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Childhood Cancer Mortality in the European Community, 1950–1989

M. Carmen Martos and Jørgen H. Olsen

A descriptive study on childhood cancer mortality was carried out in the European Community (EC) covering the period 1950–1989. An annual total of 3392 cancer deaths were seen among children in the EC during the period 1979–1988, yielding an age-standardised cancer mortality rate of 50 per 10^6. Leukaemia was the most prevalent cause of death among children with cancer (39%). Excess mortality was observed among boys for cancers at all sites combined and for cancers at specific sites, exclusive of malignant tumours of the kidney. This excess is presumed to be due mainly to sex differences in incidence. Markedly higher mortality rates of childhood cancer were seen in southern countries of the EC than in central and northern countries. This difference appeared to be due mainly to differences in cancer incidence among the countries and to a lesser degree to differences in treatment and survival. An overall decline in mortality from childhood cancer in the EC occurred from the early 1960s. In spite of the improvements in survival, however, childhood cancer remains a major cause of death in the EC, affecting about 15% of children between the ages of 1 and 14.
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INTRODUCTION

CHILDHOOD CANCER is relatively rare; nevertheless, in nearly all developed countries, it has become the second most frequent cause of death in children after the first year of life [1].

A decrease in mortality from cancer in childhood has been observed in recent decades [2–4] while the incidence has remained stable [5–7]. The decline is attributed to improved survival rates for several tumour types [8–10]. Thus, geographical and temporal comparisons of mortality rates can be used to assess differences in the adoption, application and effectiveness of control programmes between countries.

In spite of the inherent limitations in mortality data, they have the advantages of uniformity and availability at a national level. Comparable incidence data, however, can be obtained only for a few countries and for certain regions, counties and districts [1]. A data bank on deaths by sex, age and cause was set up by the World Health Organization (WHO), which is updated annually.

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Information on mortality is derived from each of the national registration systems and stored in a standardised format to facilitate international comparisons [11].

Cancer mortality and incidence in the European Community (EC) have been studied for people of all ages [12], but no comparable work has been carried out for children . This paper reports on the burden of childhood cancer in the EC measured by mortality, as well as geographical and temporal variations in mortality among member countries during the period 1950–1989.

MATERIALS AND METHODS

Numbers of childhood cancer deaths, stratified by sex, age and country over the period 1950–1989, as well as population at risk, were abstracted from files provided by WHO.

In each of the member states of the EC, mortality data are collected routinely as an integral part of the vital statistics system of the country. Data processing is based without exception on the concept that the underlying cause of death is the prime cause. After the information has been released as official national statistics in each of the states concerned, it is transmitted to the data bank at WHO. Population data are compiled by the United Nations and forwarded to WHO. Part of the information stored in the data bank is published on a regular basis in the *World Health Statistics Annual*. More details and unpublished data may be obtained through a magnetic tape service run by WHO.

Since cancer mortality data are available by topographic site only, we have limited our analysis of mortality to the major types of childhood cancer: all malignant neoplasms, leukaemias, Hodgkin's disease, non-Hodgkin lymphomas, and malignant neoplasms of the brain and nervous system, of the eye, of the kidney, of the bone and soft tissue, of the ovary, of the testis of other specified sites and of unspecified or unknown sites. Separate information on the group of neuroblastomas could not be obtained on the basis of death certification because these tumours are coded in part to the organ affected (mainly the adrenal gland), in part to the nervous system and in part to the soft tissues, depending on country-specific rules for classification and coding.

Over the 40 years covered in our study, cause of death has been classified by the 6th, 7th, 8th and 9th revisions of the *International Classification of Diseases* (ICD). All revisions consist of a detailed list of valid ICD codes and several special lists of codes. Thus, for mortality purposes, the 6th, 7th and 8th revisions consist of two special tabulations: an A list, comprising 150 subgroups of codes (16 subgroups of cancer), and a B list of 50 main groups of codes (one subgroup includes all malignant neoplasms). In the 9th revision, the A and B lists have been replaced by an abbreviated list (the basic tabulation list), which assembles the detailed ICD codes into 57 main groups (of which seven are cancers), and into a number of subgroups, by adding a third digit to the two-digit main codes. As the various member states have been using different revisions when coding death certificates and different lists when reporting mortality data over time (Fig. 1), we include in Table 1 the ICD code equivalences between revisions and between lists from each revision. The 6th and 7th revisions are grouped because, for our purposes, they are identical; furthermore, we excluded polycythemia vera and myelofibrosis, because they are classified as malignant tumours only in the 8th revision.

