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Patterns and Temporal Trends in the Incidence of Malignant Disease in Children: I. Leukaemia and Lymphoma

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Patterns and trends in incidence of leukaemia and lymphoma in children aged under 15 years and resident in the North Western Regional Health Authority area of England at diagnosis, over the 35-year time period 1954–1988, were analysed. The study included 1407 cases registered with the Manchester Children's Tumour Registry, 100% of which had a histologically or cytologically verified diagnosis. Log-linear modelling identified significant linear increases in acute lymphocytic leukaemia (ALL) (average quinquennial increase 4%) and Hodgkin's disease (HD) (10%), but not in acute non-lymphocytic leukaemia nor non-Hodgkin's lymphoma. Additionally, the χ^2 test for trend identified a significant increase in the incidence of chronic myeloid leukaemia. The possibility that the increases seen in ALL and HD are linked to increases in prevalence of unknown infectious agents is discussed.

Key words: childhood, leukaemia, lymphoma, incidence
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INTRODUCTION

IN ENGLAND and Wales, leukaemia and lymphoma combined accounted for approximately 45% of all malignancies in children under the age of 15 years between 1971 and 1980, and about 60% of this group of cases were acute lymphocytic leukaemia (ALL) [1]. Even though the cumulative risk of developing either leukaemia or lymphoma in childhood is low (1 in 1900 for leukaemia under the age of 15 years and 1 in 5700 for lymphoma), they represent a major paediatric health problem. The study of incidence patterns and time trends in these malignancies is important since information to assist in the planning of treatment services is provided and clues about aetiology may be gained.

There are several prerequisites for the study of cancer incidence patterns and for trends in particular. Complete ascertainment of cases from a known population throughout the time period under study is essential and diagnoses have to be both accurate and consistent over time. Mortality data can no longer be used to study incidence trends in childhood leukaemia or lymphoma because survival rates have improved substantially over the last 30 years [2, 3].

The Manchester Children's Tumour Registry (MCTR), which is population-based and has both high levels of ascertainment and diagnostic accuracy [4], was established in 1954, and is in a unique position within the U.K. to investigate childhood cancer incidence trends over several decades. Two previous reports from the MCTR for the 24-year period 1954–1977 identified an upward trend in the incidence of ALL, but no corresponding change in the incidence of acute myeloid leukaemia [5], and statistically non-significant upward trends in Hodgkin's disease (HD) and non-Hodgkin lymphoma (NHL) [6]. An analysis of the patterns and trends in incidence of leukaemia and lymphoma, by subtype, in north-west England over the 35-year period 1954–1988, using data from the MCTR and extending the previous studies, is reported here.

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PATIENTS AND METHODS

Cases for the study were ascertained from the MCTR. All instances of malignant disease and certain other neoplastic conditions diagnosed since 1954 in children aged under 15 years who were resident within the North Western Regional Health Authority (NWRHA) area (Manchester Regional Hospital Board area prior to 1974) at the time of diagnosis are registered with the MCTR. The majority of cases are notified directly by clinicians at the time of diagnosis, but a smaller number are ascertained through death registrations and cross-checking with pathology records and other cancer registries. For each registration, detailed abstracts or copies are taken from medical records and retained for future reference. Diagnosis of leukaemia is based on bone marrow specimens, although in the early years of the registry a small number of cases were classified on the basis of peripheral blood smears. From the outset, biopsy material from solid tumours, including lymphomas, has been obtained from all operations and postmortems and circulated to a panel of pathologists, thus ensuring diagnostic accuracy. Material is stored by the MCTR so that diagnoses can be reviewed when new diagnostic techniques are developed or diagnostic classifications change. Cases with no histological confirmation of diagnosis are only registered if there is convinc-

ing radiological and other clinical evidence for the presence of a tumour.

Final diagnoses are coded using both the topography and morphology codes from the first edition of the International Classification of Diseases for Oncology (ICD-O) [7], and then allocated to diagnostic groups using a classification scheme based on ICD-O and developed for childhood cancer [8]. The methods employed by the MCTR are described more fully elsewhere [4].

