	0.4	99.6	1.2	1.6
Ticino	124	64	60	20.2	9.7	15.3	19.4	35.5	0.8	97.6	4.8	1.6
Valais	59	59		18.6	16.9	10.2	20.3	33.9	0.0	100.0	3.4	3.4
Southern Europe												
Italy												
Alto Adige	195	119	76	23.1	11.8	13.3	14.9	36.9	0.0	97.9	2.6	0.0
Biella	57	37	20				38.6	61.4	0.0	96.5	1.8	0.0
Ferrara	127	89	38	18.1	11.0	10.2	21.3	39.4	0.0	85.8	15.7	0.8
Firenze	504	322	182	18.3	10.7	10.3	21.0	39.7	0.2	75.6	10.3	1.6
Friuli Venezia Giulia	485	306	179	19.0	9.9	9.9	22.5	38.8	0.2	93.6	10.1	1.6
Genova	249	208	41	16.9	12.9	9.2	20.9	40.2	0.0	89.6	6.4	0.0
Macerata	45	45					37.8	62.2	0.0	97.8	2.2	0.0
Marche	254	158	96	52.0	19.3	28.7			0.8	96.9	2.0	0.0
Modena	240	140	100	19.6	10.8	15.0	19.2	35.4	0.8	95.4	4.2	0.4
Napoli	259	193	66	20.5	12.4	12.4	22.8	32.0	1.2	84.9	13.9	6.2
Parma	163	101	62	14.1	11.7	17.8	22.7	33.7	0.0	93.9	11.7	0.0
Piedmont	595	420	175	48.7	23.7	27.6			0.0	97.1	1.8	0.0
Ragusa	141	95	46	17.7	12.8	13.5	20.6	35.5	0.7	95.7	8.5	2.1
Reggio Emilia	183	121	62	18.0	9.3	9.3	21.3	42.1	0.0	89.6	10.9	0.0
Romagna	369	202	167	17.3	11.1	11.1	17.9	42.5	0.5	86.4	10.8	0.0
Salerno	565	413	152	11.2	13.8	18.9	23.7	32.4	0.2	85.3	36.1	9.6
Sassari	217	140	77	10.6	10.1	12.4	29.0	37.8	4.1	90.3	9.2	0.0
Torino	166	119	47				33.1	66.9	0.0	95.8	3.0	0.6
Trento	161	122	39	22.4	9.3	10.6	23.6	34.2	1.2	68.3	42.2	1.2
Umbria	400	251	149	18.3	12.3	13.8	23.8	32.0	0.0	85.8	14.5	0.0
Varese	226	226		16.4	13.7	14.2	15.9	39.8	0.4	91.2	9.7	15.5
Veneto	655	548	107	17.7	10.5	10.4	21.4	40.0	0.2	95.3	6.3	0.9
Malta	211	121	90	21.8	15.2	10.4	19.4	33.2	0.0	99.1	0.5	0.0
Portugal												
South Portugal	542	542		17.9	8.7	14.6	21.0	37.8	0.0	98.3	4.1	0.0
Slovenia	882	542	340	17.7	8.6	14.1	22.6	37.1	0.3	99.8	1.9	0.1

(*continued on next page*)

Table 1 – *continued*

Registry	1995–2002 Number of cases	1995–1999 Number of cases	2000–2002 Number of cases	1995–2002								1995–1998
				0–4 Years (%)	5–9 Years (%)	10–14 Years (%)	15–19 Years (%)	20–24 Years (%)	DCO/ autopsy (%)	MV (%)	Unspecified cases[a] (%)	Alive with follow-up <5 years (%)
Spain												
Basque country	592	592		15.2	7.6	10.1	25.0	42.1	0.2	96.6	6.3	0.0
Comunitat Valenciana (Valencia and Castellón)	490	338	152	47.6	22.9	29.6			0.4	95.9	4.3	0.0
Girona	237	144	93	21.5	11.8	11.8	21.1	33.8	0.4	94.9	3.8	0.8
Granada	75	75		4.0	5.3	10.7	32.0	48.0	0.0	98.7	2.7	0.0
Murcia	304	304		15.5	11.8	9.9	26.3	36.5	0.0	94.7	2.6	3.0
Navarra	167	167		14.4	9.6	11.4	30.5	34.1	0.0	98.8	1.8	1.2
Tarragona	162	162		18.5	6.8	12.3	25.3	37.0	1.9	95.1	9.3	0.0
Spain RNTI-SEHOP (Barcelona only)	462	462		44.6	27.5	27.9			0.0	92.0	2.6	3.0
United Kingdom (UK) and Ireland												
Ireland	1975	1168	807	18.8	11.2	13.2	24.4	32.4	0.4	95.7	5.3	n.a.
England	3846	0	3846				37.4	62.6	0.0	98.6	3.8	n.a.
East Anglia	333	333					36.3	63.7	0.0	94.3	6.0	29.1
Mersey	307	307					39.1	60.9	0.7	90.9	2.3	n.a.
North Western	575	575					33.9	66.1	0.2	95.8	4.0	n.a.
Northern and Yorkshire	599	599					37.1	62.9	0.5	97.3	3.5	n.a.
Oxford	382	382					31.7	68.3	0.3	98.7	2.4	n.a.
South Western	948	948					35.3	64.7	0.1	83.5	8.4	n.a.
Thames	1667	1667					36.9	63.1	3.1	90.4	42.9	n.a.
Trent	561	561					37.4	62.6	1.8	93.2	3.4	n.a.
West Midlands	660	660					37.9	62.1	0.8	94.7	3.0	n.a.
England and Wales (child)	9842	6104	3738	46.7	26.6	26.7			0.1	92.4	1.9	0.3
Northern Ireland	804	526	278	21.0	12.2	11.3	20.1	35.3	0.2	91.0	9.0	n.a.
Scotland	2086	1288	798	20.4	10.8	12.8	19.3	36.8	0.2	97.3	3.4	n.a.
Wales	579	341	238				41.1	58.9	2.4	n.a.	6.4	n.a.
Total	70,579	46,302	24,277	26.3	15.0	15.9	16.2	26.6	0.4	95.5	3.8[b]	2.6

n.a. = Not applicable and MV = morphological verified cases.