All member countries of the EC were included in the spatial and temporal analysis of cancer mortality among children under the age of 15. Since the former German Democratic Republic and the Federal Republic of Germany were two separate countries during the study period, they were analysed separately. The mortality data reported to WHO were not complete for all countries over the full period 1950–1989: while information was available from 1950 for France, Ireland, The Netherlands and the U.K., it was available only from 1969 for the German Democratic Republic; nevertheless, first data were available for most countries between 1950 and 1954. Mortality data for 1989 were reported for only a few countries.

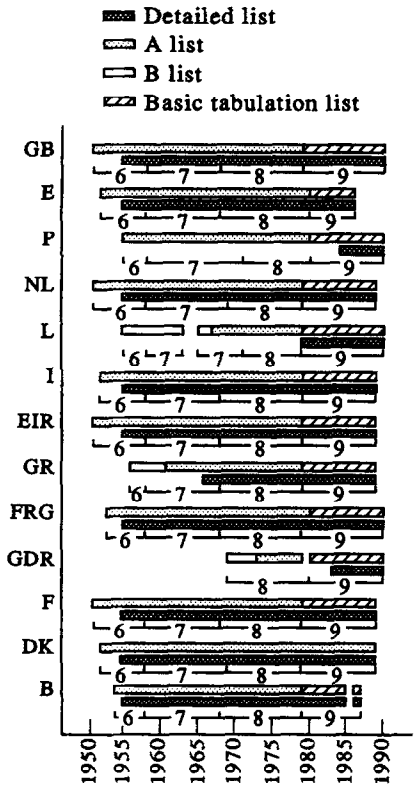

Fig. 1. Information on mortality available for each member state of the European Community, 1950–1989. B. Belgium; DK, Denmark; E, Spain; EIR, Ireland; F, France; FRG, Federal Republic of Germany; GB, United Kingdom; GDR, German Democratic Republic; GR, Greece; I, Italy; L, Luxembourg; NL, Netherlands; P, Portugal.

In order to evaluate the burden of childhood cancer mortality in the EC in recent years, the annual average numbers of deaths for the 10-year period 1979–1988 were added up, and associated annual average mortality rates per 10^6 children were derived. The mortality rates were specified by main type of tumour, sex, age group (0–4, 5–9, 10–14 years) and country. Sex ratios were calculated for tumour-specific mortality rates in each of the member states and for the entire EC. In the geographic analysis, the overall rates were age-standardised (European standard population), and comparative mortality figures were obtained by dividing the standardised rate for each country by the standardised rate for the EC. Associated 95% confidence intervals (CI) for the comparative mortality figures were determinated using the formula $CI = e^{\pm 1.96 \times S.E.}$ [13], where the standard error (S.E.) is calculated as described by Breslow and Day [14]. In the geographical analysis, malignant tumours of the brain and nervous system were subtracted from malignant tumours at all sites because of striking differences between countries in codification of these tumours under 'malignant' or 'benign'.

In the temporal analysis we used the annual mortality rate in each of eight consecutive 5-year periods, starting from

Table 1. Comparability of the various revisions of the International Classification of Diseases

	6th and 7th revisions			8th revision			9th revision	
Cancer site	List A	List B	Detailed list	List A	List B	Detailed list	Basic tabulation list	Detailed list
All malign neoplasms	A44–A59	B18	140–205	A45–A60	B19	140–207	8–14	140–208
All leukaemias	A58		204	A59		204–207	14.1	204–208
Hodgkin's disease			201			201	14.0	201
Other neoplasms of lymphoid tissue	A59*		200,202 203,205	A60†		200,202 203		200,202 203
Brain and nervous system			193			191–192	13.0‡	191–192
Eye			192			190		190
Kidney	A56		180			189§		189§
Bone			196	A52		170	11.0	170
Soft tissue			197			171		171
Ovary			175			183	12.3	183
Testis			178			186	12.5	186
Unspecified/ unknown site			165,198 199			195,196 198,199		195,196 198,199