All cases in the MCTR diagnosed with either leukaemia or lymphoma between 1954 and 1988 inclusive were included in the study. The data abstracted from the MCTR files for each case in the study consisted of sex, age at diagnosis grouped into four categories (< 1 year, 1–4 years, 5–9 years, 10–14 years), time period of diagnosis grouped into seven quinquennia (1954–1958, 1959–1963, 1964–1968, 1969–1973, 1974–1978, 1979–1983, 1984–1988) and diagnostic group. The diagnostic groups were ALL, other lymphoid leukaemia, acute non-lymphocytic leukaemia (ANLL), chronic myeloid leukaemia (CML), other and unspecified leukaemia, HD, NHL, Burkitt's lymphoma and unspecified lymphomas. For the purposes of this study, megakaryocytic leukaemia was included with ANLL instead of with other and unspecified leukaemia as in the published classification scheme [8], and Burkitt's lymphoma was combined with the NHL group for analysis instead of being considered separately. The case data were tabulated by age group, sex, quinquennium and diagnostic group simultaneously.

Annual mid-year population estimates by sex and age group for the years 1954–1988, derived from the decennial censuses of England and Wales, and adjusted for births, deaths and migration, were obtained from the NWRHA statistics unit. These were summed to produce estimates of person-years at risk by sex, age group and quinquennium defined as above. Prior to 1974, the annual population of the region aged below 15 years was approximately 1 000 000, from 1974 onwards, it was approximately 850 000.

Analyses were carried out separately for each diagnostic group with sufficiently large numbers. Age group-, sex- and quinquennium-specific annual incidence rates per million population were calculated. To allow for the change in childhood age distribution over time, incidence rates for the age group 0–14 years were age-standardised by the direct method using the world standard childhood population [9] and those for the entire time period were similarly standardised by taking a weighted average of the rates within individual quinquennia such that the weights used (0.15, 0.15, 0.16, 0.16, 0.14, 0.125, 0.115) were in proportion to the total person-years in each quinquennium. Standardisation of rates for males and females combined was not necessary.

χ^2 tests for heterogeneity between overall rates in sexes, age groups and time periods and for a linear trend over time period were carried out [10] using the computer package EPILOG [11]. Minimum numbers for application of the χ^2 test were 10 for comparison of rates between sexes, 40 for comparison between age groups and 20 for comparison between time periods. To allow for the change in childhood age distribution over time, expected numbers for the tests between rates in time periods were initially calculated within the eight sex/age group strata, using the overall within-strata observed rates, and then summed over strata to obtain total expected numbers. For tests between rates in sexes and in age groups, the expected numbers were calculated in a similar way.

To examine further the patterns in incidence rates and quantify the magnitude of effects, log-linear modelling was undertaken [10] for each diagnostic group with more than 50 cases using the computer package GLIM [12]. Various statistical models were fitted to the tabulated case data in which it was assumed that the number of cases in each category followed a Poisson distribution, with mean equal to the product of the person-years at risk and the incidence rate, and that the incidence rate was a product of factors depending on age group, sex, quinquennium and interactions between these. The variation of incidence rates over time was of special interest and, in particular, whether or not they displayed similar temporal trends for both sexes and all age groups, or exhibited a constant proportional increase from one time period to the next (i.e. a linear trend on a log scale). Initially, main effects and interactions were included in the models and their statistical significance was assessed by the maximum likelihood ratio test. Factors with a P-value greater than 0.1 were removed from the models in a stepwise manner. However, if an interaction was included, all the corresponding lower order interactions and main effects were automatically included. When no further factors could be eliminated from a model, excluded factors were individually assessed, and those found to be significant at the 0.1 level were added. This process was repeated until no more factors could be added or removed. Once a final model has been identified for each diagnostic group, the scaled deviances and residuals were examined for lack of fit. Maximum likelihood estimates of relative risks and corresponding 95% confidence intervals were calculated from the parameters of the models.

RESULTS

The number of cases identified for the study was 1407, which included 1 case classified as other lymphoid leukaemia, 3 as other and unspecified leukaemia and 2 as unspecified lymphoma. The 6 cases listed above were excluded from all further analyses. The remaining 1401 consisted of 881 cases of ALL, 203 of ANLL, 21 of CML, 137 of HD and 159 of NHL. Diagnosis was based on the histological examination of bone marrow or biopsy material for 94% of cases, the remaining 6% were all leukaemias diagnosed from a blood film, mainly in the early years of the study period.