a Unspecified diagnostic group (ICCC Ie, IIe, IIIf, VIf, VIIc, VIIIe, IXe and XIIb).

b Total excluding Denmark and Thames.

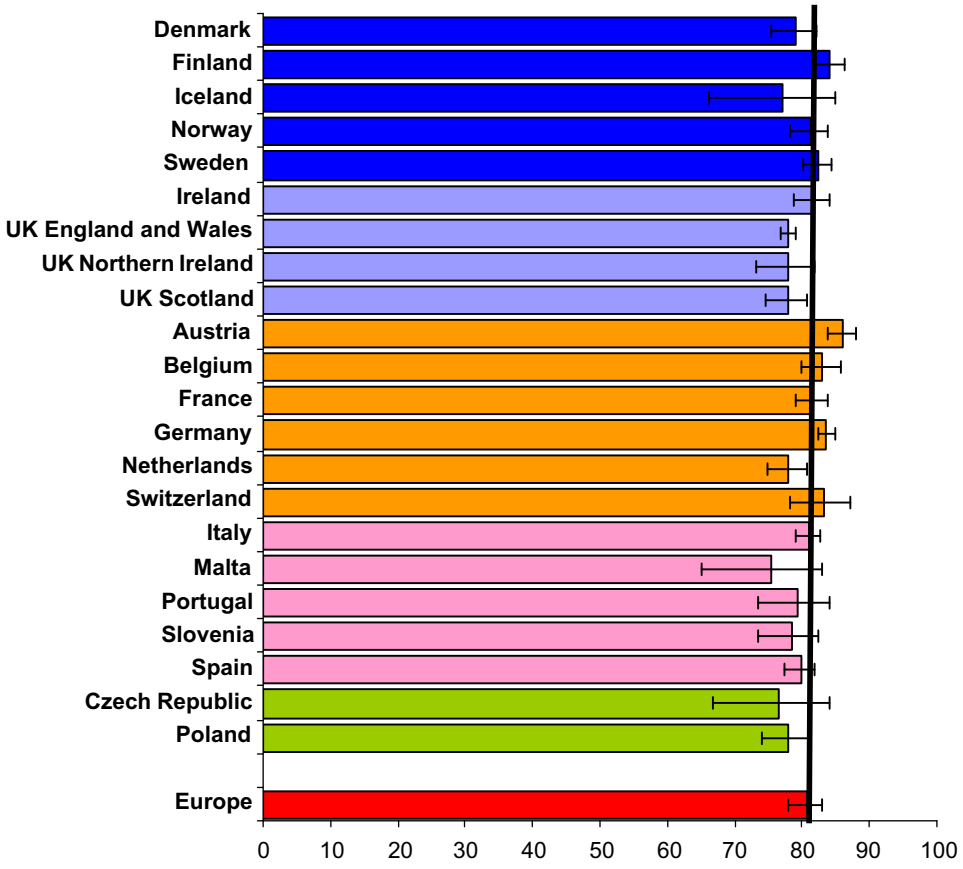

Fig. 1 – Five-year survival for all cancers combined diagnosed in 1995–2002, by country, in European children (0–14 years), both the sexes. The data are adjusted by age, sex, case mix and period of diagnosis using a Cox proportional hazards model.

Overall 26% of childhood cases were diagnosed below the age of 5 years; however, around 45% of the cases contributed by childhood cancer registries were under five. Overall 27% of cases were young adults, while 30–42% of the cases contributed by general cancer registries were young adults.

Only 0.4% of cases were known to registries only by death certificate or by autoptic diagnosis (these cases were excluded from the survival analyses). Overall, 95% of cases were microscopically verified. Trento (68%) had the lowest proportion of microscopically verified cases, while for five registries all cases were microscopically verified.

Three percent of live cases diagnosed in the period 1995–1998 had a follow-up of <5 years. Although for most registries <1% of cases had a follow-up <5 years, in seven registries the proportion exceeded 10%. The proportion of patients censored 'alive' with a follow-up <5 years was not available for registries which perform only passive follow-up (all UK general cancer registries except East Anglia).

Overall, 5.6% of cases had unspecified ICCC morphology. Since Denmark and Thames did not send morphology data, these registries were excluded from the analyses in which cases were classified into ICCC diagnostic groups. A total of 3.8% of cases had unspecified morphology after Denmark and Thames had been excluded.

Observed survival and relative survival were calculated with the SEER*Stat software (Release 6.3.6).[9] However, only observed survival is presented because it corresponds very closely to observed survival in young people, since deaths due to competing risks are rare. Observed survival was calculated by the actuarial method.[10] For cases diagnosed in 2000–2002, we used the period analysis method of Brenner and Gefeller[11] to obtain estimates of 5-year survival. More detailed information on period analysis is available elsewhere.[12]

Survival is presented: for all cancers combined by country in age groups 0–14 years and 15–24 years (Figs. 1 and 2, respectively); for 15 selected (common) ICCC diagnostic categories in children (0–14 years) for Europe as a whole and by regional grouping (Table 3); for 15 rare cancers in children for Europe as a whole (Table 4) and for malignancies characteristic of 15–24-year-olds for Europe as a whole and by regional grouping (Table 5). For the diagnosis period 1995–1999, to which all registries contributed cases, 5-year observed survival was calculated by regional grouping. For the diagnosis period 2000–2002 survival was estimated for Europe as a whole.