* Hodgkin's disease is included. † Hodgkin's disease, polycythemia vera and myelofibrosis are included. ‡ Brain only is included. § Malignant neoplasms of kidney and other and unspecified urinary organs are included.

1950–1954 and ending in 1985–1989 within the limits of the available information. Overall rates were age-standardised. Country-specific 5-year periods were not included in the combined analysis when based on less than 3 calendar years of mortality reporting.

RESULTS

Mortality, 1979–1988

An annual total of 3392 cancer deaths was seen among children of all EC member states over the most recent period, 1979–1988. The source population over the same period was 68 091 500 children below age 15, yielding an age-standardised cancer mortality rate of 50 per 10^6 (55.9 per 10^6 in boys and 43.8 per 10^6 in girls). Deaths due to cancer accounted for 5% of all deaths registered in childhood and 15% of all deaths seen in the age group 1–14 years. Though cancers are rare in children under the age of 15 compared with cancer frequencies among older ages (0.4%), mortality due to childhood cancer nevertheless accounted for approximately 5% of years of potential life lost among all cancer patients 0–70 years of age. Table 2 gives the numbers and proportions of the main types of malignancy and the corresponding sex-specific mortality rates in the EC. Leukaemia is by far the most prevalent cause of death among children with cancer (39%), followed by tumours of the brain and nervous system (22%).

Table 3 gives the age-specific mortality rates in the EC for all malignant neoplasms and for the main types of childhood cancer. The highest mortality rates from cancers at all sites combined were observed for boys aged 5–9 and for girls aged 0–4. Deaths due to malignant tumours of the eye and of the kidney were seen predominantly in children of each sex below 5 years of age.

Table 4 shows the sex ratios by cancer site in the EC, and the highest and lowest sex ratios obtained among the member states. An excess 28% cancer mortality was seen for boys compared with girls, being highest in Spain (36%) and lowest in Ireland (17%). Cancer deaths by specific site were also more common for boys, except for malignant tumour of the kidney, which was slightly more common amongst girls. Striking differences in sex ratios were seen in different countries; e.g. in Greece mortality from leukaemia was 42% higher among boys than girls, while in Ireland it was only 2% more common.

Tables 5 and 6 present comparative mortality figures and associated CIs for each member state for malignant neoplasms at all sites (exclusive of neoplasms of the brain and nervous system) and for the four most important groups of cancer among boys and girls, respectively. The lowest mortality rates compared with the EC rates for all malignant tumours and for leukaemia were seen in the countries of central Europe, such as Germany, The Netherlands, Ireland and the U.K., and the highest rates were seen in the southern countries. The rate of lymphomas in both girls and boys was higher in Italy and Spain compared with the EC rate, and this rate was also raised in Portugal and in France among boys. Excess mortality from malignant tumours of the bone and soft tissue was seen in Spain and Portugal among boys.

Striking geographical variations were observed in mortality rates from malignant tumours of the brain and nervous system in boys and girls. Thus, the rates in France were low, those in Denmark, the German Democratic Republic, Greece and Spain were high. The rate was high among boys in Belgium and Portugal and among girls in Italy.