Table 1 shows the numbers of cases by age group, sex and diagnosis for the entire 35 year period 1954–1988 and average annual incidence rates (per 1 000 000 population). ALL was the most frequently diagnosed condition, with a standardised average annual incidence rate of 27.6 per 1 000 000 population, with the rate for ANLL (6.1 per 1 000 000) being just under a quarter of that for ALL. NHL had a slightly greater standardised average annual incidence than HD (4.7 versus 3.8 per 1 000 000) and CML was rare with a rate of 0.6 per 1 000 000. The incidence of ALL, CML, HD and NHL was higher in males than in females, and these differences achieved statistical significance, except for CML where it was of borderline significance. ANLL had a borderline significantly higher incidence in females than in males. There were too few cases of CML to enable χ^2 tests for heterogeneity between age groups to be performed. There was significant variation in incidence between age groups for ALL, HD and NHL but not for ANLL; when enough cases were available to consider the sexes separately, the same results were observed, except for NHL in females.

In Table 2, the numbers of cases and incidence rates are shown by time period for each diagnostic group. Over the 35-year period, there has been a significant upward trend in the overall incidence of ALL, CML and HD, although the incidence of ANLL and NHL has not varied significantly overall. Inci-

Table 1. Number of cases and average annual incidence (per million population) by age group, sex and diagnosis, 1954–1988

		Age group (years)										χ^2 tests for heterogeneity P values	
		< 1		1–4		5–9		10–14		0–14			
Diagnostic group	Sex	No	Rate	No	Rate	No	Rate	No	Rate	No	Rate	Age	Sex
Acute lymphocytic leukaemia	M	16	13.6	254	55.0	152	26.7	91	15.8	513	31.3	< 0.00001	
	F	15	13.9	193	43.9	99	18.4	61	11.0	368	23.8	< 0.00001	
	Total	31	13.7	447	49.6	251	22.6	152	13.5	881	27.6	< 0.00001	0.00004
Acute non-lymphocytic leukaemia	M	5	4.1	27	5.7	25	4.4	34	6.0	91	5.3	0.61	
	F	7	6.2	33	7.5	38	7.1	34	6.3	112	6.9	0.92	
	Total	12	5.2	60	6.6	63	5.7	68	6.2	203	6.1	0.83	0.065
Chronic myeloid leukaemia	M	0	0.0	4	0.9	5	0.9	6	1.0	15	0.8	*	
	F	0	0.0	1	0.3	0	0.0	5	0.9	6	0.3	*	
	Total	0	0.0	5	0.6	5	0.4	11	1.0	21	0.6	*	0.065
Hodgkin's disease	M	0	0.0	12	2.5	27	4.7	63	11.1	102	5.5	< 0.00001	
	F	0	0.0	0	0.0	7	1.3	28	5.2	35	1.9	*	
	Total	0	0.0	12	1.3	34	3.1	91	8.2	137	3.8	< 0.00001	< 0.00001
Non-Hodgkin's lymphoma	M	1	0.9	35	7.6	46	8.1	27	4.6	109	6.4	0.009	
	F	0	0.0	12	2.8	22	4.0	16	2.9	50	3.0	0.17	
	Total	1	0.4	47	5.3	68	6.1	43	3.8	159	4.7	0.001	0.00001

M, male; F, female. *Not done.

Table 2. Number of cases and average annual incidence (per million population) by time period and diagnosis, 1954–1988

	Time period														χ^2 test P values	
	1954–1958		1959–1963		1964–1968		1969–1973		1974–1978		1979–1983		1984–1988		Heterogeneity	Trend
Diagnostic group	No.	Rate	No.	Rate	No.	Rate	No.	Rate	No.	Rate	No.	Rate	No.	Rate		
Acute lymphocytic leukaemia	115	24.0	126	26.1	129	24.7	158	30.1	133	30.8	119	31.3	101	27.2	0.20	0.04
Acute non-lymphocytic leukaemia	31	6.4	37	7.3	29	5.5	31	5.6	27	5.6	19	4.6	29	7.6	0.57	0.65
Chronic myeloid leukaemia	2	0.4	1	0.2	1	0.2	3	0.5	6	1.1	5	1.3	3	0.7	0.22	0.04
Hodgkin's disease	16	3.2	10	1.8	23	4.3	25	4.4	23	4.2	15	2.9	25	5.8	0.05	0.03
Non-Hodgkin's lymphoma	19	3.9	22	4.4	19	3.6	29	5.3	31	6.8	23	5.2	16	4.0	0.36	0.22

