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Childhood cancer mortality in Europe, 1970–2007

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ABSTRACT

To update trends in childhood cancer mortality in Europe, we analysed mortality data derived from the World Health Organization for all childhood neoplasms, bone and kidney cancers, non-Hodgkin's lymphomas (NHL) and leukaemias, in 30 European countries up to 2007. Between 1990–1994 and 2005–2007, mortality from all neoplasms steadily declined in most European countries (from 5.2 to 3.5/100,000 boys and from 4.3 to 2.8/100,000 girls in the European Union, EU). In 2005–2007, however, mortality rates from childhood cancers were still higher in countries from Eastern (4.9/100,000 boys and 3.9/100,000 girls) and Southern (4.0/100,000 boys and 3.1/100,000 girls) Europe than in those from Western (3.1/100,000 boys and 2.5/100,000 girls) and Northern (3.2/100,000 boys and 2.5/100,000 girls) Europe. Similar temporal trends and geographic patterns were observed for leukaemias, with declines from 1.7 to 0.9/100,000 boys and from 1.3 to 0.7/100,000 girls between 1990–1994 and 2005–2007 in the EU. For kidney cancer and NHL mortality rates were low and have been declining in larger European countries over the last 15 years. The pattern of trends was less clear for bone cancer, with no systematic downward trends at age 0–14, though some fall was evident at age 15–19. Thus, mortality from childhood cancer continued to decline over more recent years in most European countries. However, the mortality rates in Eastern – but also Southern – European countries in the mid 2000's were similar to those in the Western and Northern European ones in the early 1990's. Some further improvement in childhood cancer mortality is therefore achievable through more widespread and better adoption of currently available treatments.

1. Introduction

From the 1960's onwards, mortality from childhood leukaemias and other childhood cancers has showed substantial declines in developed areas of the world.[1–4] In the United States (USA), between 1990 and 2004 death rates declined by 1.3% per year for all neoplasms, and by 3.0% per year for childhood leukaemias.[5,6] In Western Europe, mortality from all childhood cancers and leukaemias declined by about 60% between the mid 1960's and the mid 1990's. The downward trends started later (i.e. between the mid 1970's and the late 1980's) and were appreciably smaller (by about 30%) in countries from Eastern Europe.[3]

To analyse recent patterns in childhood cancer mortality in various European countries, we updated trends up to 2007, and provided an overview of trends for all childhood cancers and leukaemias since 1970 using joinpoint regression analysis.[7]

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2. Materials and methods

We derived cancer death certification data from total cancer, and four cancer sites including bone and articular cartilage, kidney and other urinary sites (predominantly Wilm's tumour), non-Hodgkin's lymphomas (NHL) and leukaemias at age 0–14 (further subdivided in 4 age groups, 0, 1–4, 5–9 and 10–14 years) for 30 European countries for the period 1970–2007 from the World Health Organization (WHO) database.[8] Giving the higher incidence of bone cancer in adolescents, for this neoplasm we also considered death certification data at age 15–19 years.

For Ukraine and the Russian Federation data were available only for NHL, leukaemias and all cancers. For Albania, Croatia, the Czech Republic, Estonia, Latvia, Lithuania, the Republic of Moldova, the Russian Federation, Slovakia, Slovenia and Ukraine data were available only since the early-mid 1980's. For Portugal data were available only up to 2003; for Albania and Bulgaria up to 2004; for Estonia, Hungary, Slovakia, Spain and Ukraine up to 2005; and for Croatia, Denmark, France, Germany, Italy, Norway, Poland, the Russian Federation, Sweden and Switzerland up to 2006.

During the calendar period considered, three different Revisions of the International Classification of Diseases (ICD) were used.[9–11] For most countries, there were no major changes in the classification or coding of the cancers considered between various ICD Revisions. We recoded classification of cancer deaths – for all calendar periods and countries – according to the 10th Revision of the ICD. It was impossible to obtain meaningful death certification data for neoplasms of the nervous system, on account of difficulties in histopathological classification and for changes in the classification of neuroblastoma, which is coded in part to the organ affected (chiefly, the adrenal gland, i.e. with cancers of endocrine organs), in part to connective and soft-tissue sarcomas, and in part to the nervous system. In the present analysis, we did not consider mortality from other childhood cancers (i.e. eye (retinoblastoma) and Hodgkin's lymphomas, HL), because of the limited number of deaths in most European countries (less than 10 deaths for each sex registered in the whole Europe).

We obtained estimates of the resident population at age 0–14 and 15–19 years from the same WHO database.[8] From the matrices of certified deaths and resident population, we computed age-standardised mortality rates at age 0–14 per 100,000 boys and girls, using the direct method on the basis of the world standard population.[12] We computed also age-standardised rates for the European Union (EU) as a whole (defined as the 27 member states as in January 2007, excluding Cyprus, for which data were not available and Belgium, for which data were provided only up to 1997), and for four European subareas, i.e. Eastern (Albania, Bulgaria, Croatia, the Czech Republic, Estonia, Hungary, Latvia, Lithuania, Poland, the Republic of Moldova, Romania, Slovakia, Slovenia and Ukraine), Southern (Greece, Italy, Portugal and Spain), Western (Austria, France, Germany, the Netherlands and Switzerland), and Northern (Denmark, Finland, Ireland, Norway, Sweden and the United Kingdom) Europe. In a few countries, data were missing for one or more calendar years. No extrapolation was made for the missing data.

We also computed cumulative risk of death at age 0–14 years (i.e. the probability that a child would die from a specific cancer before 14 years of age, in the absence of any competing causes of death) on the basis of age-specific rates for the period 2005–2007 (unless otherwise specified).[13]

To identify significant changes in trend for all childhood neoplasms and leukaemias, we performed joinpoint regression analyses using the software provided by the Surveillance Research Program of the US National Cancer Institute.[14] The aim of this analysis is to identify possible points where a significant change in the linear slope of the trend (on a log-scale) is detected over the study period.[7] In joinpoint analysis, the best fitting points, called 'joinpoints', are chosen where the rate changes significantly. The analysis starts with the minimum number of joinpoints (e.g. 0 joinpoints, namely a straight line), and tests whether one or more joinpoints (up to 3) are significant and must be added to the model. Each significant joinpoint that indicates a change in the slope (if any) is retained in the final model. To describe linear trends by period, the estimated annual percent change (APC) is then computed for each of those trends by fitting a regression line to the natural logarithm of the rates using calendar year as a regressor variable.