Random variation was seen for other specific sites, owing to small numbers of deaths; however, a few features stand out. Among girls, significant excess mortality was observed in Italy

Table 2. Numbers of deaths and standardised mortality rates (annual average) in the European Community, 1979–1988

Site	Annual deaths		Standardised mortality rate × 10^6	
	No.	%	Boys	Girls
All sites	3392	100	55.9	43.8
Leukaemia	1327	39	22.0	16.6
Hodgkin's disease	37	1	0.6	0.3
Lymphomas	243	7	4.8	2.1
Brain and nervous system	748	22	11.9	9.9
Eye	30	1	0.5	0.4
Kidney	126	4	1.9	2.0
Bone and soft tissue	301	9	4.4	4.0
Ovary	15	0	—	0.4
Testis	8	0	0.2	—
Other specified sites	423	12	7.2	5.8
Unspecified and unknown sites	134	4	2.0	1.9

Table 3. Age-specific mortality rates per 10^6 in the European Community, 1979–1988

Site	Boys			Girls		
	0–4	5–9	10–14	0–4	5–9	10–14
All sites	57.1	59.7	50.8	48.7	43.5	38.6
Leukaemia	19.1	26.0	21.4	16.0	18.4	15.3
Hodgkin's disease	0.2	0.8	1.0	0.1	0.3	0.8
Lymphomas	3.8	5.9	4.9	2.2	1.9	2.1
Brain and nervous system	12.4	13.1	10.2	10.8	11.2	7.6
Eye	0.9	0.4	0.1	0.8	0.3	0.1
Kidney	3.0	1.9	0.6	2.8	2.3	0.7
Bone and soft tissue	2.8	4.0	6.6	2.9	3.0	6.3
Ovary	—	—	—	0.2	0.1	0.9
Testis	0.4	0.2	0.2	—	—	—
Other specified sites	11.4	5.4	4.1	9.4	4.5	3.1
Unspecified and unknown sites	2.6	1.8	1.7	2.8	1.4	1.4

Table 4. Sex ratios (× 100) for mortality from cancer, European Community, 1979–1988*

Site	EEC	Highest	Lowest
All sites	128	136 (Spain)	117 (Ireland)
Leukaemia	133	142 (Greece)	102 (Ireland)
Hodgkin's disease	200	1606 (Portugal)	101 (United Kingdom)
Lymphomas	229	986 (Denmark)	162 (Belgium)
Brain and nervous system	120	157 (Portugal)	105 (Greece)
Eye	125	312 (Spain)	76 (Greece)
Kidney	95	186 (Portugal)	80 (Denmark)
Bone and soft tissue	110	163 (Portugal)	74 (Belgium)
Other specified sites	124	161 (GDR)	92 (Denmark)
Unspecified and unknown	105	205 (Ireland)	51 (Netherlands)

* Luxembourg excluded due to unstable mortality rates.

Table 5. Comparative mortality (CMF) for cancer and confidence intervals (CI) in the European Community, 1979–1988; boys

	All sites*		Leukaemia		Lymphomas†		Brain/ nervous system		Bone/ soft tissue	
	CMF	CI	CMF	CI	CMF	CI	CMF	CI	CMF	CI
South Europe										
Greece	109	99–118	115	102–129	104	81–133	146	127–169	112	86–147
Italy	121	117–126	122	116–128	114	103–126	105	97–113	98	87–111
Spain	128	123–134	121	114–129	146	130–163	119	110–130	116	101–133
Portugal	132	119–147	118	106–131	173	132–225	125	101–134	137	100–187
France	107	103–111	104	99–110	112	100–124	65	60– 72	98	86–111
Central and north Europe										
GDR	79	71– 88	76	67– 86	85	64–114	126	107–147	122	93–161
FRG	69	65– 72	74	69– 79	67	58– 58	96	88–104	88	77–101
Luxembourg	86	50–149	144	79–260	—	—	53	13–212	—	—
Belgium	103	92–115	90	76–106	75	52–108	146	122–175	69	44–108
Netherlands	84	77– 91	80	71– 90	95	76–119	102	88–118	102	81–128
United Kingdom	85	81– 88	89	83– 94	69	61– 79	95	88–102	100	89–113
Ireland	80	69– 92	79	65– 97	95	65–137	107	84–136	75	47–119
Denmark	93	81–106	106	88–126	132	96–181	155	125–191	88	56–137

* Malignant tumours of the brain and nervous system excluded. † Hodgkin's disease included.

for malignant tumours of the kidney and the ovary, and a significant default was seen in the Federal Republic of Germany for malignant tumours of the kidney. Among boys, excess mortality from malignant tumours of the eye was seen in Spain with a decrease in the Federal Republic of Germany, a significantly high mortality rate for malignant tumors of the kidney was seen in Portugal, with the lowest rate in the U.K.