Table 3. Acute lymphocytic leukaemia: number of cases and average annual incidence (per million population) by age-group, sex and time period 1954–1988

Age group (years)		1954–1958		1959–1963		1964–1968		1969–1973		1974–1978		1979–1983		1984–1988		χ^2 test P values	
	Sex	No.	Rate	No.	Rate	No.	Rate	No.	Rate	No.	Rate	No.	Rate	No.	Rate	Heterogeneity	Trend
< 1	M	2	11.7	6	31.6	1	4.9	2	10.9	1	7.8	2	14.8	2	14.2	ND	ND
	F	1	6.2	1	5.5	2	10.4	4	23.2	1	8.3	4	31.2	2	14.9	ND	ND
1–4	M	31	41.8	38	53.5	40	49.3	48	62.1	39	67.4	33	64.9	25	46.4	0.34	0.21
	F	33	47.5	20	29.7	31	40.3	34	46.4	27	49.3	23	47.5	25	48.7	0.62	0.29
5–9	M	21	25.7	23	28.0	22	24.7	28	28.8	26	30.6	16	23.1	16	25.1	0.97	0.90
	F	9	11.6	17	21.6	18	21.3	18	19.5	11	13.7	15	23.0	11	18.2	0.60	0.58
10–14	M	12	15.5	10	11.8	7	8.7	19	21.9	17	19.6	14	16.8	12	17.5	0.38	0.24
	F	6	8.1	11	13.5	8	10.4	5	6.0	11	13.3	12	15.2	8	12.3	0.60	0.37

M, male; F, female; ND, not done.

Table 4. Poisson regression modelling of incidence rates: maximum likelihood ratio tests for inclusion/removal of effects from final models

Diagnostic group		Age	Sex	Age–sex Interaction	Linear time trend		Non-linear time trend	
					Uniform*	Age–sex dependent	Uniform*	Age–sex dependent
Acute lymphocytic leukaemia	χ^2	250	16.96	1.70	4.19	5.28	4.41	37.69
	df	3	1	3	1	10	5	50
	P value	< 0.00001	0.00004	0.6	0.04	0.9	0.5	0.9
Acute non-lymphocytic leukaemia	χ^2	0.90	3.39	2.39	0.23	11.01	4.92	43.98
	df	3	1	6	1	14	6	54
	P value	0.8	0.07	0.9	0.7	0.7	0.5	0.8
Hodgkin's disease	χ^2	ND	ND	8.74	4.70	2.77	8.47	22.40
	df			2	1	5	5	35
	P value			0.01	0.03	0.7	0.14	0.96
Non-Hodgkin's lymphoma	χ^2	20.925	19.483	2.179	1.481	9.703	6.42	45.351
	df	3	1	3	1	11	6	51
	P value	0.0001	0.00001	0.5	0.2	0.5	0.4	0.7

*Identical for each sex and age group combination. df, Degrees of freedom; ND, not done since age–sex interaction significant.

dence rates for ALL, the largest diagnostic group, are shown in Table 3 by time period within sex/age group strata. There were no significant time trends within any of the strata.

Modelling was carried out for all groups except CML, and the results are shown in Tables 4–7. Table 4 shows comparisons of selected models with the final model. The results of significance tests for removing individually factors included in the final model are shown with P values less than 0.1. Tests between models containing additional factors and the final models are shown with P values greater than or equal to 0.1. Because the tests are relative to the final model, they do not represent the actual steps in the modelling process, and also the degrees of freedom (df) vary between diagnostic groups. For example, the final model for ALL includes age, sex and a uniform linear time trend, and the model that also includes an age–sex interaction accounts for a further 3 df. However, the final model for ANLL includes only sex and the model that also includes an age–sex interaction must also include the main effects of age, which accounts for a total of 6 df. The df for HD are less than for other diagnostic groups because no cases were diagnosed under 1 year of age. The absence of all age–sex interactions in the underlying rates implies that in every time period the risk in females relative to males is identical across age groups, and that the risk in one age group relative to another is the same for both sexes. A linear time trend is equivalent to a constant relative risk between adjacent time periods. For each diagnostic group, Tables 5–7

