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HIGHLIGHTS

Incidence

- Approximately 15% of childhood malignancies were lymphomas making them the third most frequent type of cancer in children following leukemia and malignant brain tumors. The percentage of childhood cancer that were lymphoma varied by age from only 3% for children younger than 5 years of age to 24% for 15-19 year olds (Figure II.1).
- The two predominant types of lymphomas were Hodgkin's disease and the non-Hodgkin's lymphomas (NHL). For younger children NHL was more frequent than Hodgkin's disease, while the reverse was true for adolescents (Figure II.3).
- In the US, approximately 1,700 children and adolescents younger than 20 years of age are diagnosed with lymphomas each year of which approximately 850-900 are cases of Hodgkin's disease and 750-800 are cases of NHL.
- The most common subtypes of Hodgkin's disease were nodular sclerosis (70% of cases); mixed cellularity (16% of cases); lymphocytic predominance (7% of cases); cases not otherwise specified (NOS) (6% of cases); and lymphocytic depletion subtype (<2% of cases) among children younger than 20 years of age. The relative frequencies of the mixed cellularity and nodular sclerosis subtypes were age and sex dependent (Figure II.2 and Table II.2).
- The incidence of Hodgkin's disease for children and adolescents younger than 20 years of age decreased slightly between 1975 and 1995, from 14.5 per million (1975-79) to 12.1 per million (1990-95) (Table II.3).
- The non-Hodgkin's lymphomas of children are a heterogeneous group of tumors, with Burkitt's and Burkitt-like tumors predominating among 5-14 year olds, and with diffuse large cell lymphomas being the most common subtype among 15-19 year olds (Figure II.9).
- The incidence of NHL varied much less by age than Hodgkin's disease (Figure II.3). NHL incidence increased up until age 4 years where it reached a plateau of approximately 10 per million (Figure II.4), which was maintained until the second decade of life when rates increased again.
- The incidence of NHL was higher in males than females (Figure II.10) and higher among whites than blacks (Figure II.12).
- The incidence of NHL among children younger than 15 years of age was fairly constant over the past 21 years, while there appeared to have been a slight increase in incidence for the 15-19 year old population (Table II.3 and Figure II.13).

Survival

- The 5-year survival rate was 91% for Hodgkin's disease (Figure II.8) for children and adolescents younger than 20 years of age, compared to 72% for NHL (Figure II.14).
- The 5-year survival rate for those younger than 20 years of age with NHL increased from 56% in 1975-84 to 72% in 1985-94 (Figure II.14).

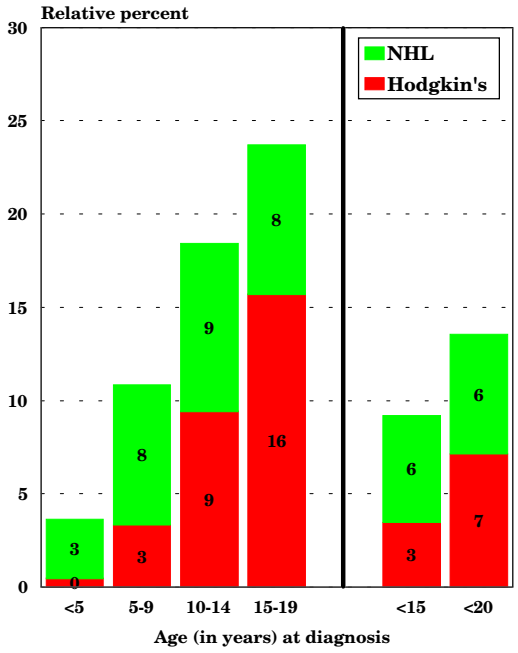
Risk factors

- For Hodgkin's disease arising in young adults, genetic susceptibility may be a factor for some cases, based on the greatly increased risk for Hodgkin's disease in young adult monozygotic twins of patients with Hodgkin's disease compared to the risk of dizygotic twins of patients with Hodgkin's disease (Table II.4).
- Congenital immunodeficiency syndromes and acquired immunodeficiency syndrome (AIDS) are associated with an increased risk of NHL (Table II.6).

INTRODUCTION

The lymphomas, combining Hodgkin's disease and the non-Hodgkin's lymphomas (NHL), are the third most frequent type of cancer in children following leukemia and malignant brain tumors. NHL and Hodgkin's disease are both malignancies of lymphoid cells, and each includes distinctive biological subtypes. In the US, approximately 1,700 children and adolescents younger than 20 years of age are diagnosed with lymphomas each year, of which 850-900 are Hodgkin's disease and 750-800 are non-Hodgkin's lymphoma. The lymphomas account for 10% of malignancies among children younger than 15 years of age and 15% of malignancies among those younger than 20 years of age. Figure II.1 illustrates that the contribution of Hodgkin's disease and the non-Hodgkin's lymphomas to the overall childhood cancer burden is markedly age dependent, increasing from only 3% of cancers among children younger than 5 years of age to 24% of cancers arising among those 15-19 years of age.