The highest mortality rates from tumours at unspecified or unknown site for both boys and girls were seen in southern European countries such as Greece, Italy and Spain, and the lowest rates were noted in central European countries such as Germany, The Netherlands, Ireland and the U.K. Belgium, however, had raised rates for this group of tumours.

Trends in mortality, 1950–1989

An overall decline in mortality from childhood cancer was observed from the early 1960s in the two sexes combined. The reduction in mortality rate was 1.4% between 1960–1964 and 1965–1969 but increased to 19.8% between the two most recent 5-year periods.

Mortality trends for leukaemia, non-Hodgkin lymphomas and malignant tumours of the brain and nervous system are plotted in Fig. 2 and those for other specified sites in Fig. 3. Mortality rates for leukaemia and non-Hodgkin lymphoma decreased in 1960–1964. Certified mortality from malignant tumours of the brain and nervous system increased slightly between 1955 and 1979 and showed a downward trend thereafter. Mortality from

Table 6. Comparative mortality (CMF) for cancer and confidence intervals (CI) in the European Community, 1979–1988; girls

	All sites*		Leukaemia		Lymphomas†		Brain/ nervous system		Bone/ soft tissue	
	CMF	CI	CMF	CI	CMF	CI	CMF	CI	CMF	CI
South Europe										
Greece	105	95–117	108	93–125	86	56–132	167	144–195	109	82–147
Italy	122	117–127	120	113–127	122	104–142	108	100–118	98	86–112
Spain	118	112–124	115	106–124	134	112–161	121	110–133	107	91–124
Portugal	129	113–146	137	121–154	130	80–211	96	74–125	91	59–141
France	106	101–111	106	100–113	110	93–129	55	49– 61	93	81–106
Central and north Europe										
GDR	77	68– 87	75	64– 86	119	81–173	129	108–155	111	82–150
FRG	69	65– 73	74	68– 80	71	57– 87	97	89–107	87	75–101
Luxembourg	92	50–172	97	40–233	243	61–972	128	48–343	69	10–491
Belgium	114	101–130	99	81–119	104	64–168	122	98–152	100	67–152
Netherlands	83	75– 92	83	72– 96	88	61–125	100	85–118	103	80–132
U.K.	92	88– 97	87	82– 94	75	62– 92	100	91–109	113	100–128
Ireland	88	75–103	103	83–128	87	48–158	112	86–146	85	53–137
Denmark	87	73–104	102	82–128	34	13– 92	167	133–210	101	64–159

* Malignant tumours of the brain and nervous system excluded. † Hodgkin's disease included.

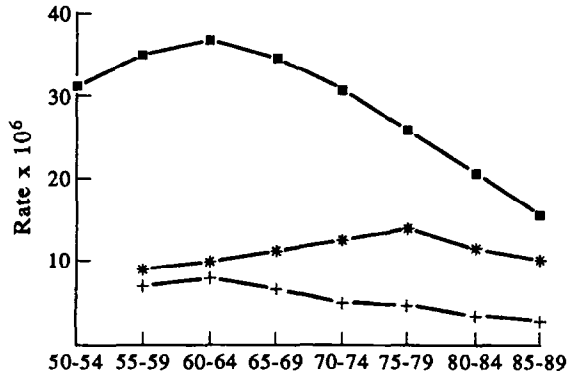

Fig. 2. Trends in mortality from leukaemia (-■-), non-Hodgkin lymphoma (+) and tumours of the brain and nervous system (*) in children, European Community, 1950–1989, two sexes combined.