3. Results

Table 1 shows the age-standardised 0–14 years mortality rates from all childhood cancers and leukaemias per 100,000 boys and girls in various European countries and in the EU in the periods 1990–1994, 2000–2004, and 2005–2007, and the average annual number of certified deaths for the most recent period. The histograms of the age-standardised 0–14 years mortality rates in the period 2005–2007 are also presented in Fig. 1. In 1990–1994, mortality rates from all childhood neoplasms varied by about a factor of 3, between the highest rates in Estonia, the Albania, the Republic of Moldova, Romania and Ukrain (over 9/100,000 boys and over 7/100,000 girls), as well as in other Eastern and Southern European countries, and the lowest ones in Ireland (3.6/100,000 boys and 2.6/100,000 girls), and other Northern European countries. Rates were 5.3/100,000 boys and 4.3/100,000 girls in the EU. For almost all countries mortality from all childhood neoplasms steadily declined over the last 15 years. In 2005–2007, the highest mortality rates were in the Republic of Moldova, Romania and Ukrain (over 6/100,000 boys and over 4.5/100,000 girls) and other Eastern European countries, followed by southern European countries, and the lowest ones in Austria, Denmark and Norway (around 2/100,000 boys and 1.3/100,000 girls) and other Northern European countries (Fig. 1). Overall rates were 3.5/100,000 boys and 2.8/100,000 girls in the EU. Similar geographic patterns and temporal trends were observed for leukaemia. In 1990–1994, the highest mortality rates were in Latvia, the Republic of Moldova, Romania and Ukraine (over 2.7/100,000 boys and over 2.4/100,000 girls), followed by other Eastern and Southern European countries, and the lowest ones in Ireland (1.0/100,000 boys and 0.4/100,000 women) and other Northern countries. Overall leukaemia rates in the EU were 1.7/100,000 boys and 1.3/100,000 girls. In 2005–2007, the highest mortality rates from leukaemias were in

Table 1 – Age-standardised 0–14 years (world population) mortality rates from all childhood cancers and leukaemias per 100,000 boys and girls in various European countries and in the European Union (EU) in 1990–1994, 2000–2004 and 2005–2007, and average annual number of certified deaths for the most recent period.

	Boys				Girls			
	1990–1994	2000–2004	2005–2007	No. of deaths	1990–1994	2000–2004	2005–2007	No. of deaths
All cancers (malignant/benign)								
Albania (1992–1994)	9.54	6.49	–	29	7.97	4.70	–	19
Austria	3.61	2.92	2.27	15	3.85	2.23	2.06	13
Bulgaria	7.70	5.17	–	30	5.39	3.89	–	22
Croatia (2005–2006)	5.23	4.50	4.51	17	4.02	3.42	2.60	8
Czech Republic	6.93	3.91	3.36	24	4.71	3.20	2.20	16
Denmark (2005–2006)	5.23	3.86	2.25	12	4.51	3.33	1.55	8
Estonia (2005)	10.08	5.80	5.39	6	8.58	4.76	4.16	4
Finland	3.65	3.36	3.16	14	3.16	2.66	3.16	14
France (2005–2006)	4.72	3.45	3.06	176	3.89	2.99	2.53	138
Germany (2005–2006)	4.04	2.94	2.94	174	3.42	2.63	2.28	129
Greece	4.20	3.68	3.13	26	3.26	2.81	3.14	24
Hungary (2005)	6.00	5.23	3.17	25	5.06	3.83	3.70	26
Ireland	3.64	2.90	2.70	12	2.61	2.30	2.27	10
Italy (2000–2003, 2006)	5.92	4.30	4.34	183	4.64	3.45	3.06	124
Latvia	9.08	6.35	5.62	9	6.36	4.93	3.14	5
Lithuania	7.90	4.10	3.63	10	6.85	5.21	3.34	8
Netherlands	4.19	3.79	3.74	56	3.54	2.79	2.99	43
Norway (2005–2006)	3.63	2.71	2.20	10	3.03	3.10	1.28	6
Poland (2005–2006)	5.86	4.24	3.65	116	4.85	3.61	3.21	94
Portugal (2000–2003)	6.39	4.34	–	37	6.32	3.89	–	31
Republic of Moldova	11.92	8.65	6.72	23	9.29	6.86	5.86	17
Romania	9.39	7.03	6.07	101	7.68	6.01	4.78	76
Russian Federation (2005–2006)	8.26	5.97	5.24	561	6.76	5.22	4.51	454
Slovakia (1992–1994, 2005)	5.21	4.24	3.52	16	4.63	3.64	4.15	17
Slovenia	3.37	3.85	2.56	4	5.08	1.81	2.77	4
Spain (2005)	5.64	4.29	4.35	142	4.64	3.26	3.14	95
Sweden (2005–2006)	4.09	3.22	3.67	29	3.77	3.16	2.87	21
Switzerland (2005–2006)	4.34	3.77	3.60	21	4.35	2.76	2.66	15
Ukraine (2005)	9.83	7.11	6.94	234	7.74	5.93	5.15	164
United Kingdom	4.26	3.41	3.33	182	3.51	2.91	2.51	131
EU	5.25	3.88	3.51	1398	4.32	3.24	2.80	1052
Leukaemias								
Albania (1992–1994)	1.76	1.66	–	7	1.27	1.33	–	6
Austria	1.14	0.62	0.22	2	0.95	0.54	0.53	3
Bulgaria	2.60	1.63	–	10	1.16	1.26	–	7
Croatia (2005–2006)	1.45	1.20	1.50	6	0.84	0.53	0.58	2
Czech Republic	2.06	0.89	0.66	5	1.48	0.73	0.36	3
Denmark (2005–2006)	1.83	0.88	0.51	3	1.25	0.80	0.55	3
Estonia (2005)	1.88	1.77	1.75	2	1.91	0.88	0.76	1
Finland	0.93	1.14	0.98	4	0.97	0.49	1.05	5
France (2005–2006)	1.47	0.87	0.76	44	1.11	0.68	0.57	31
Germany (2005–2006)	1.29	0.75	0.66	40	0.85	0.66	0.55	30
Greece	1.23	0.94	0.68	6	1.30	0.94	0.49	4
Hungary (2005)	1.87	1.12	0.76	6	1.52	1.03	0.83	6
Ireland	0.96	0.76	0.90	4	0.38	1.00	0.38	2
Italy (2000–2003, 2006)	1.99	1.25	1.20	51	1.47	0.82	0.74	31
Latvia	3.12	1.61	1.98	3	2.63	1.42	0.32	1
Lithuania	2.58	1.45	0.83	3	2.33	1.70	1.38	3
Netherlands	1.23	1.11	1.15	17	0.78	0.55	0.77	11
Norway (2005–2006)	1.09	1.01	0.79	4	0.75	1.05	0.19	1
Poland (2005–2006)	1.76	1.31	0.95	31	1.27	0.92	0.90	27
Portugal (2000–2003)	2.04	1.44	–	13	2.20	1.09	–	9
Republic of Moldova	3.58	2.59	1.04	4	3.15	2.44	1.45	5
Romania	2.70	2.21	1.72	29	2.39	1.84	1.39	22
Russian Federation (2005–2006)	2.69	1.76	1.64	177	2.16	1.47	1.40	140
Slovakia (1992–1994, 2005)	1.70	1.22	0.68	3	0.99	1.09	0.65	3
Slovenia	0.94	0.73	0.38	1	2.04	0.36	1.42	2
Spain (2005)	1.98	1.44	1.37	45	1.64	1.02	0.89	27
Sweden (2005–2006)	1.33	0.90	0.98	9	1.05	1.17	0.88	6
Switzerland (2005–2006)	1.79	1.02	0.85	5	1.21	0.83	0.51	3
Ukraine (2005)	3.13	2.25	2.04	69	2.54	1.66	1.60	48
United Kingdom	1.37	0.93	0.73	41	0.90	0.84	0.54	28
EU	1.68	1.09	0.88	369	1.27	0.86	0.69	262