Table 5. Estimates of risk in females relative to males allowing for age group and time period

Diagnosis	Relative risk	95% confidence interval
Acute lymphocytic leukaemia	0.76	0.66–0.86
Acute non-lymphocytic leukaemia	1.30	0.98–1.71
Hodgkin's disease		
1–4 years	0	—
5–9 years	0.27	0.12–0.63
10–14 years	0.47	0.30–0.73
Non-Hodgkin's lymphoma	0.48	0.35–0.68

Table 6. Estimates of risk in each age group relative to age group with highest estimated incidence rate allowing for sex and time period

	Age group (years)							
	< 1		1–4		5–9		10–14	
Diagnosis	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
Acute lymphocytic leukaemia	0.28	0.20–0.40	1	—	0.46	0.39–0.54	0.28	0.23–0.33
Acute non-lymphocytic leukaemia	0.81	0.44–1.51	1	—	0.86	0.61–1.23	0.93	0.66–1.32
Hodgkin's disease								
Male	0	—	0.24	0.13–0.44	0.43	0.28–0.68	1	—
Female	0	—	0	—	0.25	0.11–0.58	1	—
Non-Hodgkin's lymphoma	0.07	0.01–0.52	0.85	0.58–1.23	1	—	0.63	0.43–0.92

RR, Relative risk; CI, confidence interval.

contain estimates of the relative risk and 95% confidence intervals for females relative to males, each age group relative to the age group with the highest estimated incidence and for each time period relative to the preceding time period; the effects of the other two variables are controlled for in all tables. If any of these relative risks depends upon one of the other two variables, the tables contain multiple entries.

For ALL, there was a significant linear increase in incidence over time which did not vary significantly by age group or sex; there was no evidence of a non-linear time effect. The age–sex interaction was non-significant, but the variation in incidence by both age and sex was highly significant. Males had a higher incidence than females, and the age group of greatest risk was 1–4 years.

The results for ANLL are quite different from those of ALL. There is no evidence of variation in incidence rates over time or with age, but there is a suggestion that rates in females are higher than in males.

HD has shown a significant linear increase in incidence over time which did not vary substantially by age or sex. The risk in females relative to males changed significantly with age group, it was always less than 1 but increased with age. No cases were seen under the age of 1 year in either sex, in females no cases were seen under 5 years of age and the incidence increased with age in both sexes.

There were no significant time trends in the incidence of NHL nor age–sex interactions in relative risk. The differences in incidence between sexes and age groups were highly significant; the incidence in males was approximately double that in females, only 1 case was seen under the age of 1 year and the incidence rate peaked in the 5–9 years age group.

Table 7. Estimates of risk in one time period relative to preceding time period allowing for sex and age group*

Diagnosis	Relative risk	95% confidence interval
Acute lymphocytic leukaemia	1.036	1.002–1.072
Acute non-lymphocytic leukaemia	0.98	0.92–1.06
Hodgkin's disease	1.10	1.01–1.20
Non-Hodgkin's lymphoma	1.05	0.97–1.14

*Estimates obtained from fitting time as a linear trend in log linear model.

Examination of the scaled deviance and residuals from the final models indicated a reasonable fit to the incidence rates for each of the four diagnostic groups.

Figures 1–5 show the age standardised annual incidence (per 1 000 000 population) by time period for males and females separately for ALL, ANLL, CML, HD and NHL together with the rates predicted by the final models except for CML.

DISCUSSION

In order to examine trends in incidence, it is essential that throughout the time period under study case ascertainment is unbiased and has a high level of completeness, and that diagnoses are made in a consistent fashion. It has been estimated that the level of completeness achieved by the MCTR during the first 20 years of operation was between 95 and 98% [13], and *ad hoc* checks since have not revealed any reduction. The MCTR maintains a collection of clinical records and pathology material

