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Original paper

Incidence of Non-Hodgkin's Lymphoma in Children Between 1970 and 1990 in Nine European Countries

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Data from population-based cancer registries in Europe (nine countries) were used to monitor the incidence of non-Hodgkin's lymphoma in children aged 0–14 years over the 20 year period 1970–1990. The overall annual change in incidence was small—an increase of 0.76% annually, and there was no change at all in infants under one year of age. This differs markedly from the pattern in adults, where quite large increases have occurred. © **1999 Elsevier Science Ltd. All rights reserved.**

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INTRODUCTION

One of the most dramatic changes in cancer risk in recent decades has been the increase in the rates of non-Hodgkin's lymphoma (NHL) in many different countries [1, 2]. However, these changes largely reflect changes in rates amongst adults. Rather less is known of trends in childhood NHL, the third most common cancer of childhood [3]. In this study, data from population-based cancer registries in nine European countries have been used to monitor the incidence of NHL in children aged 0–14 years from 1970–1990.

MATERIALS AND METHODS

The datasets comprised anonymous listings of all cases of childhood (aged 0–14 years) lymphoma registered during the period 1970–1990, and were supplied by cancer registries in nine European countries, participating in the European Childhood Leukaemia–Lymphoma Incidence Study and other collaborative projects. Annual estimates of the childhood population at risk in the registry areas were also supplied. The registries were Bas Rhin (France), Western Switzerland (cantons of Geneva, Neuchatêl and Vaud), Finland, Norway, Slovenia, England and Wales, Scotland, Sweden and Slovakia. The relatively recent registries in France and Switzerland could provide data only since 1975.

The histological diagnosis was supplied according to the International Classification of Diseases for Oncology, or other coding schemes (Finland, Slovenia, Sweden). Cases were allocated to one of the diagnostic groups of the International Classification of Childhood Cancer [4]. For analytical purposes, categories 2b (NHL), 2c (Burkitt's lymphoma) and 2e (unspecified lymphoma) were considered as 'NHL', the latter category included on the assumption that the great majority of Hodgkin's disease cases in childhood would have been correctly diagnosed and coded as such.

Incidence rates per million person-years were calculated for age groups under 1, 1–4, 5–9 and 10–14 years, and age-standardised according to the World Standard Population for comparison between different time periods.

To examine variations in incidence between the populations and over time, Poisson regression was used to model the logarithms of the rates in terms of age, sex, registry and year of diagnosis, using the GLIM statistical software package [5].

RESULTS

A total of 2560 cases were recorded, 1833 amongst boys and 727 amongst girls. The numbers of cases in each area varied from 22 in Switzerland to 1350 from England and Wales. The great majority of cases had been microscopically verified diagnoses (MV) (97.7% in total, ranging from 93.4% in Scotland to 100% in Finland, Bas Rhin and Slovakia), although the precision of the diagnostic coding varied considerably between centres. There was little change in % MV between the two decades.

Table 1 shows the age specific incidence rates (per million) for the combined data, comparing the period of the 1970s

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Table 1. Age specific incidence rates (per million) for the combined data, comparing the period of the 1970s with the 1980s[a]

	Males		Females	
Age (years)	1970–1980	1981–1990	1970–1980	1981–1990
<1	4.4	2.4	5.5	2.6
1–4	9.3	9.2	4.0	4.9
5–9	11.4	12.3	4.3	3.9
10–14	10	11.7	4.2	4.8

[a]Incidence rates of non-Hodgkin's lymphoma (per million person-years) by sex and age and period. European registries.

Table 2. Age-standardised incidence rates (per million) for boys and girls in the 1970s and 1980s from nine different populations

	Males		Females	
	1970–1980	1981–1990	1970–1980	1981–1990
France (Bas-Rhin)	13.6	15.1	20.5	6.5
Switzerland (three registries)	13.2	12.5	4.1	0.9
Scotland	7.2	8.7	3.8	3.7
England	8.6	8.9	3.8	3.8
Finland	15.0	12.1	7.1	6.5
Norway	8.7	13.3	2.5	6.5
Sweden	12.1	12.6	4.9	4.7
Slovenia	11.3	11.3	4.4	3.8
Slovakia	14.4	17.3	5.2	6.3
Nine registries $n = 2560$	9.8	10.6	4.3	4.4

Age-standardised incidence rates (per million) in two time periods (1970–1980 and 1981–1990) in the nine European populations.

with the 1980s. Table 2 shows the age-standardised incidence rates (per million) for boys and girls at the same two time periods, from the nine different populations. The two tables indicate that there were rather higher rates for boys than for girls, except in infancy (under 1 year of age); that there was an increase in incidence between the two time periods, except in infants under one year of age, which was possibly more marked in boys than in girls. Some variation in risk between populations, and also in the changes over time between populations was seen.

These aspects were investigated with a regression model. Table 3 shows the results from sequential addition of variables to the basic model, which included only age group. The overall sex ratio (M:F) was 1/0.41 or 2.5 (model 2) but, as noted above, this differed by age (model 8), confirming the higher risk in infant girls, and a higher risks in boys thereafter.