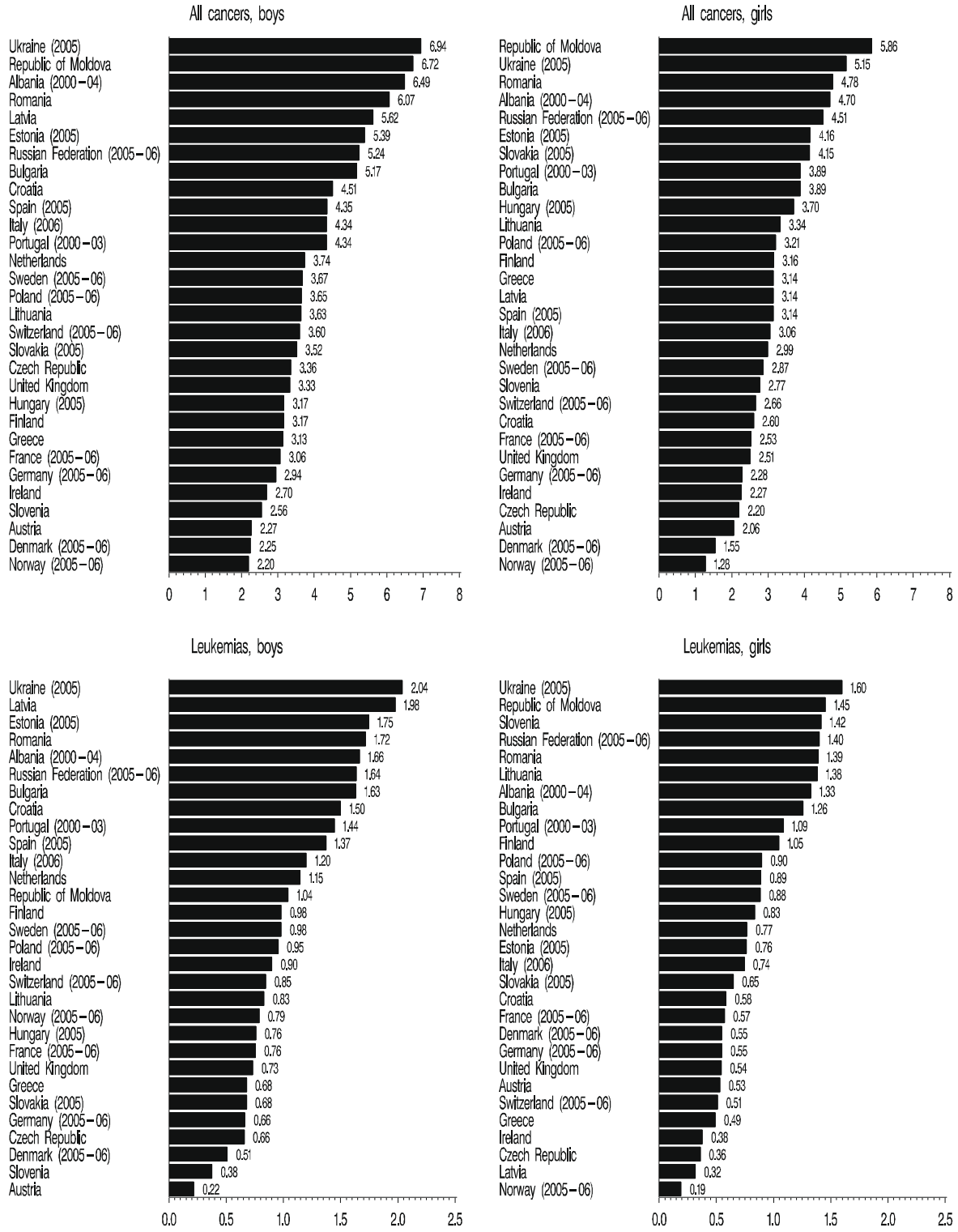

Fig. 1 – Age-standardised 0–14 years (world standard population) death certification rates from all childhood cancers and leukaemias in boys and girls from selected European countries, 2005–2007.

Ukraine (2.0/100,000 boys and 1.6/100,000 girls), and the lowest ones in Austria for boys (0.2/100,000) and in Norway for girls (0.2/100,000). Rates in the EU were 0.9/100,000 boys and 0.7/100,000 girls.

Tables 2 gives the age-standardised 0–14 years mortality rates from bone and kidney cancers and NHL per 100,000 boys and girls in 9 larger European countries and in the EU in the periods 1990–94, 2000–2004, and 2005–2007, and the average

Table 2 – Age-standardised 0–14 years (world population) mortality rates from selected childhood cancers per 100,000 boys and girls in larger European countries in the European Union (EU) in 1990–1994, 2000–2004 and 2005–2007, and average annual number of certified deaths for the most recent period.

	Boys				Girls			
	1990–1994	2000–2004	2005–2007	No. of deaths	1990–1994	2000–2004	2005–2007	No. of deaths
Bone and articular cartilage								
France (2005–2006)	0.21	0.16	0.08	6	0.13	0.15	0.12	7
Germany (2005–2006)	0.12	0.10	0.11	8	0.13	0.09	0.13	9
Italy (2000–2003, 2006)	0.19	0.15	0.25	12	0.23	0.12	0.26	12
Poland (2005–2006)	0.19	0.13	0.16	6	0.15	0.14	0.10	4
Romania	0.33	0.32	0.28	5	0.39	0.33	0.20	4
Spain (2005)	0.18	0.10	0.31	11	0.24	0.17	0.14	5
United Kingdom	0.13	0.17	0.14	8	0.15	0.22	0.12	7
EU	0.18	0.15	0.15	71	0.19	0.15	0.15	66
Kidney and other urinary sites								
France (2005–2006)	0.10	0.09	0.08	5	0.12	0.09	0.04	2
Germany (2005–2006)	0.10	0.09	0.03	2	0.12	0.04	0.07	4
Italy (2000–2003, 2006)	0.12	0.08	0.15	6	0.18	0.10	0.11	4
Poland (2005–2006)	–	0.21	0.12	4	–	0.18	0.10	3
Romania	–	0.19	0.27	4	–	0.42	0.21	3
Spain (2005)	0.10	0.07	0.13	4	0.13	0.07	0.10	3
United Kingdom	0.12	0.10	0.08	4	0.18	0.13	0.14	7
EU	0.13	0.10	0.09	36	0.16	0.11	0.11	39
Non-Hodgkin's lymphomas								
France (2005–2006)	0.22	0.16	0.18	11	0.21	0.09	0.05	3
Germany (2005–2006)	0.15	0.14	0.12	7	0.11	0.10	0.08	5
Italy (2000–2003, 2006)	0.43	0.25	0.19	8	0.15	0.16	0.12	5
Poland (2005–2006)	–	0.31	0.29	10	–	0.12	0.03	1
Romania	–	0.60	0.51	9	–	0.20	0.34	6
Russian Federation (2005–2006)	–	0.35	0.36	40	–	0.18	0.17	18
Spain (2005)	0.51	0.24	0.44	15	0.20	0.15	0.16	5
Ukraine (2005)	–	–	0.39	17	–	–	0.20	7
United Kingdom	0.23	0.20	0.15	8	0.09	0.06	0.05	3
EU	0.31	0.22	0.21	90	0.16	0.11	0.08	34