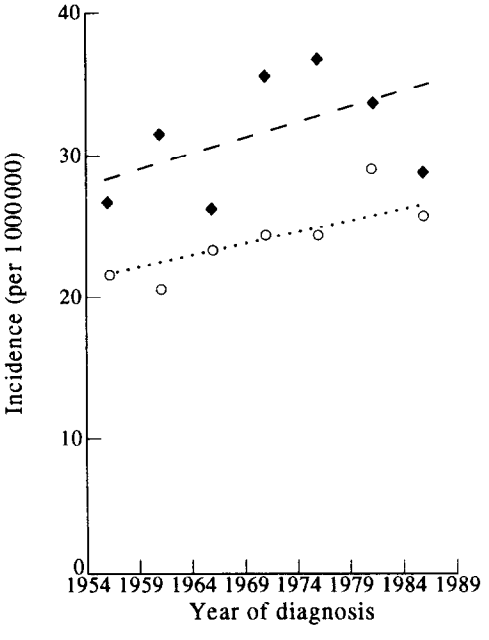

Figure 1. Acute lymphocytic leukaemia: age-standardised annual incidence (per 10^6) by time period for males and females. ♦ Male incidence, ○ female incidence. - - - Male regression curve, . . . female regression curve.

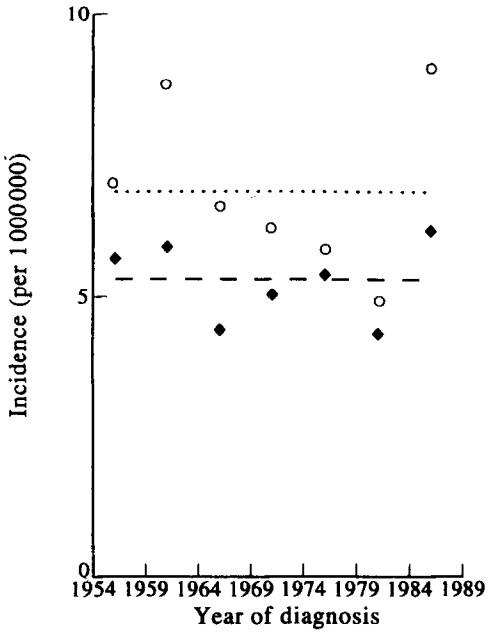

Figure 2. Acute non-lymphocytic leukaemia: age-standardised annual incidence (per 10^6) by time period for males and females. ♦ Male incidence, ○ female incidence. - - - Male regression curve, . . . female regression curve.

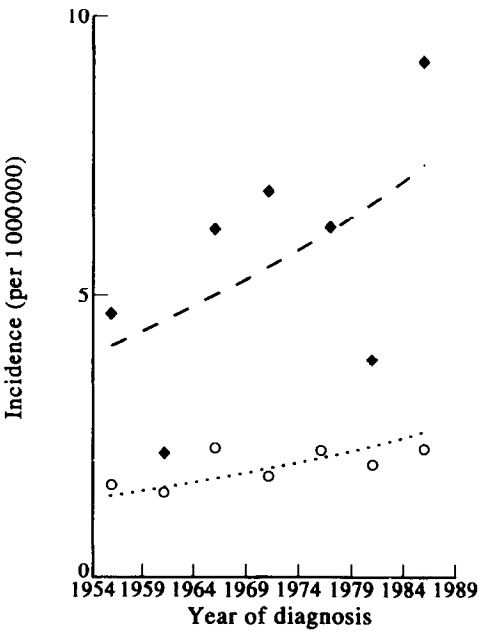

Figure 4. Hodgkin's disease: age-standardised annual incidence (per 10^6) by time period for males and females. ♦ Male incidence, ○ female incidence. - - - Male regression curve, . . . female regression curve.

so that diagnoses can be reviewed when appropriate. For all cases in this study, the diagnosis was based on the histological and/or cytological examination of bone marrow, biopsy material and blood smears, and we conclude that the observed significant increases in incidence are likely to be real rather than due to artifacts in the data. The fact that these increases were specific to particular disease groups adds weight to this conclusion.

