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Sex-specific patterns and trends in the incidence of hematologic malignancies in 0-24 year olds from Northern England, 1968-2005

Sex-specific patterns and trends in the incidence of childhood cancer have consistently been demonstrated,[1] and can provide insights into pathogenesis. Unfortunately often only pooled results have been given. Potentially this may have masked sex-specific temporal trends, especially over a prolonged time period.

A previous study from the Northern Region of England examined the incidence of leukemias and lymphomas diagnosed in cases aged 0–24 years during the period 1968–1995.[2] This analysis found an overall increase in the incidence in the area. Similar increases have been found in other studies from the UK and elsewhere.[1]

The aim of the present study was to update the previous analyzes from the Northern Region and to determine whether there were sex-specific trends in incidence. We analysed all hematologic malignancies diagnosed in cases aged 0–24 years who were resident in the Northern Region during the period 1968 – 2005. Analyses were made separately for boys and girls (aged 0-14) and adolescent/young adult males and females (aged 15-24).

Case details were extracted from the specialist Northern Region Young Persons' Malignant Disease Registry (NRYPMDR). All cases of cancer within the region occurring in residents aged less than 25 years are reported to the registry. Data are carefully cross-checked with regional and national cancer registries at regular intervals. This guarantees that information is very accurate and complete. The overall completeness of ascertainment for cases aged 0-24 years has been estimated to be more than 98%.[2] The International Classification of Diseases for Oncology (ICDO-2) was used for coding morphology and primary site of diagnosis.[3] Cases were grouped using the International Classification of Childhood Cancer (ICCC).[4]

The NRYPMDR is exempted (under Section 60 of the UK Health and Social Care Act 2001) from the need to obtain patient consent for recording and analysis of data.

Age-standardized rates (ASRs) and 95% confidence intervals (CIs) were calculated based on a standard world population.[5] Rates were calculated for the entire study period (1968–2005) and for three shorter time periods (1968–1980, 1981–1993, 1994–2005). Temporal trends in annual ASRs were analyzed using linear regression. Statistical significance was taken as $p<0.05$.

Full results are given in Tables 1 and 2. For both sexes lymphoid leukemia predominates in the younger age-group whilst Hodgkin's lymphoma (HL) predominates in the older age-group. There is a striking surplus of male over female cases of childhood lymphoma. This excess is less marked in the adolescent/young adult age group. There was an overall statistically significant increase in the incidence of hematologic malignancies in boys (0.6% per annum, 95% CI: 0.1% to 1.2%) and an overall significant decrease in adolescent/young adult males (-1.0% per annum, 95% CI: -1.9% to -0.1%). However, these overall trends obscure the pattern of changes in incidence in specific diagnostic groups. For the leukemias there was a marginally significant increase for boys (0.5% per annum, 95% CI: -0.1% to 1.2%), which was driven by childhood peak cases (1-4 years). There was no evidence for any significant temporal changes for older males or for females of any age. In contrast, for lymphomas there was a significant upward trend for childhood cases of lymphoma in girls (3.5% per annum, 95% CI: 1.3% to 5.6%), due to a marked increase in the incidence of HL. A significant downward trend in the incidence of adolescent/young adult cases of lymphoma in males (-1.4% per annum, 95% CI: -2.5% to -0.3%) was due to a decrease in the incidence of HL (-1.8% per annum, 95% CI: -3.0% to -0.5%).

Increases in the incidence of childhood leukemia have been previously reported from the UK, Europe and the USA, which were especially marked for childhood peak cases.[6] The present study has shown that the upward trend was confined to males diagnosed with lymphoid leukemia at ages 1-4 years. Current epidemiological evidence suggests a role for infections in etiology,[6] possibly in combination with other environmental agents.[1] The male-specific increase in the incidence of lymphoid leukemia in the Northern Region is consistent with greater susceptibility of boys to an etiological agent.

Higher risk of childhood leukemia has been associated

Table 1. Numbers of cases aged 0-14 years, age-standardized rates (per million population) and 95% CIs, average annual percentage rate changes and 95% CIs, by diagnosis, sex and time period and test for sex-difference in temporal trend (*p* value).