annual number of certified deaths for the most recent period. For other European countries, the number of deaths from bone and kidney cancers and NHL were very few, and it was thus not possible to give meaningful mortality rates. For kidney cancer and NHL rates were low and have been declining in major European countries over the last decade. For kidney cancer, mortality rates in the EU dropped from 0.13/100,000 boys and 0.16/100,000 girls in 1990–1994 to 0.09/100,000 boys and 0.11/100,000 girls in 2005–2007. Corresponding figures for NHL were 0.31/100,000 boys and 0.16/100,000 girls in 1990–1994 and 0.21/100,000 boys and 0.08/100,000 girls in 2005–2007. In 2005–2007, NHL mortality in both sexes was, however, still about 2-fold higher in Romania, Russia, Ukraine and Spain compared to other larger European countries. Likewise, an excess mortality was observed for kidney cancer in Romania, up to the most recent years. The pattern of trends was less clear for bone cancer. More important, no systematic downward trend over the last 15 years was observed for bone cancer across the 7 larger European countries considered. For both sexes, rates were higher in Italy, Romania and Spain as compared to other large European countries. In the EU, mortality rates were 0.18/100,000 boys and 0.19/100,000 girls in 1990–1994, and 0.15/100,000 boys and 0.15/100,000 girls in 2005–2007. However, some decline in bone cancer mortality was observed in adolescents. At age 15–19 years, bone cancer mortality in the EU was 0.91/100,000 boys and 0.54/100,000 girls in 1990–1994 and 0.69/100,000 boys and 0.46/100,000 girls in 2005–2007. In 2005–2007, in adolescents bone cancer mortality was lower in Germany and other Western European countries, and higher in Eastern Europe.

Table 3 gives the cumulative risk of death at age 14 years for all childhood cancers and leukaemias per 1000 boys and girls in various European countries and in the EU for the period 2005–2007. For all neoplasms, cumulative risk of death was highest in the Republic of Moldova and Ukraine (1.0 for boys and 0.8 for girls) and was lowest in Norway (0.32 for boys and 0.20 for girls); in the EU, it was 0.52 for boys and 0.42 for girls. For leukaemia, the highest cumulative rate was in Ukraine for both boys and girls (0.30 and 0.23, respectively), and the lowest one was in Austria for boys (0.04) and in Norway for girls (0.03); in the EU, it was 0.13 for boys and 0.10 for girls.

Fig. 2 shows the trends in age-standardised 0–14 years mortality rates from all childhood cancers and leukaemias in the EU in 1985–2007. Over this calendar period, mortality rates dropped from 6.2 to 3.5/100,000 boys and from 5.0 to 2.8/100,000 girls for all childhood neoplasms, and from 2.0 to 0.9/100,000 boys and from 1.6 to 0.7/100,000 girls for leukaemias.

Fig. 3 shows the trends in age-standardised 0–14 years mortality rates from all childhood cancers and from leukaemias in four European subareas in 1985–2007. Mortality rates from all childhood neoplasms steadily declined in all areas

Table 3 – Cumulative risk of death at age 14 years for all childhood cancers and leukaemias per 1000 boys and girls in various European countries and in the European Union (EU) for the period 2005–2007 (unless otherwise specified).

	Cumulative risk of death at 14 years			
	All cancers (malignant/benign)		Leukaemias	
	Boys	Girls	Boys	Girls
Albania	0.94	0.68	0.24	0.20
Austria	0.34	0.31	0.04	0.08
Bulgaria	0.76	0.58	0.25	0.19
Croatia (2005–2006)	0.68	0.37	0.23	0.09
Czech Republic	0.49	0.32	0.09	0.05
Denmark (2005–2006)	0.33	0.23	0.07	0.08
Estonia (2005)	0.84	0.63	0.28	0.13
Finland	0.47	0.47	0.14	0.16
France (2005–2006)	0.46	0.37	0.11	0.08
Germany (2005–2006)	0.44	0.34	0.10	0.08
Greece	0.47	0.47	0.10	0.07
Hungary (2005)	0.47	0.53	0.11	0.12
Ireland	0.40	0.35	0.13	0.06
Italy (2006)	0.64	0.46	0.18	0.12
Latvia	0.81	0.46	0.29	0.05
Lithuania	0.55	0.48	0.13	0.20
Netherlands	0.55	0.44	0.17	0.11
Norway (2005–2006)	0.32	0.20	0.13	0.03
Poland (2005–2006)	0.55	0.47	0.14	0.13
Portugal (2000–2003)	0.65	0.58	0.22	0.16
Republic of Moldova	1.01	0.84	0.16	0.22
Romania	0.89	0.71	0.26	0.20
Russian Federation (2005–2006)	0.77	0.66	0.24	0.20
Slovakia (2005)	0.53	0.60	0.10	0.10
Slovenia	0.38	0.40	0.06	0.21
Spain (2005)	0.66	0.46	0.21	0.13
Sweden (2005–2006)	0.55	0.42	0.16	0.12
Switzerland (2005–2006)	0.52	0.38	0.12	0.08
Ukraine (2005)	1.01	0.75	0.30	0.23
United Kingdom	0.50	0.37	0.11	0.08
EU	0.52	0.42	0.13	0.10

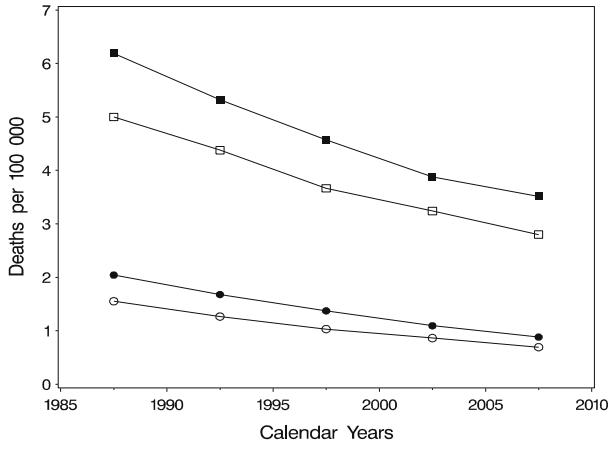

Fig. 2 – Trends in age-standardised 0–14 years (world standard population) death certification rates from all childhood cancers and leukaemias in the European Union, 1985–2007. Boys, all cancers ■—■; girls, all cancers □—□; boys, leukaemias ●—●; and girls, leukaemias ○—○.