To ensure survival comparability, for each cancer, the survival of children (age 0–14 years) in each regional grouping was adjusted to the age distribution of all European children diagnosed in the period 2000–2002 with that cancer. For age standardisation, three age classes were generally used (0–4, 5–9 and 10–14 years). For neuroblastoma, the age classes were <1, 1–4 and 5–14 years. For two other cancers, data are presented for a single age class: <5 years for retinoblastoma; 10–14 years for osteosarcoma. Age adjustment was not applied to patients 15–24-year-old.

Since the nation-wide registries of the UK and Germany contributed the largest proportions of cases, survival in Europe as a whole was obtained by directly weighting the regional grouping survival estimates with factors proportional to the population in each regional grouping. This procedure assumes that the population covered by registration is representative of the country to which it belongs. The weightings employed were 5.64 for Northern Europe, 14.62 for the UK and Ireland, 42.69 for Central Europe, 11.49 for Eastern Europe and 25.56 for Southern Europe.

A Cox proportional hazard model[13] was used to compare survival for all cancers combined between countries, adjusting by sex, age class, period of diagnosis (1995–1999 versus 2000–2002) and case mix. In the model for children, three age classes were used (0–4, 5–9, and 10–14 years) and 10 diagnostic categories to adjust for case mix: (1) lymphoid

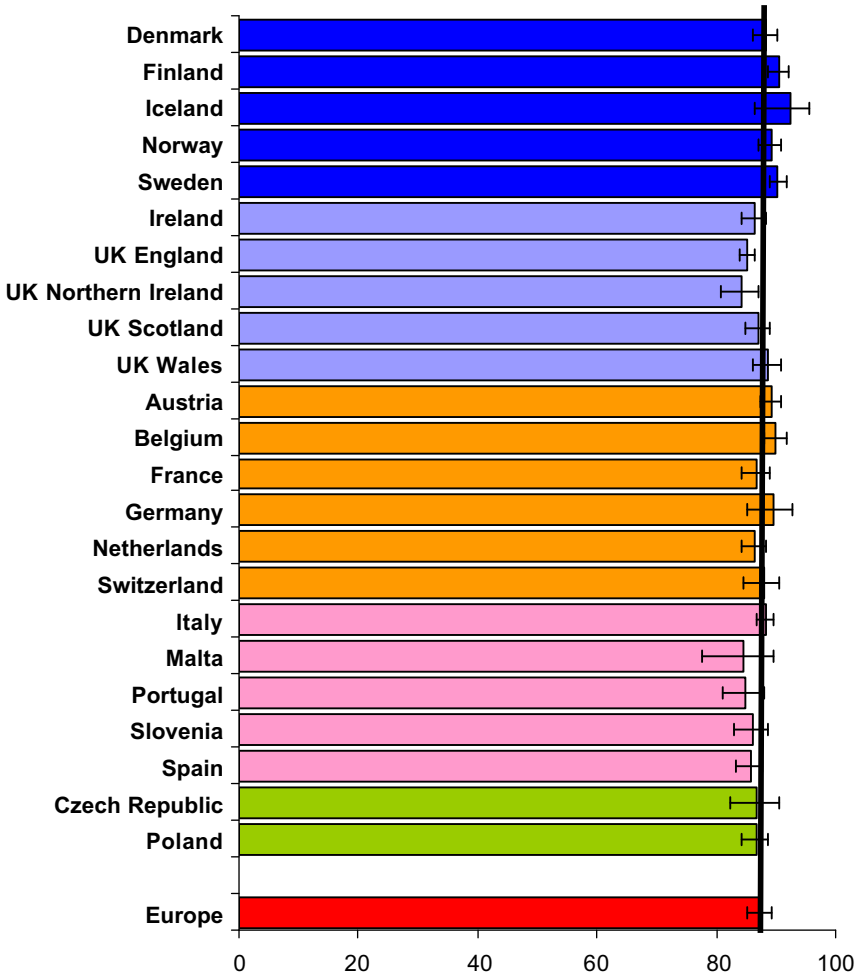

Fig. 2 – Five-year survival for all cancers combined, by country, in young Europeans (15–24 years) of both the sexes diagnosed in 1995–2002. The data are adjusted by age, sex, case mix and period of diagnosis using a Cox proportional hazards model.

Table 2 – Relative risks (RRs) of death for all malignant cancers adjusted by country, case mix, diagnosis period, sex and age.

	RR	95% Confidence interval (CI)
0–14 years		
2000–2002 versus 1995–1999	0.92	0.88–0.97
Male versus female	1.09	1.04–1.14
5–9 versus 0–4 years	0.95	0.90–1.00
10–14 versus 0–4 years	1.02	0.96–1.08
15–24 years		
2000–2002 versus 1995–1999	0.87	0.82–0.93
Male versus female	1.18	1.12–1.25
20–24 versus 15–19 years	1.01	0.95–1.07

Table 3 – Five-year survival (%) with 95% confidence intervals for Europe as a whole and five regional groupings for 15 common cancers diagnosed in children (0–14 years) in 2000–2002 (period analysis) and in 1995–1999 (cohort analysis).