		1968-1980		*1981-1993*		*1994-2005*		*1968-2005*		*% Ann.Inc*	*M/F diff*
Leukemias	M	181	40.5 (34.5,46.5)	173	46.7 (39.7,53.7)	153	48.8 (40.9,56.6)	507	44.8 (40.9,48.8)	0.5 (-0.1,1.2)	0.58
	F	141	33.7 (28.0,39.3)	142	40.5 (33.8,47.3)	104	35.2 (28.4,42.1)	387	36.3 (32.6,40.0)	0.2 (-0.6,1.1)	
Lymphoid leukemia	M	149	33.7 (28.2,39.2)	149	40.6 (34.0,47.1)	129	41.3 (34.1,48.6)	427	38.1 (34.4,41.7)	0.7 (-0.1,1.4)	0.33
	F	110	26.8 (21.8,31.9)	127	36.3 (29.9,42.7)	78	26.3 (20.4,32.2)	315	29.7 (26.4,33.0)	0.1 (-0.9,1.0)	
Acute non-lymphocytic	M	30	6.4 (4.1,8.7)	19	4.9 (2.9,7.7)	20	6.4 (3.9,9.9)	69	5.9 (4.5,7.3)	-0.6 (-2.5,1.4)	0.36
	F	26	5.7 (3.7,8.4)	12	3.4 (1.8,6.0)	20	7.0 (4.2,10.8)	58	5.3 (3.9,6.7)	1.0 (-1.6,3.6)	
Chronic myeloid	M	1	0.2 (0.0,1.0)	4	0.9 (0.3,2.4)	3	0.8 (0.2,2.4)	8	0.6 (0.3,1.2)	4.0 (-2.2,10.1)	0.29
	F	3	0.7 (0.1,2.2)	2	0.5 (0.1,2.0)	2	0.6 (0.1,2.0)	7	0.6 (0.2,1.3)	-1.2 (-8.5,6.2)	
Other specified	M	1	0.2 (0.0,1.0)	0	–	1	0.2 (0.0,1.4)	2	0.1 (0.0,0.5)	1.2 (-11.6,14.0)	0.56
	F	0	–	1	0.3 (0.0,1.5)	2	0.6 (0.1,2.4)	3	0.3 (0.1,0.8)	6.3 (-4.5,17.1)	
Unspecified	M	0	–	1	0.3 (0.0,1.7)	0	–	1	0.1 (0.0,0.6)	-1.2 (-19.1,16.7)	0.78
	F	2	0.4 (0.0,1.4)	0	–	2	0.8 (0.1,2.9)	4	0.4 (0.1,1.0)	1.6 (-7.6,10.8)	
Lymphomas	M	73	14.2 (10.9,17.5)	74	17.9 (13.8,22.0)	66	18.1 (13.7,22.6)	213	16.4 (14.2,18.7)	0.9 (-0.1,1.9)	0.04
	F	20	4.1 (2.5,6.3)	20	5.4 (3.2,8.3)	33	9.4 (6.2,12.7)	73	6.0 (4.6,7.4)	3.5 (1.3,5.6)	
Hodgkin's lymphoma	M	34	6.2 (4.1,8.3)	35	8.3 (5.5,11.0)	34	9.0 (5.9,12.0)	103	7.6 (6.1,9.1)	1.6 (0.2,3.0)	0.22
	F	7	1.4 (0.5,2.8)	5	1.2 (0.4,2.7)	13	3.4 (1.8,5.8)	25	1.9 (1.2,2.7)	4.3 (0.2,8.4)	
Non-Hodgkin's lymphoma	M	39	8.0 (5.4,10.5)	36	8.8 (5.9,11.7)	16	4.8 (2.7,7.8)	91	7.3 (5.8,8.8)	-1.9 (-3.7,-0.1)	0.03
	F	13	2.7 (1.4,4.7)	13	3.6 (1.9,6.2)	14	4.3 (2.3,7.3)	40	3.5 (2.4,4.5)	1.5 (-1.0,4.1)	
Burkitt's lymphoma	M	0	–	2	0.5 (0.1,1.9)	14	3.9 (2.1,6.5)	16	1.2 (0.7,2.0)	11.9 (6.9,16.8)	0.84
	F	0	–	2	0.6 (0.1,2.1)	6	1.7 (0.6,3.8)	8	0.7 (0.3,1.3)	10.9 (2.5,19.3)	
Misc. lymphoreticular	M	0	–	0	–	1	0.3 (0.0,1.6)	1	0.1 (0.0,0.4)	10.3 (-8.9,29.6)	—
	F	0	–	0	–	0	–	0	–	–	
Unspecified lymphomas	M	0	–	1	0.3 (0.0,1.7)	1	0.3 (0.0,1.6)	2	0.2 (0.0,0.7)	2.3 (-11.3,15.8)	–
	F	0	–	0	-	0	–	0	–	–	
TOTAL	M	254	54.6 (47.8,61.5)	247	64.6 (56.5,72.7)	219	66.9 (57.9,75.9)	720	61.3 (56.7,65.8)	0.6 (0.1,1.2)	0.90
	F	161	37.7 (31.8,43.6)	162	45.9 (38.8,53.0)	137	44.7 (37.1,52.3)	460	42.3 (38.4,46.2)	0.7 (-0.1,1.5)	