over this calendar period. In more recent years (2005–2007), however, mortality rates from childhood cancers were still higher in Eastern (4.9/100,000 boys and 3.9/100,000 girls) and Southern (4.0/100,000 boys and 3.1/100,000 girls) Europe than in Western (3.1/100,000 boys and 2.5/100,000 girls) and Northern (3.2/100,000 boys and 2.5/100,000 girls) Europe. Moreover, mortality rates in Eastern and Southern European countries in 2005–2007 were at levels of Western and Northern European ones in 1990–1994 (4.3/100,000 boys and 3.7/100,000 girls, and 4.2/100,000 boys and 3.5/100,000 girls, respectively). Similar patterns were observed for leukaemia (Fig. 3), with mortality rates of 1.3/100,000 boys and 1.1/100,000 girls in Eastern Europe, 1.1/100,000 boys and 0.7/100,000 girls in Southern Europe, and 0.8/100,000 boys and 0.6/100,000 girls in Western and Northern Europe in 2005–2007.

Fig. 4 and Table 4 show the findings from the joinpoint analysis for the age-standardised 0–14 years mortality rates for all childhood cancers and leukaemias in selected European countries over the period 1970–2007. In most European countries, mortality from all childhood cancers steadily declined over the whole period, with APCs between 2% and 4% in both boys and girls. The declines were smaller or more recent for countries of Eastern Europe, such as Bulgaria, the Czech Republic, Romania, Hungary and the Russian Federation. For leukaemia, the declines were between 3% and 6% per year in most European countries. As for all childhood

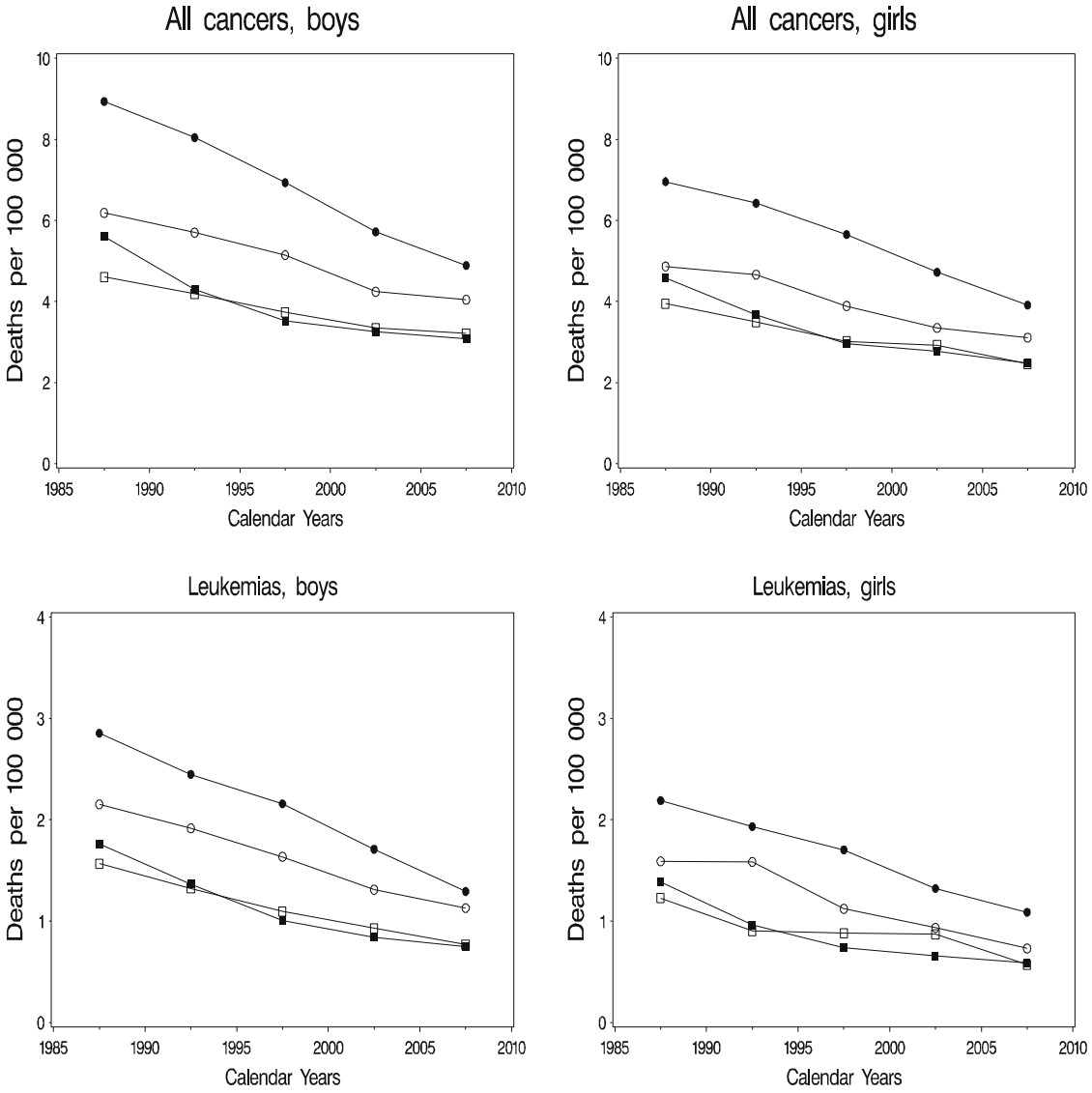

Fig. 3 – Trends in age-standardised 0–14 years (world standard population) death certification rates from all childhood cancers and leukaemias in boys and girls from four European subareas, 1985-2007. Eastern Europe ●—●; Southern Europe ○—○; Western Europe ■—■; and Northern Europe □—□.

cancers, the declines started later in Bulgaria, Romania, as well as in the Russian Federation.

4. Discussion

The present updated report of geographic patterns and temporal trends in childhood cancer mortality in European countries indicates and further quantifies a continuing decline in mortality from childhood neoplasms and leukaemias in most European countries over the last 15 years. As confirmed by joinpoint regression analysis, the rates steadily declined in most European countries up to the most recent calendar years. Although the declines were later in Eastern Europe as compared to Northern and Western Europe,[3] significant downward trends were also observed in Eastern European countries over the last decade. Still, in the mid 2000's mortality rates from all childhood cancers, leukaemias, and other childhood cancers, in Eastern – as well as in Southern European – countries were at the same levels as those of Northern and Western Europe in the early 1990's. Thus, an appreciable variation in childhood cancer mortality still persists across Europe.