Diagnostic group	1995–2002	2000–2002	1995–1999				
	Number of cases	Population-weighted 5-year survival	Age-standardised 5-year survival				
			Northern Europe	UK and Ireland	Central Europe	Southern Europe	Eastern Europe
Haemopoietic tumours							
Ia Lymphoid leukaemia	11,259	85.4	85.2	81.4	86.8	82.5	74.8
		83.7–87.1	82. 7–87.6	79.7–83.2	85.7–88.0	79.9–85.1	65.8–83.7
Ib Acute myeloid leukaemia	2037	66.8	67.7	60.1	61.1	59.8	44.4[a]
		61.8–71.9	60.3–75.1	55.2–65.1	57.1–65.2	52.0–67.6	21.0–67.8
IIa Hodgkin lymphoma	2169	95.2	93.4	93.8	95.7	93.7	96.8[a]
		93.0–97.5	89.2–97.7	91.2–96.5	94.0–97.3	90.4–96.9	90.6–100.0
IIb Non-Hodgkin lymphoma	2066	82.3	85.5	78.9	86.6	78.2	60.0[a,b]
		78.2–86.5	79.7–91.3	74.5–83.3	83.9–89.2	72.2–84.1	29.0–91.0
IIc Burkitt lymphoma	719	84.4	93.3	85.8	91.7	88.4	66.7[a,b]
		75.2–93.7	85.7–100.0	78.9–92.6	87.5–95.8	82.6–94.2	12.3–100.0
CNS tumours							
III All CNS tumours	6483	62.8	61.4	56.1	63.1	57.6	57.6
		60.0–65.7	57.3–65.5	53.4–58.9	60.6–65.5	53.6–61.5	47.2–67.9
IIIa Ependymoma	840	62.0[c]	65.7	61.1	67.6	55.3	56.3[a]
		55.7–68.3	53.2–78.1	54.0–68.2	61.4–73.8	45.4–65.2	24.1–88.6
IIIb Astrocytoma	2193	62.9	62.9	61.5	68.3	65.0	63.1
		57.4–68.5	51.8–73.9	57.0–66.1	64.4–72.3	58. 2–71.8	46.7–79.4
IIIb Astrocytoma (including 9421/1)	4298	77.7	83.3	78.6	81.1	75.8	65.5
		73.4–82.0	78.1–88.6	75.8–81.4	78.7–83.5	70.9–80.6	50.4–80.7
IIIc Embryonal CNS tumours	2056	65.8	56.3	55.5	60.8	58.1	46.3
		60.5–71.1	47.2–65.5	50.8–50.2	56.7–64.9	50.0–66.2	24.2–68.3
Other solid tumours							
IVa Neuroblastoma	3102	71.9	65.5	61.3	78.9	64.0	72.4
		67.9–75.9	58.7–72.3	57.4–65.2	76.4–81.3	58.5–69.4	56.9–87.9
V Retinoblastoma[d]	806	97.5	96.8	97.4	97.9	95.0	100.0[a]
		94.6–100	92.3–100.0	95.1–99.7	95.3–100.0	90.2–99.9	100.0–100.0
VIa Nephroblastoma[e]	2382	89.1	89.8[a]	86.7	89.5	87.3	83.0
		85.8–92.5	84.6–95.0	83.4–90.0	87.2–91.9	82.5–92.0	68.5–97.6
VIIIa Osteosarcoma[f]	710	77.3	64.9	63.4	71.5	69.5	75.0[a]
		70.8 –83.9	49.1–80.6	54.9–71.9	65.3–77.7	58.1–80.9	44.4–100.0
VIIIc Ewing sarcoma	806	66.5	76.3	69.2	72.6	64.0	44.0[a]
		58.2–74.7	62.4–90.2	61.1–77.4	66.9–78.2	53.4–74.6	21.7—66.3
IXa Rhabdomyosarcoma	1480	69.1	78.4	66.5	70.0	64.6	64.9
		62.9–75.4	68.1–88.6	61.0–72.0	65.6–74.3	56.6–72.7	34.0–95.9

a <10 Cases.
b Not age standardised.
c No 2000–2002 cases diagnosed from Eastern Europe (the final survival value is calculated as the weighted sum of Northern Europe, the UK and Ireland, Central Europe and Southern Europe).
d Children aged 0–4 years only.
e Nephroblastoma and other non-epithelial renal tumours.
f Children aged 10–14 years only.

Table 4 – Five-year survival (%) of European children (0–14 years) diagnosed with rare cancers in 1995–2002.

ICCC	Cancer	1995–2002	1995–2002
		Number of cases	Five-year survival (95% CI)
Ic	Chronic myeloproliferative diseases	248	64.1 (57.5–70.7)
IVb	Pheochromocytoma/paraganglioma	44	73.1 (59.1–87.1)
VIb	Renal carcinomas	51	78.8 (66.8–90.8)
VIIa	Hepatoblastomas	335	74.2 (69.1–79.3)
VIIb	Hepatic carcinomas	77	45.4 (33.5–57.3)
VIIIb	Chondrosarcomas	38	73.2 (55.9–90.5)
IXb	Fibrosarcomas	243	75.9 (70.0–81.8)
Xc	Germ cell: testis	267	96.8 (94.6–99.0)
Xc	Germ cell: ovary	363	95.3 (92.8–97.8)
Xd	Carcinoma: ovary	24	70.0 (50.9–89.1)
XIa	Adrenocortical carcinomas	59	59.5 (45.5–73.5)
XIb	Thyroid carcinomas	353	98.8 (97.6–100.0)
XIc	Nasopharyngeal carcinomas	58	90.5 (82.4–98.6)
XId	Malignant melanoma[a]	272	88.1 (84.0–92.2)

a Twenty four visceral melanoma cases.