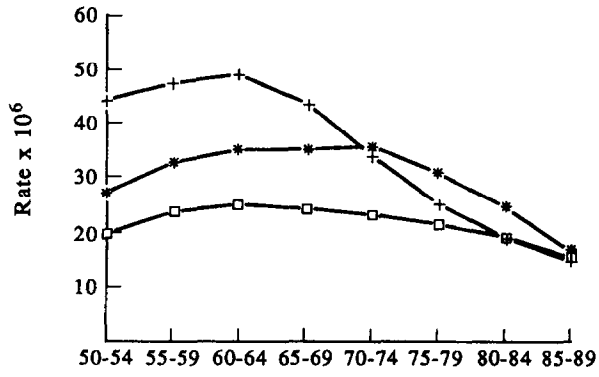

Fig. 5. Age-specific trends in mortality from leukaemia, (+ 0–4, * 5–9, -□- 10–14) European Community, 1950–1989, two sexes combined.

Hodgkin's disease decreased over the study period. That from malignant tumours of the kidney also declined in 1960–1964, and mortality from malignant tumours of the eye decreased from the next quinquennium. Mortality rates from cancers at other specified sites decreased from the early 1970s. A reduction of 66.6% was observed for malignant tumours of unspecified or unknown site between 1955 and 1989.

Figure 4 gives trends in mortality from leukaemia in southern and central Europe. The southern countries showed higher mortality rates during the study period, 1950–1989. Age-specific mortality trends for leukaemia and for cancers at all sites exclusive of leukaemia are shown in Figs 5 and 6. The reduction in mortality from leukaemia was most distinct in the age group 0–4. Thus, mortality rates for this age group were highest in the first periods studied, and lowest in the last 5-year-period. This phenomenon was not observed for cancers at all other sites.

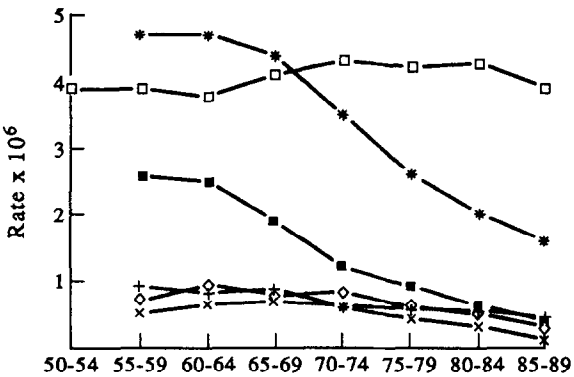

Fig. 3. Trends in mortality from Hodgkin's disease (-■-), cancer of the bone and soft tissue (-□-), eye (+), testis (×), kidney (*) and ovary (-◇-), European Community, 1950–1989, two sexes combined.

DISCUSSION

Our review of cancer mortality among children of 0–14 years of age in the EC over the period 1979–1988 showed five childhood cancer deaths per 100 000 children-years, equivalent to approximately 3400 deaths per year. Leukaemia was the most common cause of death among children with cancer, accounting for 39% of all childhood cancer deaths. In spite of advances in therapy during the past two decades, mortality from childhood cancer still occurs with a peak in early life, which has nevertheless occasionally been postponed by several years, e.g. for leukaemia. Childhood cancer was responsible for around 5% of all years of potential life lost due to cancer between 0 and 70 years of age, ranking among the 10 most important causes of cancer, measured by years of potential life lost.

Overall, an excess 28% cancer mortality was observed in boys, ranging from 17% in Ireland to 36% in Spain. A broad variation in mortality from cancers at different sites was seen, however, the differences in mortality between boys and girls cannot be attributed to differences in survival [9, 15], as higher cancer

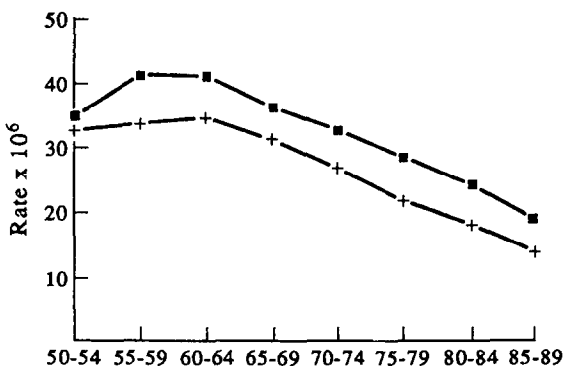

Fig. 4. Trends in mortality from leukaemia, southern (-■-), and central Europe (+) (excluding Luxembourg), 1950–1989, two sexes combined (mortality data for Spain and Portugal since 1965–1969).