Changes in diagnosis, a death certification accuracy and random variation are unlikely to have materially affected the observed trends in most (major) countries. Over the period considered the incidence of childhood cancers in European countries has remained relatively stable and is unlikely to have decreased.[15,16] Thus, the falls in childhood cancer mortality are largely due to the adoption of effective multidrug chemotherapy protocols (together with the introduction of various supportive measures to overcome toxicity), as well as the availability of more refined radiotherapy treatments, bone marrow transplantation and improved diagnostic techniques.[17] Even in the absence of any single breakthrough,

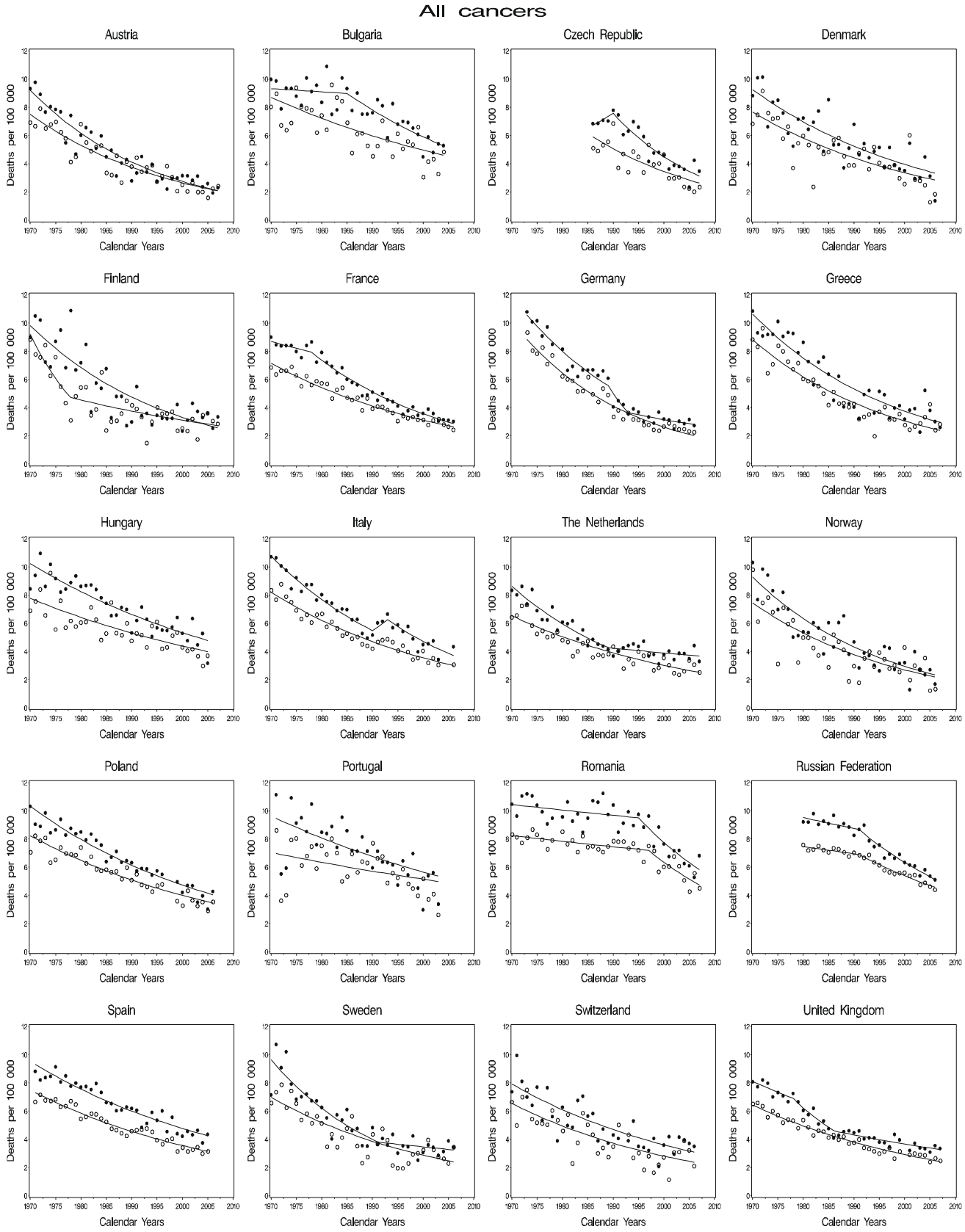

Fig. 4 – Joinpoint analysis for age-standardised 0-14 years (world standard population) death certification rates from all childhood cancers and leukaemias in selected European countries, 1970-2007. Boys ●—● and girls ○—○.