leukaemias (ICCC Ia); (2) acute myeloid leukaemias (ICCC Ib); (3) Hodgkin lymphomas (ICCC IIa); (4) non-Hodgkin lymphomas (ICCC IIb); (5) CNS tumours (ICCC III); (6) kidney (ICDO C64.9, C65.9); (7) eye and orbit (ICDO C69); (8) bone (ICDO C40–41); (9) soft tissues (ICDO C49) and (10) other sites. In the model for adolescents and young adults, two age classes (15–19 and 20–24) were used, and the case mix categories were: (1) Hodgkin lymphomas (ICCC IIa); (2) non-Hodgkin lymphomas (ICCC IIb); (3) leukaemias (ICCC Ia, Ib); (4) testis and ovary (ICDO C62, C56.9); (5) skin melanoma (ICDO C44, 8720–8790); (6) CNS tumours (ICCC III); (7) bone (ICDO C40–41); (8) thyroid (ICDO C739); (9) soft tissues (ICDO C49) and (10) other sites.

Difference in 5-year survival in relation to the four covariates such as sex, age, period of diagnosis and diagnostic category is presented as relative risks (RRs) of death. Geographic variation in survival is presented as country-specific survival estimates, using the marginal distribution of the other four covariates as common covariates. Interactions between country and diagnostic period were investigated, but were not significant. Proportionality of risk among the other covariates was assumed.

A Cox proportional hazard model[13] was also applied to each diagnostic group to estimate RR of death for 2000–2002 versus 1995–1999, adjusting to by regional grouping, diagnosis period, sex and age.

To assess changes in between-country survival differences, data from EUROCARE-3 (diagnosis period 1990–1994) and EUROCARE-4 (diagnosis period 1995–1999) were compared for cancer registries that provided data for both the periods.

3. Results

3.1. *All cancers combined*

Five-year survival estimates by country for all cancers combined diagnosed in 1995–2002 are shown in Fig. 1 (children) and Fig. 2 (adolescents/young adults). For most countries survival in children ranged between 78% and 83%. Malta and Czech Republic had lower survival (75% and 76%, respectively), which did not, however, differ significantly from mean European survival (81%). Austria had the highest survival (86%). For adolescents/young adults, 5-year survival was 87% overall, and the range was even narrower than that in children: from 84% in Northern Ireland to 92% in Iceland (neither significantly different from the European mean).

As shown in Table 2, RRs of death for all cancers combined reduced significantly, by 8% in children and by 13% in young adults, from 1995–1999 to 2000–2002. Outcomes were better for girls than for boys, but survival did not differ with age.

3.2. *Childhood cancers*

Five-year period survival estimates (with 95% confidence intervals (CIs)) for the entire European pool of children diagnosed in 2000–2002 are shown in Table 3 for the major diagnostic groups. For most haemopoietic cancers, 5-year survival was high (85% for lymphoid leukaemia, 82% for non-Hodgkin lymphoma, 84% for Burkitt lymphoma and 95% for Hodgkin lymphoma), although for acute myeloid leukaemia survival was only 67%.

Five-year survival for CNS cancers was modest, with limited variation in relation to morphology: 62% for ependymoma, 66% for embryonal tumours, mainly medulloblastoma and other primitive neuroectodermal tumours (PNET) and 63% for astrocytoma. When pilocytic astrocytoma (49% of all astrocytomas) was included, survival for astrocytoma increased to 78%.

Five-year survival for retinoblastoma was very high at 98%. Survival was also good (89%) for nephroblastoma and other non-epithelial renal tumours, a category consisting overwhelmingly of nephroblastoma but with other renal cancers accounting for 5% of cases. For other solid tumours, survival decreased in the order osteosarcoma (77%), neuroblastoma (72%), rhabdomyosarcoma (69%), and Ewing sarcoma (67%).

Table 5 – Five-year survival (%) of young adults (15–24 years) diagnosed in 2000–2002 and 1995–1999 with cancers characteristic of this age group, for Europe as a whole and for regional groupings.