*Figures are counts, ASRs with 95% CIs, Annual Percentage Change in ASR with 95% CIs (estimated from linear regression model) and p value for testing M/F difference in trend (obtained from year *sex interaction term in linear regression model).*

Table 2. Numbers of cases aged 15-24 years, age-standardized rates (per million population) and 95% CIs, average annual percentage rate changes and 95% CIs, by diagnosis sex and time period and test for sex-difference in temporal trend (*p* value).

		1968-1980		*1981-1993*		*1994-2005*		*1968-2005*		*% Ann Inc*	*M/F diff*
Leukemias	M	70	23.6 (18.1,29.1)	72	24.9 (19.2,30.7)	54	23.9 (17.5,30.3)	196	24.1 (20.7,27.5)	-0.2 (-1.7,1.3)	0.93
	F	44	15.1 (10.6,19.5)	45	15.7 (11.1,20.3)	33	15.0 (9.9,20.1)	122	15.3 (12.5,18.0)	-0.1 (-1.7,1.5)	
Lymphoid leukemia	M	28	9.5 (6.3,13.8)	40	13.9 (9.6,18.2)	26	11.5 (7.5,16.9)	94	11.6 (9.3,14.0)	0.6 (-1.3,2.5)	0.71
	F	21	7.2 (4.5,11.0)	21	7.4 (4.5,11.3)	17	7.8 (4.5,12.5)	59	7.4 (5.5,9.3)	-0.1 (-3.0,2.8)	
Acute non-lymphocytic	M	27	9.1 (6.0,13.3)	26	9.0 (5.9,13.2)	19	8.5 (5.1,13.3)	72	8.9 (6.8,11.0)	-0.8 (-3.0,1.4)	0.71
	F	19	6.5 (3.9,10.1)	19	6.6 (3.9,10.3)	12	5.4 (2.8,9.4)	50	6.2 (4.5,7.9)	-0.2 (-2.8,2.5)	
Chronic myeloid	M	11	3.6 (1.8,6.5)	5	1.7 (0.5,3.9)	7	3.0 (1.2,6.3)	23	2.8 (1.7,4.1)	-0.9 (-5.0,3.1)	0.23
	F	1	0.3 (0.0,1.8)	4	1.4 (0.4,3.5)	3	1.3 (0.3,3.8)	8	1.0 (0.4,1.9)	3.4 (-2.4,9.3)	
Other specified	M	0	–	0	–	2	0.8 (0.1,3.1)	2	0.2 (0.0,0.8)	14.5 (-0.5,29.6)	0.08
	F	1	0.4 (0.0,2.0)	1	0.4 (0.0,2.1)	0	–	2	0.3 (0.0,0.9)	-4.4 (-18.4,9.6)	
Unspecified	M	4	1.3 (0.3,3.3)	1	0.4 (0.0,2.0)	0	–	5	0.6 (0.2,1.4)	-8.0 (-14.5,-1.6)	0.57
	F	2	0.7 (0.1,2.5)	0	-	1	0.5 (0.0,2.6)	3	0.4 (0.1,1.2)	-4.4 (-14.8,6.0)	
Lymphomas	M	163	54.5 (46.1,62.8)	170	57.3 (48.6,65.9)	80	35.0 (27.3,42.7)	413	50.1 (45.2,54.9)	-1.4 (-2.5,-0.3)	0.09
	F	84	28.3 (22.2,34.3)	120	40.2 (33.0,47.4)	64	28.8 (21.7,35.8)	268	32.8 (28.8,36.7)	0.0 (-1.2,1.2)	
Hodgkin's lymphoma	M	129	42.9 (35.5,50.3)	120	40.4 (33.1,47.6)	55	24.1 (17.7,30.4)	304	36.7 (32.6,40.9)	-1.8 (-3.0,-0.5)	0.06
	F	65	21.8 (16.5,27.2)	95	31.9 (25.4,38.3)	49	22.0 (15.8,28.2)	209	25.5 (22.1,29.0)	0.0 (-1.3,1.4)	
Non-Hodgkin's lymphoma	M	33	11.2 (7.4,15.1)	42	14.3 (10.0,18.7)	19	8.2 (5.0,12.9)	94	11.5 (9.2,13.8)	-1.1 (-3.1,1.0)	0.76
	F	18	6.1 (3.6,9.7)	24	8.0 (5.1,11.9)	12	5.4 (2.8,9.5)	54	6.6 (4.9,8.4)	-0.6 (-2.9,1.6)	
Burkitt's lymphoma	M	0	–	2	0.7 (0.1,2.5)	6	2.7 (1.0,5.9)	8	1.0 (0.4,2.0)	7.6 (0.4,14.7)	0.91
	F	0	–	1	0.3 (0.0,1.7)	3	1.3 (0.3,3.9)	4	0.5 (0.1,1.2)	8.4 (-3.7,20.6)	
Misc. lymphoreticular	M	1	0.3 (0.0,1.8)	0	–	0	–	1	0.1 (0.0,0.6)	-12.7 (-28.1,2.6)	–
	F	0	–	0	–	0	–	0	–	–	
Unspecified lymphomas	M	0	–	6	1.9 (0.7,4.1)	0	–	6	0.7 (0.3,1.5)	0.4 (-6.0,6.7)	0.27
	F	1	0.3 (0.0,1.8)	0	–	0	–	1	0.1 (0.0,0.6)	-10.5 (-28.4,7.4)	
TOTAL	M	233	78.0 (68.0,88.1)	242	82.2 (71.8,92.6)	134	58.9 (48.9,68.9)	609	74.2 (68.3,80.1)	-1.0 (-1.9,-0.1)	0.15
	F	128	43.3 (35.8,50.8)	165	55.9 (47.3,64.4)	97	43.8 (35.0,52.5)	390	48.0 (43.3,52.8)	0.0 (-1.0,0.9)	