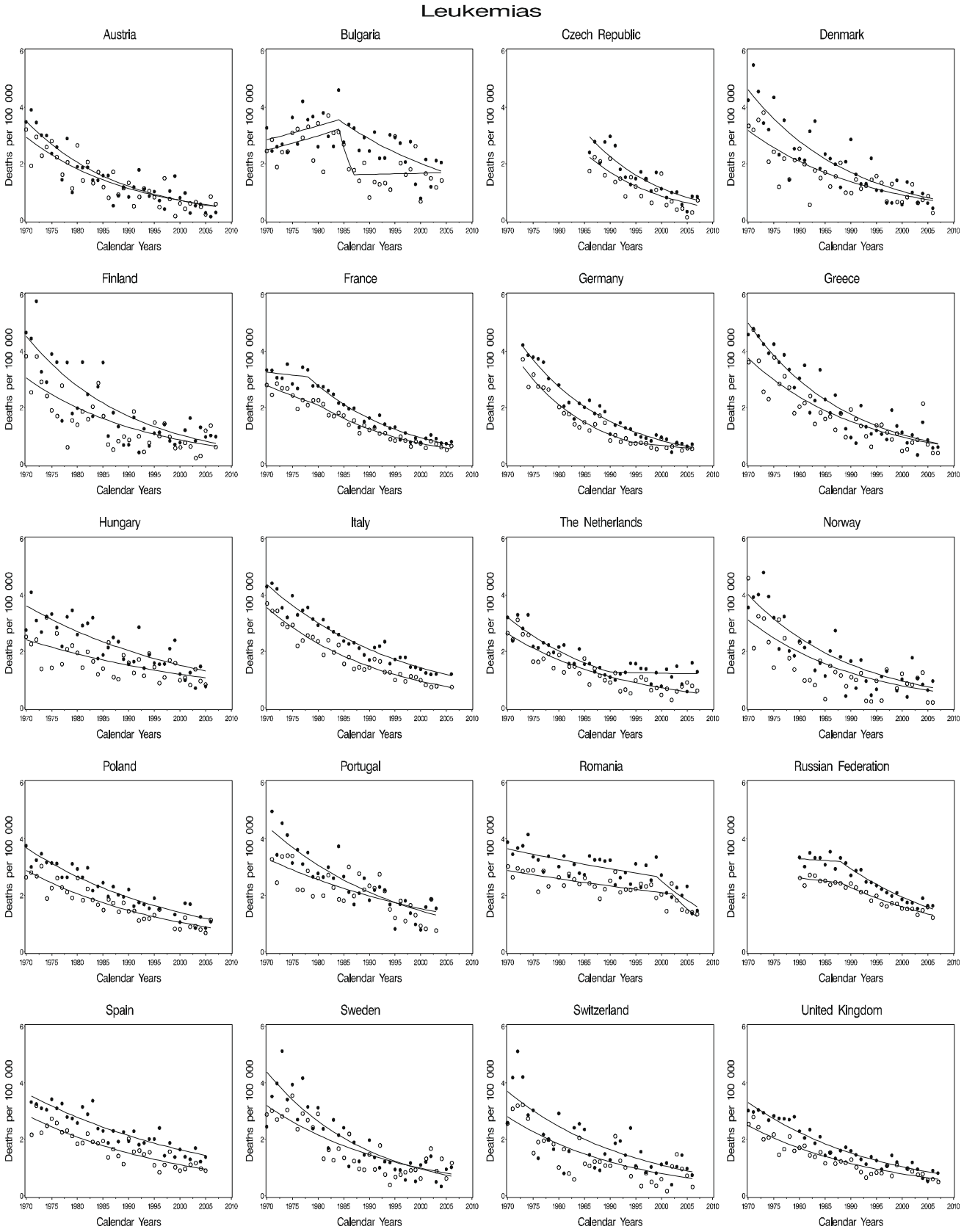

Fig. 4 *(continued)*

these complex and integrated therapeutic advancements have led to steady improvements in survival for leukaemias, lymphomas, as well as for other childhood cancers over the last decades.[18,19]

Table 4 – Joinpoint analysis for mortality from all childhood cancers and leukaemias (in boys and girls) for selected European countries, 1970–2007.

	Boys						Girls					
	Trend 1		Trend 2		Trend 3		Trend 1		Trend 2		Trend 3	
	Years	APC	Years	APC	Years	APC	Years	APC	Years	APC	Years	APC
All cancers												
Austria	1970–2007	–3.96[a]					1970–2007	–3.42[a]				
Bulgaria	1970–1985	–0.24	1985–2004	–2.76[a]			1970–2004	–1.87[a]				
Czech Republic	1986–1990	3.10	1990–2007	–5.10[a]			1986–2007	–3.78[a]				
Denmark	1970–2006	–2.80[a]					1970–2006	–2.72[a]				
Finland	1970–2007	–3.57[a]					1970–1978	–8.04[a]	1978–2007	–1.88[a]		
France	1970–1978	–1.14	1978–2006	–3.58[a]			1970–2006	–2.73[a]				
Germany	1973–1989	–3.94[a]	1989–1993	–10.10	1993–2006	–2.00[a]	1973–2006	–4.41[a]				
Greece	1970–2007	–3.42[a]					1970–2007	–3.47[a]				
Hungary	1970–2005	–2.15[a]					1970–2005	–1.89[a]				
Italy	1970–1990	–3.33[a]	1990–1993	4.51	1993–2006	–3.94[a]	1970–2006	–2.76[a]				
Netherlands	1970–1989	–3.65[a]	1989–2007	–0.82			1970–2007	–2.55[a]				
Norway	1970–2006	–3.75[a]					1970–2006	–3.33[a]				
Poland	1970–2006	–2.57[a]					1970–2006	–2.38[a]				
Portugal	1971–2003	–1.76[a]					1971–2003	–1.04[a]				
Romania	1970–1995	–0.38	1995–2007	–3.99[a]			1970–1997	–0.50[a]	1997–2007	–4.09[a]		
Russian Federation	1980–1991	–0.85[a]	1991–2006	–3.42[a]			1980–1991	–0.71[a]	1991–2006	–2.71[a]		
Spain	1971–2005	–2.27[a]					1971–2005	–2.46[a]				
Sweden	1970–1991	–4.33[a]	1991–2006	–1.07			1970–2006	–2.92[a]				
Switzerland	1970–2006	–2.59[a]					1970–2006	–2.78[a]				
United Kingdom	1970–1978	–2.00[a]	1978–1986	–4.93[a]	1986–2007	–1.61[a]	1970–2007	–2.60[a]				
Leukaemias												
Austria	1970–2007	–5.23[a]					1970–2007	–4.69[a]				
Bulgaria	1970–1984	1.60	1984–2004	–3.51[a]			1970–1984	1.85	1984–1987	–20.68	1987–2004	0.25
Czech Republic	1986–2007	–6.64[a]					1986–2007	–6.63[a]				
Denmark	1970–2006	–4.91[a]					1970–2006	–4.16[a]				
Finland	1970–2007	–4.79[a]					1970–2007	–4.15[a]				
France	1970–1978	–0.65	1978–2006	–5.30[a]			1970–1980	–2.81[a]	1980–2006	–5.14[a]		
Germany	1973–2006	–5.79[a]					1973–1994	–6.83[a]	1994–2006	–2.88		
Greece	1970–2007	–5.09[a]					1970–2007	–4.45[a]				
Hungary	1970–2005	–2.87[a]					1970–2005	–2.32[a]				
Italy	1970–2006	–3.67[a]					1970–2006	–4.33[a]				
Netherlands	1970–1990	–4.55[a]	1990–2007	–0.28			1970–2007	–4.27[a]				
Norway	1970–2006	–4.69[a]					1970–2006	–4.52[a]				
Poland	1970–2006	–3.19[a]					1970–2006	–3.32[a]				
Portugal	1971–2003	–3.67[a]					1971–2003	–2.53[a]				
Romania	1970–1999	–1.07[a]	1999–2007	–6.20[a]			1970–2002	–1.04[a]	2002–2007	–9.62		
Russian Federation	1980–1988	–0.40	1988–2006	–4.08[a]			1980–1988	–0.87	1988–2006	–3.46[a]		
Spain	1971–2005	–2.64[a]					1971–2005	–3.15[a]				
Sweden	1970–2006	–4.98[a]					1970–2006	–3.88[a]				
Switzerland	1970–2006	–4.01[a]					1970–2006	–4.18[a]				
United Kingdom	1970–2007	–3.83[a]					1970–2007	–3.82[a]				

a Significantly different from 0 ($p < 0.05$). APC, estimated annual percent of change.

Indeed, between 1983–1992 and 1993–1997, 5-year survival in Europe increased from 65% to 75% for all childhood cancers, from 79% to 86% for renal tumours, from 91% to 93% for HL, from 66% to 79% for NHL, and from 65% to 77% for leukaemias.[19] The improvement was smaller for bone neoplasms.[19,20] Five-year survival has long been over 90% for HL and retinoblastoma, which now cause a very low number of deaths in Europe.