		1995–2002	2000–2002	1995–1999				
		Number of cases	Population-weighted 5-year survival	Five-year survival				
				Northern Europe	UK and Ireland	Central Europe	Southern Europe	Eastern Europe
ICCC Ia	Lymphoid leukaemias	1301	49.5 42.5–56.5	59.5 51.9–67.1	52.6 47.3–57.8	50.1 42.4–57.8	51.7 43.5–59.9	60.4 38.6–82.2
ICCC Ib	Acute myeloid leukaemias	1020	59.1 50.3–67.9	47.0 37.0–57.0	49.1 43.6–54.7	47.4 37.4–57.8	47.8 38.8–56.8	45.6 17.6–73.5
ICCC IIa	Hodgkin lymphomas	4945	93.1 91.4–94.9	95.4 93.6–97.1	92.9 91.4–94.3	94.7 92.8–96.7	93.5 91.6–95.4	93.4 89.2–97.7
ICCC IIb	Non-Hodgkin lymphomas	1763	74.4 69.2–79.5	74.8 68.6–81.0	69.6 65.0–74.2	69.4 63.1–75.8	73.4 68.5–78.3	71.8 57.4–86.2
ICCC Xc	Germ cell: testis	3952	96.9 95.6–98.3	95.4 93.5–97.4	93.7 92.1–95.3	94.0 91.9–96.2	92.9 90.5–95.3	87.6 80.3–95.0
ICCC Xc	Germ cell: ovary	372	98.4 96.3–100.0	97.6 92.7–100	91.7 85.6–97.7	93.7 86.8–100	95.7 89.8–100	88.8 73.9–100
ICDO-3 C440–449[a]	Melanoma of skin	3201	92.2 89.6–94.9	97.2 95.6–98.8	91.3 89.3–93.2	93.4 90.9–95.9	92.8 89.9–95.7	86.3 74.9–97.7
ICDO-3 C71[a]	Brain	2064	61.7 56.5–67.0	65.5 59.9–71.1	57.2 52.9–61.4	62.1 55.5–68.8	57.0 50.7–63.3	64.2 51.0–77.5
ICCC IIIb	Astrocytomas	1028	55.8 48.3–63.4	51.6 39.6–63.6	48.6 42.1–55.0	58.3 49.1–67.5	54.9 45.8–64.0	65.0 46.0–83.9
ICCC IIIb	Astrocytomas (including 9421/1)	1361	64.2 57.8–70.6	65.1 55.8–74.4	57.9 52.5–63.4	68.4 61.1–75.7	61.7 53.8–69.6	66.0 47.5–84.6
ICDO–3 C40–41[a]	Bone	1551	61.8 55.8–67.8	66.8 59.5–74.0	53.6 48.9–58.3	66.5 59.6–73.5	53.8 46.7–60.9	54.3 37.4–71.1
ICCC VIIIa	Osteosarcomas	702	59.8 51.2–68.5	63.2 52.3–74.1	54.9 47.3–62.5	66.7 56.8–76.6	60.1 49.6–70.6	52.0 25.5–78.5
ICCC VIIIc	Ewing tumour	436	48.0 35.3–60.6	58.0 40.8–75.2	41.8 33.1–50.5	47.0 33.0–61.0	33.6 22.0–45.2	50.0 18.4–81.6
ICDO-3 C739[a]	Thyroid carcinomas	1755	99.5 98.9–100	99.6 98.7–100.0	99.3 98.4–100.0	100.0 100 –100	98.8 98.7–100.0	100.0 100–100
ICCC IX	Soft tissue sarcomas	1415	67.5 62.3–72.8	67.7 59.6–75.8	58.6 52.8–64.4	65.8 58.8–72.8	70.6 64.6–76.7	47.4 32.2–62.5
ICDO-3 C53[a]	Cervix	594	85.7 73.2–98.1	91.2 84.9–97.6	82.0 76.5–87.5	93.6 87.5–99.8	81.0 63.9–98.1	83.3 61.8–100
ICCC Xd	Ovary carcinoma	319	83.3 74.1–92.4	92.6 82.5–100.0	80.0 71.1–89.0	82.8 71.6–93.9	89.1 79.8–98.4	90.9 73.6–100
ICDO-3 C18[a]	Colon[b]	554	80.2 70.4–90.1	89.6 83.0–96.1	71.7 63.0–80.5	93.8 89.0–98.7	77.9 65.5–90.3	100.0[c] 100–100
ICDO-3 C500–509[a]	Breast	405	85.5 79.2–91.8	78.2 62.4–94.1	67.4 58.7–76.1	80.6 69.6–91.6	75.8 64. 9–86.7	100.0[c] 100–100
ICDO-3 C339–340[a]	Lung	214	72.1[d] 55.9–88.3	85.7 72.5–98.9	59.8 45.8–73.7	73.1 55.7–90.5	75.8 60.9–90.7	100.0[c] 100–100

a Morphology-melanoma of skin: 8720–8790; brain: excluding 9530–9539 and 9590–9989; bone, thyroid, cervix, colon, breast: excluding 9590–9989; lung: excluding 9590–9989 and 9050–9055.

b Includes 209 cases of appendix cancer; excluding these, European 5-year survival for 2000–2002 becomes 57.5% and the rank of regional groupings does not change.

c <10 Cases.

d No 2000–2002 cases diagnosed from Eastern Europe (the final survival value is calculated as the weighted sum of Northern Europe, the UK and Ireland, Central Europe and Southern Europe).

Table 6 – Relative risks (RRs) of death for children (0–14 years) diagnosed in 2000–2002 compared to those diagnosed in 1995–1999 for each diagnostic group, adjusted by regional grouping, sex and age.

	RR	95% CI
Ia Lymphoid leukaemias	0.85	0.74–0.97
Ib Acute myeloid leukaemias	0.89	0.74–1.06
IIa Hodgkin lymphomas	0.62	0.35–1.10
IIb Non-Hodgkin lymphomas	0.95	0.74–1.22
III CNS tumours	0.85	0.77–0.94
IIIa Ependymomas	0.97	0.72–1.30
IIIb Astrocytomas	0.96	0.80–1.14
IIIc Embrional CNS tumours	0.70	0.59–0.84
IVa Neuroblastoma	0.99	0.85–1.17
VIa Nephroblastoma[a]	0.86	0.63–1.17
VIIIa Osteosarcomas	0.99	0.74–1.32
VIIIc Ewing tumour	1.17	0.84–1.62
IXa Rhabdomyosarcomas	0.99	0.78–1.26

a Nephroblastoma and other non-epithelial renal tumours.