There was significant heterogeneity of risk between the nine populations (model 3) and overall, an increase in risk with time (model 4). The annual percentage change in risk was + 0.76% (95% confidence interval (CI) + 0.10 to + 1.40).

This time trend was similar in the two sexes (model 7), but varied by age (model 5). In fact, there was a decline in risk in infants aged under 1 year (− 5.3% p.a., 95% CI − 9.6 to 1.6) compared with an increase at older ages of 0.9% pa (95% CI 0.97 to 1.11). Similarly, there was significant heterogeneity in the time trends between registries (model 6), although no one population had a change in risk which differed significantly from the overall trend of 1.0076.

DISCUSSION

The incidence of NHL in adults has shown marked increases in many countries, of as much as 3–4% per year [2, 6]. In the U.S.A. these increases have been most pronounced among the elderly, while changes in the young are small or non-existent. However, in recent years there is clearly an even more dramatic upturn in incidence in the U.S.A. due to AIDS-related NHL in young and middle-aged males [6].

Table 3. Regression analysis results

Model	Values	RR	(95% CI)	χ^2		
1. Age	<1	1				
	1–4	1.83	(1.46–2.32)			
	5–9	2.17	(1.75–2.75)			
	10–14	2.04	(1.65–2.59)			
2. Age + sex	Male	1				
	Female	0.41	(0.38–0.45)	438.3	df = 1	$P<0.001$
3. Age + sex + registry	Switzerland	1				
	Slovakia	1.40	(0.92–2.19)	105.5	df = 8	$P<0.001$
	Scotland	0.77	(0.50–1.24)			
	England	0.83	(0.55–1.29			
	Norway	0.99	(0.65–1.59)			
	Slovenia	1.03	(0.65–1.69)			
	France	1.73	(1.04–2.92)			
	Sweden	1.10	(0.73–1.74)			
	Finland	1.28	(0.84–2.03)			
4. Age + sex + registry + (year)	Year	1.0076	(1.001–1.014)	4.98	df = 1	$P<0.03$
5. Model 4 + Age*(year)				11.2	df = 3	$P<0.01$
6. Model 4 + registry*(year)				19.0	df = 8	$P<0.02$
7. Model 4 + sex*(year)				1.0	df = 1	NS
8. Model 4 + sex*age				32.9	df = 3	$P<0.001$

Square brackets denote a continuous variable. *Indicates an interaction between variables (as well as main effects). CI, confidence interval.

This seems to be less evident in Europe—a study in France showed a steep increase in incidence of NHL in adults in the 1980s (10.9% a year) without a single HIV-positive case being recorded [7] and the proportion of lymphomas of childhood which are AIDS-related must be very small in Europe. There is little evidence that the trends are birth cohort specific, however [8]. These age-specific patterns of increase are not observed in all countries, but the pattern in the U.K. appears to be similar to that in the U.S.A. (greatest increases at older ages).

The picture in childhood is much less clear. Most large-scale studies do not indicate any major changes in incidence—for example, in data from the SEER programme between 1973 and 1991 [9], in the Manchester Children's Tumour Registry (U.K.) between 1954 and 1988 [10] and in The Netherlands between 1973 and 1985 [11]. However, a significant increase of 2.9% p.a. in the 20 year period 1970–1989 was observed in the Greater Delaware Valley Tumor Registry (U.S.A.) [12]. Increases confined to boys were observed in Queensland between 1973 and 1988 [13] and (for NHL and Hodgkin's disease combined) in Denmark between 1943 and 1984 [14].

The possibility that some of the dramatic increase in the incidence of NHL in adults over the last decades is due to improved diagnosis has been critically examined by several authors [15]. Although improved diagnosis (for example, less misclassification of Hodgkin's disease, or of certain leukaemias) could account for small changes in reported incidence, the net effect is probably quite small. Such changes could account for the very small increases which we have observed in children in Europe (for example, misclassification of NHL as Hodgkin's disease which many have been greater in the 1970s than 1980s), although it should be noted that the level of microscopical verification of diagnosis was consistently high throughout the 20 year period, and there appear to be no reports of declines in childhood Hodgkin's disease.

A study of childhood leukaemia and lymphoma in The Netherlands over a 13 year period (1973–1985) did not suggest that change in diagnostic classification had occurred—the 19% of NHL cases with >25% lymphoblasts in the bone marrow, which could have been classified as lymphomatous leukaemia, were spread throughout the study period [11].

Whatever is responsible for the dramatic changes in incidence of NHL in adults, it is clear that the effect in childhood, if any, is much smaller. This supports the idea that some environmental exposure is responsible, and that this exposure(s) is specific to adulthood and/or requires a relatively prolonged duration of exposure to produce an effect. One hypothesis receiving considerable attention recently is the possible link between NHL risk and exposure to ultraviolet radiation, the latter possibly acting via immunosuppression [16, 17]. Such exposure is likely to be less in childhood than in adult life, and in any case, cannot have been very prolonged. Skin tumours (melanomatous and non-melanomatous) are rare in childhood, but are increasing in incidence in adults. Another possibility is that, given the differences in the predominant subtypes of lymphoma in children and adults, distinct aetiological factors might be involved.

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