In contrast, trends in mortality were less favourable for childhood bone cancer, partly because of the impact of conservative treatments,[21] and partly because chemotherapy for bone tumours (based on doxorubicin, cisplatin, high dose methotrexane, and ifosfamide) has not substantially evolved over the last two decades.[22] Some declines in bone cancer mortality have been observed in adolescents, particularly among boys who have appreciably higher incidence of the disease than girls at age 15–19 years.[20]

With reference to patterns across geographical areas, after earlier delays in the adoption of therapies,[23] survival from most childhood cancer is now comparable in Western and Northern Europe and in the USA in more recent years,[24–26] although Eastern European countries still have lower survival rates as compared to other European countries (5-year survival for all childhood neoplasms was 62% in Eastern, 77% in Northern, 72% in Southern and 75% in Western Europe in 1988–1997).[18,19,27,28] Over more recent calendar years, marked – and in proportional terms, larger – improvements have, however, been observed in those areas of the continent, with a consequent reduction of the differences in survival across Europe.[18,19,27,28] In particular, childhood cancer

mortality rates for selected Eastern European countries, such as the Czech Republic and Slovenia, are now comparable to those of some Western and Northern European countries. In those countries, other relevant childhood health indicators, such as infant mortality, are now comparable to most developed Western European countries.[29]

The differences in the pattern of childhood cancer mortality in various European areas mainly reflect differences in the availability and adoption of modern therapeutic protocols for childhood cancer, with a delay particularly in Eastern Europe.[18,27] Thus, some further improvement in childhood cancer mortality is achievable through more widespread and better adoption of currently available integrated treatment protocols in Eastern – and also in some areas of Southern – Europe, where a substantial number of deaths from childhood cancer could be avoided in the future.

Conflict of interest statement

None declared.

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REFERENCES

1. Levi F, La Vecchia C, Lucchini F, Negri E, Boyle P. Patterns of childhood cancer incidence and mortality in Europe. *Eur J Cancer* 1992;**28A**:2028–49.
2. Levi F, La Vecchia C, Lucchini F, Negri E, Boyle P. Patterns of childhood cancer mortality: America, Asia and Oceania. *Eur J Cancer* 1995;**31A**:771–82.
3. Levi F, La Vecchia C, Negri E, Lucchini F. Childhood cancer mortality in Europe, 1955–1995. *Eur J Cancer* 2001;**37**:785–809.
4. Yang L, Fujimoto J, Qiu D, Sakamoto N. Childhood cancer in Japan: focusing on trend in mortality from 1970 to 2006. *Ann Oncol* 2009;**20**:166–74.
5. Linet MS, Ries LA, Smith MA, Tarone RE, Devesa SS. Cancer surveillance series: recent trends in childhood cancer incidence and mortality in the United States. *J Natl Cancer Inst* 1999;**91**:1051–8.
6. Trends in childhood cancer mortality-United States, 1990–2004. *MMWR Morb Mortal Wkly Rep* 2007;**56**:1257–61.
7. Kim HJ, Fay MP, Feuer EJ, Midthune DN. Permutation tests for joinpoint regression with applications to cancer rates. *Stat Med* 2000;**19**:335–51 [Erratum in: *Stat Med* 2001;**20**:655].
8. World Health Organization Statistical Information System. WHO Mortality Database. <http://www3.who.int/whosis/menu.cfm/2007>.
9. World Health Organization. *International Classification of Disease*. 8th revision. Geneva: World Health Organization; 1967.
10. World Health Organization. *International Classification of Disease*. 9th revision. Geneva: World Health Organization; 1977.
11. World Health Organization. *International Statistical Classification of Disease and Related Health Problems*. 10th revision. Geneva: World Health Organization; 1992.
12. Doll R, Smith PG. Comparison between registries: age-standardized rates. In: Waterhouse JAH, Muir CS, Shanmugaratnam K, Powell J, Peacham D, Whelan S, editors. *Cancer incidence in five continents*, vol. IV. IARC Sci Publ No. 42. Lyon: IARC; 1982. p. 671–5.
13. Day NE. Cumulative rate and cumulative risk. In: Parkin DM, Muir CS, Whelan SL, Gao YT, Ferlay J, Powell JE, editors. *Cancer incidence in five continents*, vol. VI. IARC Scientific Publ. No. 120. Lyon, France: International Agency for Research on Cancer; 1992. p. 862–4.
14. National Cancer Institute. *Joinpoint Regression Program, version 3.3.1*. <http://srab.cancer.gov/joinpoint/2008>.
15. Gonzalez JR, Fernandez E, de Toledo JS, et al. Trends in childhood cancer incidence and mortality in Catalonia, Spain, 1975–1998. *Eur J Cancer Prev* 2004;**13**:47–51.
16. Steliarova-Foucher E, Stiller C, Kaatsch P, et al. Geographical patterns and time trends of cancer incidence and survival among children and adolescents in Europe since the 1970s (the ACCISproject): an epidemiological study. *Lancet* 2004;**364**:2097–105.
17. Wayne AS, Reaman GH, Helman LJ. Progress in the curative treatment of childhood hematologic malignancies. *J Natl Cancer Inst* 2008;**100**:1271–3.
18. Gatta G, Capocaccia R, Stiller C, et al. Childhood cancer survival trends in Europe: a EUROCARE Working Group Study. *J Clin Oncol* 2005;**23**:3742–51.
19. Magnani C, Pastore G, Coebergh JW, et al. Trends in survival after childhood cancer in Europe, 1978–1997: report from the Automated Childhood Cancer Information System project (ACCIS). *Eur J Cancer* 2006;**42**:1981–2005.
20. Stiller CA, Bielack SS, Jundt G, Steliarova-Foucher E. Bone tumours in European children and adolescents, 1978–1997. Report from the Automated Childhood Cancer Information System Project. *Eur J Cancer* 2006;**42**:2124–35.
21. Stiller CA, Bunch KJ. Trends in survival for childhood cancer in Britain diagnosed 1971–85. *Brit J Cancer* 1990;**62**:806–15.
22. Craft AW. Challenges in the management of bone tumors – 1996. *Ann NY Acad Sci* 1997;**824**:167–79.
23. La Vecchia C, Levi F, Lucchini F, et al. Trends in childhood cancer mortality as indicators of the quality of medical care in the developed world. *Cancer* 1998;**83**:2223–7.
24. Gatta G, Capocaccia R, Coleman MP, Ries LA, Berrino F. Childhood cancer survival in Europe and the United States. *Cancer* 2002;**95**:1767–72.
25. Linabery AM, Ross JA. Childhood and adolescent cancer survival in the US by race and ethnicity for the diagnostic period 1975–1999. *Cancer* 2008;**113**:2575–96.
26. Pulte D, Gondos A, Brenner H. Trends in 5- and 10-year survival after diagnosis with childhood hematologic malignancies in the United States, 1990–2004. *J Natl Cancer Inst* 2008;**100**:1301–9.
27. Sankila R, Martos Jimenez MC, Miljus D, et al. Geographical comparison of cancer survival in European children (1988–1997): report from the Automated Childhood Cancer Information System project. *Eur J Cancer* 2006;**42**:1972–80.
28. Gatta G, Zigon G, Capocaccia R, et al. Survival of European children and young adults with cancer diagnosed 1995–2002. *Eur J Cancer* 2009;**45**:992–1005.
29. Zatonski W, Mikucka M, La Vecchia C, Boyle P. Infant mortality in Central Europe: effects of transition. *Gac Sanit* 2006;**20**:63–6.