In general, previous studies have considered trends in incidence either for all children as a single group or for several groups separately, defined in terms of age and sex, and have made no attempt to formally test the null hypothesis that trends are identical for both sexes and all age groups. In this study, one of the main objectives was to determine whether or not differential incidence trends existed between sexes or age groups. The χ^2 test identified a significant trend in the incidence of ALL overall, but not in any of the individual sex/age group strata; this discrepancy could be accounted for by the reduced power within

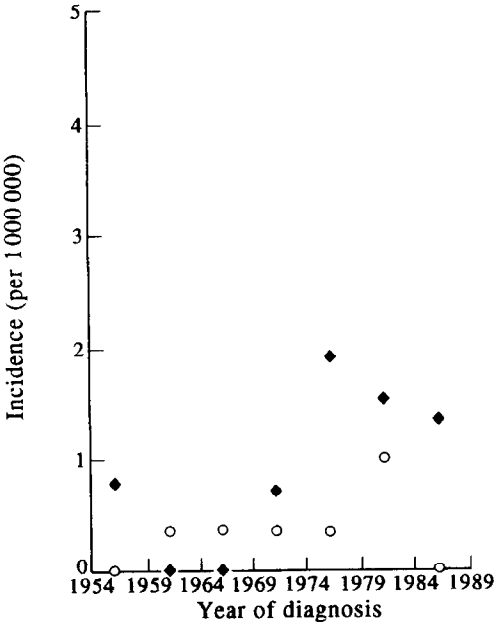

Figure 3. Chronic myeloid leukaemia: age-standardised annual incidence (per 10^6) by time period for males and females. ♦ Male incidence, ○ female incidence.

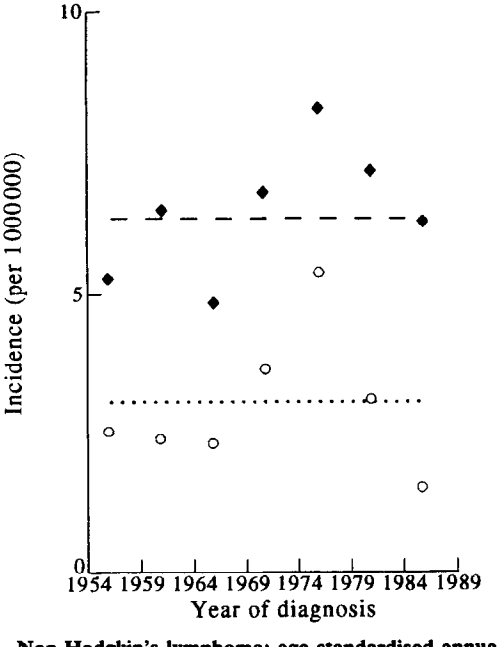

Figure 5. Non-Hodgkin's lymphoma: age standardised annual incidence (per 10^6) by time period for males and females. ♦ Male incidence, ○ female incidence. - - - Male regression curve, . . . female regression curve.

the strata to detect trends. The χ^2 test also identified significant trends in the overall incidence of CML and HD, but not ANLL and NHL. When log-linear models were fitted to all diagnostic groups, except CML for which there were insufficient cases, statistically significant increases in the incidence of ALL and HD were detected over the 35-year time period 1954–1988. On a log scale, these trends were not significantly non-linear and did not vary significantly by sex or age group. Over the same time period, the incidence of ANLL and NHL did not exhibit a significant change overall nor significantly different temporal trends between age groups or sexes. However, it should be noted that the power to detect time trends will decrease both with the size of the trend and the underlying incidence rate, and the power to detect dissimilar time trends in sexes or age groups with a low incidence will be small. The same is also true for age–sex interactions. Conversely, multiple tests of time trends and other factors have been carried out, and it is possible that some significant results are due to chance alone. Nevertheless, the models upon which these results are based provided a reasonable fit to the data. It is possible that other models, such as age–period–cohort models, not considered in this analysis could fit the data at least as well as the final models and provide alternative interpretations. It is planned to fit age–period–cohort models to ALL incidence rates in the future.

Between 1954 and 1988, the estimated percentage increase in annual incidence of ALL in North West England was 4% per 5-year time interval; this was slightly less than but compatible with that previously reported for the period 1954–1977 [5], and the recent data show that the previously reported increase in incidence has been maintained. An increase in childhood ALL in Great Britain in children born between 1964 and 1978 has also been reported [14]. CML in childhood is rare, and the observation in this study of a significant increase in overall incidence is based on only 21 cases occurring over 35 years. The incidence of HD has increased on average by an estimated 10% every 5 years over the period of the study. A significant upward trend in the incidence of childhood HD has not previously been reported in the U.K.