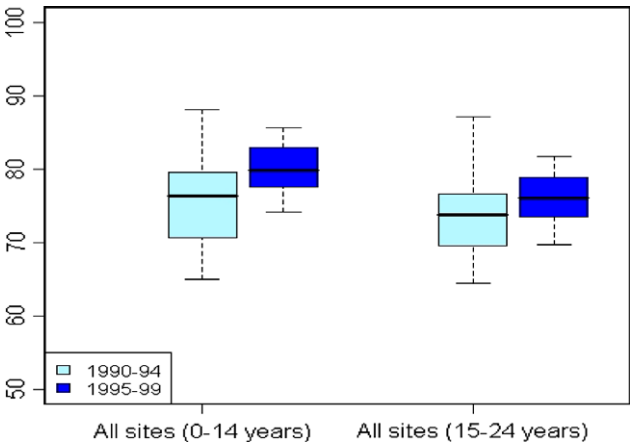

Fig. 3 – Changes in 5-year country-specific survival for all cancers combined in European children (0–14 years) and adolescents/young adults (15–24 years) from diagnosis period 1990–1994 to diagnosis period 1995–1999. In the whisker plots, the heavy line is the median, the box represents the interquartile range and vertical line (whisker) extends from the lowest to the highest survival. Countries are represented only by registries that contributed data for both periods.

Five-year survival for 15 common cancers diagnosed in children in 1995–1999 is also shown, for each European regional grouping, in Table 3. Central and Northern Europe had highest survival for most cancers; Eastern Europe had lowest survival for several cancers. The survival gap was marked for leukaemias, non-Hodgkin lymphoma, PNET and Ewing sarcoma.

Five-year survival for 15 rare cancers in children is shown in Table 4. Survival was relatively poor for hepatic carcinoma (45%), adrenocortical carcinoma (60%) and chronic myeloproliferative disease (64%), while for the other rare malignancies survival was $\geqslant$70%.

3.3. *Cancer in adolescents and young adults*

Five-year period survival estimates (with 95% CIs) for the European pool of adolescents and young adults diagnosed in 2000–2002 are shown in Table 5. As with children, haemopoietic cancers were the most common, but unlike children, lymphomas were more common than leukaemias. Survival was high for Hodgkin lymphoma (93%), intermediate for non-Hodgkin lymphoma (74%) and relatively low for acute myeloid leukaemia (59%) and lymphoid leukaemia (50%). Pilocytic astrocytoma accounted for 24% of astrocytoma cases in this age group; their inclusion increased survival for all astrocytomas from 56% to 64%.

Gonadal germ cell cancer and skin melanoma were the second and third most common malignancies in adolescents and young adults; both had relatively high survival (97% and 92%, respectively).

Survival variation by regional grouping is shown in Table 5. Survival was generally highest in Northern Europe and lowest in Eastern Europe.

3.4. *Survival changes over time*

Table 6 shows the RRs of dying from major malignancies for children diagnosed in 2000–2002 compared to those diagnosed in 1995–1999. Table 7 shows a similar comparison for adolescents and young adults diagnosed with cancers characteristic of this age range.

For children, there was a significant reduction in the RRs of dying for acute lymphoid leukaemia and all CNS cancers,

Table 7 – Relative risks (RRs) of death for adolescents and young adults (15–24 years) diagnosed with cancers in 2000–2002 compared to those diagnosed in 1995–1999, adjusted by regional grouping, sex and age.

		RR	95% CI
ICCC Ia	Lymphoid leukaemias	0.91	0.75–1.12
ICCC Ib	Acute myeloid leukaemias	0.81	0.65–1.01
ICCC IIa	Hodgkin lymphomas	0.87	0.63–1.19
ICCC IIb	Non-Hodgkin lymphomas	0.70	0.56–0.88
ICDO-3 C440–449, M8720–8790	Melanoma of skin	0.99	0.70–1.40
ICDO-3 C71	Brain	0.89	0.74–1.06
ICCC IIIb	Astrocytomas	0.99	0.80–1.24
ICDO-3 C40–41	Bone	0.99	0.82–1.20
ICCC VIIIa	Osteosarcomas	1.25	0.95–1.64
ICCC IX	Soft tissue sarcomas	0.93	0.75–1.15

most conspicuously PNET. For adolescents and young adults, only for non-Hodgkin lymphoma was the RR significantly lower in the later period.

Fig. 3 shows the ranges of 5-year country-specific survival for all cancers combined in 1990–1994 compared with those in 1995–1999 in the countries that contributed data for both the periods.[14,4] Survival increased for all cancers combined and between-country survival differences narrowed both for children and for adolescents/young adults.

4. Discussion

The two major – and encouraging – findings of our study are that survival for all cancers combined improved significantly across Europe (more for adolescents/young adults than for children) and that the survival gap between countries reduced. Considering individual cancers, survival increased significantly for leukaemias and PNET in children, and for non-Hodgkin lymphoma in adolescents/young adults.

For all cancers combined, notable increases in survival were achieved by countries with poor survival in EUROCARE-3 (i.e. Poland, the Czech Republic and Slovenia[14,4]); while for Northern Europe (with high survival in EUROCARE-3) 5-year survival remained stable. Enrolment in clinical trials, development of international collaboration, access to effective protocols and development of health infrastructures/allocation of resources may all have contributed to the improved survival in Eastern Europe.[15]

Although the survival improvement was most marked for adolescents/young adults, these older patients had significantly worse survival, in 2000–2002, than children for lymphoid leukaemia (50% versus 85%) and osteosarcoma (60% versus 77%) (compare Tables 3 and 5). Survival was also lower in older patients for acute myeloid leukaemia, non-Hodgkin lymphoma and Ewing sarcoma, although none of these differences were statistically significant. In the earlier periods, survival was much higher for acute lymphoid leukaemia than for acute myeloid leukaemia, in both adolescents/young adults and children.[4] However, for adolescents/young adults, survival for acute myeloid leukaemia improved so much in 2000–2002 that it was higher than for acute lymphoid leukaemia.