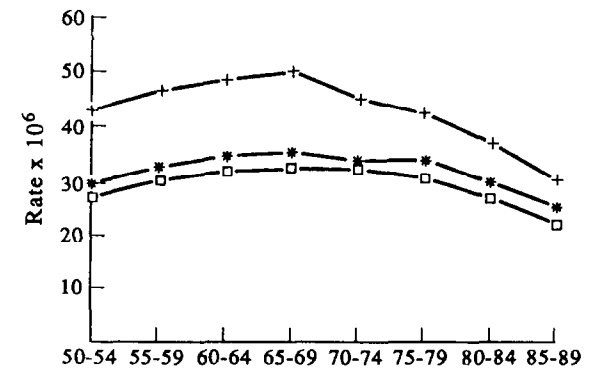

Fig. 6. Age-specific trends in mortality from cancers at all sites other than leukaemia, (+ 0–4, * 5–9, -□- 10–14) European Community, 1950–1989, two sexes combined.

incidence rates in boys than in girls have been reported from several population-based cancer registries [6, 16, 17].

Only the main groups of childhood cancer were studied, firstly, because topographical coding schemes were used which are not fully adequate for a detailed classification of cause of death [18,19] and, secondly, because this was the only realistic way of reducing the problem of international comparison.

The main limitation of studies based on mortality data is possible inaccuracies in diagnoses based on death certification. Although the mortality data collected at the national level and stored by WHO are based on internationally agreed guidelines, they are not subject to quality control at WHO. Thus, the increase in mortality from childhood cancer seen over the first periods of the study, particularly in Spain and Portugal, may be due to misclassification and underreporting. Some quality control is, however, undertaken at a national level, and the completeness of mortality data in developed countries can be considered to be reasonably satisfactory [11]. Several studies have been made of the accuracy of death certification for a diagnosis of cancer in people of all ages [20–22], although no comparable study has been carried out for children.

In spite of the fact that mortality data suffer from certain deficiencies, they have the advantage that they are probably the most uniformly reliable and complete data on childhood cancer that are widely available for all member countries of the EC. Incidence data from population-based cancer registries, which would be the most suitable, are not available in countries such as Greece and Luxembourg; and in others, such as France, Italy, Ireland, Portugal and Spain they exist only for certain regions [23].

The geographical analysis showed several differences in mortality among member states of the EC, the clearest being those between southern and central/northern Europe. The first explanation that comes to mind is that there is better survival in central and northern Europe. Time trend analysis of leukaemia in these two groups of countries, however, showed higher mortality rates in the southern countries throughout the study period, even before improvement of treatment in the early 1960s. Higher incidence rates of childhood cancer have also been reported by population-based cancer registries in those areas [24]. The variations in mortality between southern and central/northern Europe can thus be explained at least partly by differences in incidence.

The analysis of time trend showed decreased mortality from all childhood cancers and from cancer of several specific sites. Since incidence rates, calculated from population-based cancer registries, have remained constant over the past few decades [5–7, 16], the reduction in mortality can be fully attributed to improvement of survival from these tumours [8–10, 15, 16].

The pronounced decrease in the age group 0–4, particularly marked for leukaemia, can be attributed to the postponement of some deaths among children under 5 years. Although childhood cancer is rarer than adult cancer, gains in life expectancy are more important, since the avoidance of one death in childhood is more valuable than the saving of a life in older ages.

This study is mainly of descriptive value, in that it documents the burden of childhood mortality from cancer in the EC and provides associated time trends based on geographical and temporal differences between southern and central/northern Europe. The study provides the only information on childhood cancer available for each country in the EC. Mortality rates can thus be a tool for evaluation progress in cancer control at regional, national or international levels, although an acceptable quality of death certification is necessary. No study of the accuracy of death certification for childhood cancer has been carried out in the EC, and this might be an important future project.

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