In a study which used data from the first four volumes of *Cancer Incidence in Five Continents* [15], there was no evidence for an overall worldwide increase in the incidence of leukaemia, but between areas there was great variation in trends. There was some evidence for a worldwide increase in the incidence of HD, but none for NHL.

There have been several other studies of incidence trends in childhood leukaemia and lymphoma [16–26]; the patterns seen in the MCTR data are not present in all of these. The results of the study from the Connecticut Tumour Registry, covering the years 1935–1979 [16], were generally consistent with those of the present study apart from leukaemia other than ALL (predominantly acute and chronic myelocytic and monocytic) for which significant decreases were seen in females aged under 10 years. The trends in Queensland, Australia in children aged less than 13 years between 1973 and 1988 [25] followed a different pattern; a significant increase in ANLL and in NHL in males, a significant decrease in HD and a non-significant trend in ALL were observed, although the number of cases was less than half those in the present study.

There has been much recent speculation about a possible infective aetiology for childhood leukaemia and, in particular, in relation to the 'common' immunophenotypic sub-type of ALL. Data relating to such hypotheses have been recently reviewed by Alexander [27]. One possible explanation for the increase in incidence of ALL seen in the present study might be an increased prevalence of relevant infectious aetiological agents. If such an infectious agent(s) is responsible for the increased incidence, then it would appear that the various age groups are equally affected. This would be compatible with the aberrant response model (an extension of the Greaves hypothesis for the childhood peak to all childhood ALL) described by Alexander [27].

An infectious aetiology for at least a portion of childhood HD has also been suggested [28]. Again, if an infectious agent(s) was involved in the increase in incidence of HD found in the present study, then the influence of such an agent(s) cannot be specific to any particular age-group.

Some data suggest that ALL rates might be higher in rural than in urban areas [27]. In order to explore the hypothesis that the observed increase might be more marked in rural areas, the cases were classified as urban or rural on the basis of their address at diagnosis, using an Office of Population Censuses and Surveys categorisation of the electoral wards as defined at the time of the 1981 census [29]. Cases resident in wards categorised as 'wholly' or 'predominantly' urban were allocated to the urban group and the remainder to the rural group. However, the area covered by the MCTR is mainly urban and only 12 cases of ALL occurred in rural areas.

Reasons for the observed increases in incidence of childhood ALL and HD are, therefore, at present unclear. Analyses of spatial and temporal clustering of cases are planned and may shed some light on possible aetiological factors.

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Patterns and Temporal Trends in the Incidence of Malignant Disease in Children: II. Solid Tumours of Childhood

V. Blair and J.M. Birch

Incidence patterns and trends, in children, of individual types of non-reticulo-endothelial solid tumours and of all cancers combined (including leukaemia and lymphoma) were analysed. The study included 3360 cases diagnosed in residents under 15 years of age of the North Western Regional Health Authority area of England during 1954–1988. Log-linear modelling identified significant increases of juvenile astrocytoma (average quinquennial increase 15%) in males, of medulloblastoma (19%) and neuroblastoma (17%) in females, and of non-skin epithelial tumours (18%) overall, and a significant decrease of unspecified malignant neoplasms around 1974 by approximately 80%. The χ^2 trend test identified significant increases in gonadal germ cell tumours and skin cancers, and borderline significant increases in craniopharyngioma and hepatoblastoma. The incidence of all cancers combined increased significantly in those aged under 1 year (8%), 1–4 years (5%) and 10–14 years (8%). Age–sex patterns were similar to those in other Caucasian populations. Studies of incidence trends can provide the basis for investigations of the aetiology of childhood cancers.

Key words: childhood, neoplasms, incidence
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INTRODUCTION

NON-RETICULO-ENDOTHELIAL (RE) solid tumours (hereafter referred to as solid tumours) accounted for 55% of childhood malignancies in England and Wales during 1971–1980, just under half of these occurred in the central nervous system (CNS) [1]. There are fewer published studies of incidence of solid tumours in childhood than of haematopoietic and RE neoplasms. Studies of incidence patterns in neoplastic disease are important for several reasons; they may provide an indication that levels of environmental carcinogens are changing, identify aetiological factors which could ultimately lead to the development of preventative measures and supply information for the planning

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