Fewer adolescent/young adult cancer patients participate in clinical trials than children,[16,17] but this alone cannot explain worse survival: age is a major prognostic factor for several cancers,[3] and for similar cancers biological behaviour may differ with age.[3] There is a debate as to whether adolescents with cancer should be treated as children or adults.[18] For acute lymphoblastic leukaemia, adolescents have better survival when treated with paediatric rather than adult protocols.[19,20]

This study took the opportunity of analysing survival for 15 rare cancers in children, defined as those with an incidence of <2 cases per million per year.[21] It was found that 5-year survival for rare cancers was generally good at $\geqslant$70%, but low for hepatic carcinoma (45%), adrenocortical carcinoma (60%) and chronic myeloproliferative disease (64%). The rarity of these malignancies renders clinical and biological research very difficult (rare tumours as almost never the object of clinical trials for example). However, studies coordinated by the Childhood Liver Tumours Strategy Group (SIOPEL) have shown that international collaboration is feasible and that trials on rare cancers can be conducted successfully.[22] The Italian project on rare tumours in paediatric age (TREP)[21] is a national initiative in this area that has established a collaborative network of specialists and is developing diagnostic and therapeutic guidelines for individual rare cancers.

Variations in data quality and data comparability can vitiate comparison of cancer survival between populations. Major indicators of data quality are the proportion of DCO/autoptic cases, proportion of cases lost to follow-up and proportion of cases microscopically verified. In the present study, the proportion of DCO cases was very low (typically 0%, overall 0.4%) and for three registries only it was in the range of 3–4% (Table 1). With very few exceptions, registries followed their cases for at least 5 years. Six registries only had between 10% and 29% of cases with a follow-up of less than 5 years.

Microscopic confirmation was also high at 95% overall with only two registries conspicuously lower (range 68–80%) than the average. Microscopic confirmation is particularly important for childhood cancers, which are primarily classified by histologic type. CNS cancers had the lowest proportion of microscopic confirmation at 86%, and the figure was below 80% in three of the five geographical areas considered in this study: lowest (72%) in Eastern Europe, highest (95%) in Central Europe. This variability may bias inter-regional survival comparison since absence of microscopic verification may result in less well-tailored treatment and lower survival. In fact regional survival for CNS tumours was high in Central Europe where microscopic confirmation was high and was low in Eastern Europe where microscopic confirmation was low.

Another major indicator of data quality is the proportion of cases allocated to unspecified categories within a major diagnostic group. The number of unspecified cases among EUROCARE-4 children and adolescents/young adults was low overall at 3.8%. However, the Italian registries of Salerno and Trento had very high proportions of unspecified cases. As noted in Section 2, Thames and Denmark did not provide ICD-O morphology codes for any cancer (only ICD-10 classified data), and their data were excluded from several analyses.

Changes in cancer coding can impair the comparability of results between different time periods. EUROCARE-4 is the first EUROCARE study to use the latest (ICD-O-3) coding system. ICD-O-3 differs in several respects from previous editions, particularly as regards the classification of myelodysplastic syndromes, chronic myeloproliferative disease, polycythemia rubra vera, ovarian carcinomas of borderline malignancy, and pilocytic astrocytoma. For persons under 25 years, the most important of these changes is that pilocytic astrocytoma has been downgraded to borderline behaviour. This tumour accounts for about half the astrocytomas diagnosed in children and a quarter of those diagnosed in adolescents/young adults. The effects of this on survival estimates for astrocytoma and all CNS cancers are evident in Section 3 and should be borne in mind whenever results from different time periods are compared.

A disappointing aspect of the latest EUROCARE data is that countries from Eastern Europe are poorly represented. Although cancer registries from Poland and the Czech Republic participated, the national registries of Slovakia and Estonia – included in EUROCARE-3 – dropped out of EUROCARE-4 because local laws obstructed patient follow-up.

This is undesirable particularly because the previous studies consistently indicated worse survival in Eastern European countries than in the rest of Europe. Cancer survival in patients under 25 years is particularly poorly documented in Eastern Europe, and cancer registration is far from attaining national coverage.

National registration should be a priority for these countries as an essential part of a policy for effective cancer control in Europe. Not only should full cancer registration and efficient outcome surveillance be promoted, but also initiatives to maintain and improve the quality of the collected data are also important (particularly morphology data in childhood and adolescent/young adult cancers). In some countries, privacy legislation impedes the collection of follow-up and mortality data.[14] The European Commission has an important role in promoting these policies and principles throughout Europe.

To conclude, cancers are rare in people under 25 years, but unlike most rare cancers they can be effectively treated in the majority of cases. To ensure the best outcomes, young people who develop malignancies should be referred to specialist-care centres and treated in accordance with national or international protocols. Where such protocols are not available they should be developed. Multi-institutional co-operation and European inter-group co-operative studies have an important role to play in developing treatment protocols and also in organising and co-ordinating clinical research in these cancers.

Conflict of interest statement

None declared.

EUROCARE-4 Working Group

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Acknowledgements

We thank Don Ward for help with the English and Samba Sowe for editorial support. The research was supported by the Compagnia di San Paolo, Torino, Italy. The Spanish RNTI-SEHOP is in the ISCIII-RTICC RD06/0020 and receives partial support from the Scientific Foundation of the Asociación Española Contra el Cáncer and the Fundación Villavecchia.

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