*Figures are counts, ASRs with 95% CIs, Annual Percentage Change in ASR with 95% CIs (estimated from linear regression model) and p value for testing M/F difference in trend (obtained from year *sex interaction term in linear regression model).*

with areas of unusual population mixing and higher socio-economic status.[7,8] However, the Northern Region of England has two notable demographic characteristics. First, there are low levels of migration into or out of the region.[9] Thus, in general there is less opportunity for unusual population mixing to occur (with the striking exception of parts of Cumbria around Seascale where leukemia clusters have been observed).[10] Secondly, the region contains some of the most socio-economically deprived areas of the country.[11] An upward trend was seen for lymphoid leukemia (amongst boys) in spite of these particular demographic patterns that are seen in the region.

Although the explanation for the increase in the incidence of HL is not known, Epstein-Barr virus (EBV) has been linked as a putative agent.[12] Exposure to EBV is likely to be correlated with socio-economic deprivation. The present findings suggest that there has been increased exposure to an etiological agent in children within the region. There is also an indication that increased exposure to such an agent may have been more pronounced for girls or that girls may be genetically more susceptible to these exposures.

The reasons for decreases in the incidence of HL amongst adolescent/young adult males and boys with non-Hodgkin's lymphoma (NHL) are not known.

It should be acknowledged that some analyses are based on limited numbers of cases and so results must be treated with caution. The present study has several other limitations. Diagnostic accuracy was not assessed as no blinded pathological review was carried out. Since the study period was 38 years, the applied pathological criteria will have inherently varied over time. For example, some true NHL cases might have been diagnosed as HL, and vice versa. Also accuracy of diagnosis might have varied between hospitals.

In conclusion, this study suggests the operation of sex-specific etiological factors which should be investigated in future studies.

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