Figure II.1: Hodgkin's disease and NHL as a percent of total childhood cancer, by age, all races, both sexes SEER, 1990-95



MATERIAL AND METHODS

The International Classification for Childhood Cancers (ICCC) Group II of Lymphomas and Reticuloendothelial Neoplasms is divided into 5 subgroups [1]:

a. Hodgkin's disease;
b. Non-Hodgkin's lymphoma;
c. Burkitt's lymphoma;
d. Miscellaneous lymphoreticular neoplasms; and
e. Unspecified lymphomas.

Table II.1: Number of cases of lymphoma by type and sex, age <20, all races, SEER, 1975-95

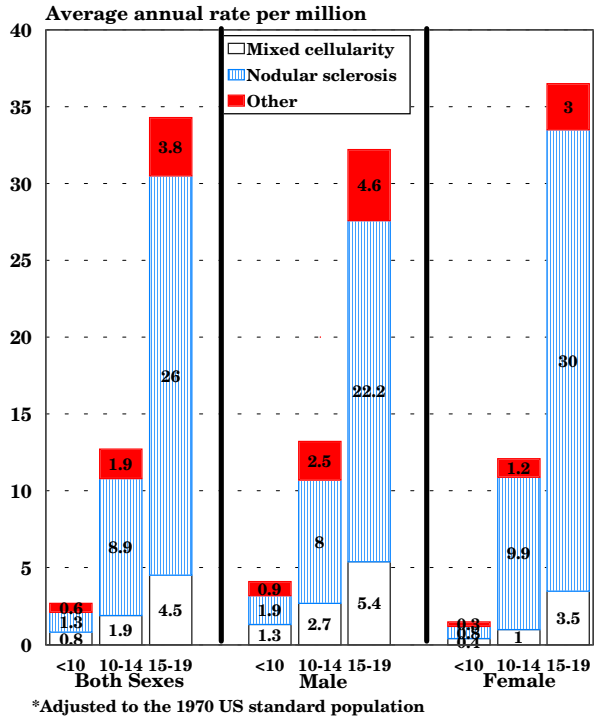
	Total	Males (%)	Females (%)
Total	4595	2734 (59%)	1861 (41%)
Hodgkin's (IIa)	2613	1353 (52%)	1260 (48%)
NHL (IIb,c,e)	1903	1334 (70%)	569 (30%)
Miscellaneous (IId)	79	47 (59%)	32 (41%)

Since only 3% of the registered childhood lymphomas and reticuloendothelial neoplasms in the Surveillance, Epidemiology and End Results (SEER) program for the period 1975-95 were not histologically confirmed, all cases were included in the analyses. Table II.1 shows the frequency distribution of these cases by sex among children younger than 20 years of age diagnosed with lymphoma. For the purposes of this chapter, Hodgkin's disease (defined by subgroup IIa) and NHL (defined by subgroups IIb, IIc, and IIe) are considered separately because of their distinctive nature. The miscellaneous lymphoreticular neoplasms (IId) are excluded from further analysis as there were few cases (only 79 cases) in this subgroup from 1975-95.

HODGKIN'S DISEASE

Hodgkin's disease is an unusual malignancy of lymphoid cells whose distinctive hallmark is the Reed-Sternberg cell. In most cases Reed-Sternberg cells appear to be clonal in nature and from the B lymphocyte lineage, as evidenced by immunoglobulin gene rearrangements in these cells [2-5]. Reed-Sternberg cells account for only a small percentage of the tumor mass [6], with most of the tumor composed of a reactive infiltrate of lymphocytes, plasma cells, and eosinophils. The Reed-Sternberg cells of some patients with Hodgkin's disease contain copies of the Epstein-Barr virus (EBV) genome [7,8]. Detection of EBV in Reed-Sternberg cells is more common among cases diagnosed in young children and for cases of the mixed cellularity subtype [7,8] (see Histologic subtype and Risk Factors sections below).

Figure II.2: Hodgkin's disease age-adjusted* incidence rates by Rye classification, sex and age all races, SEER (10 areas), 1977-95



*Adjusted to the 1970 US standard population

Table II.2: Percent distribution of Hodgkin's by subtype, age and sex all races, SEER, 1975-95

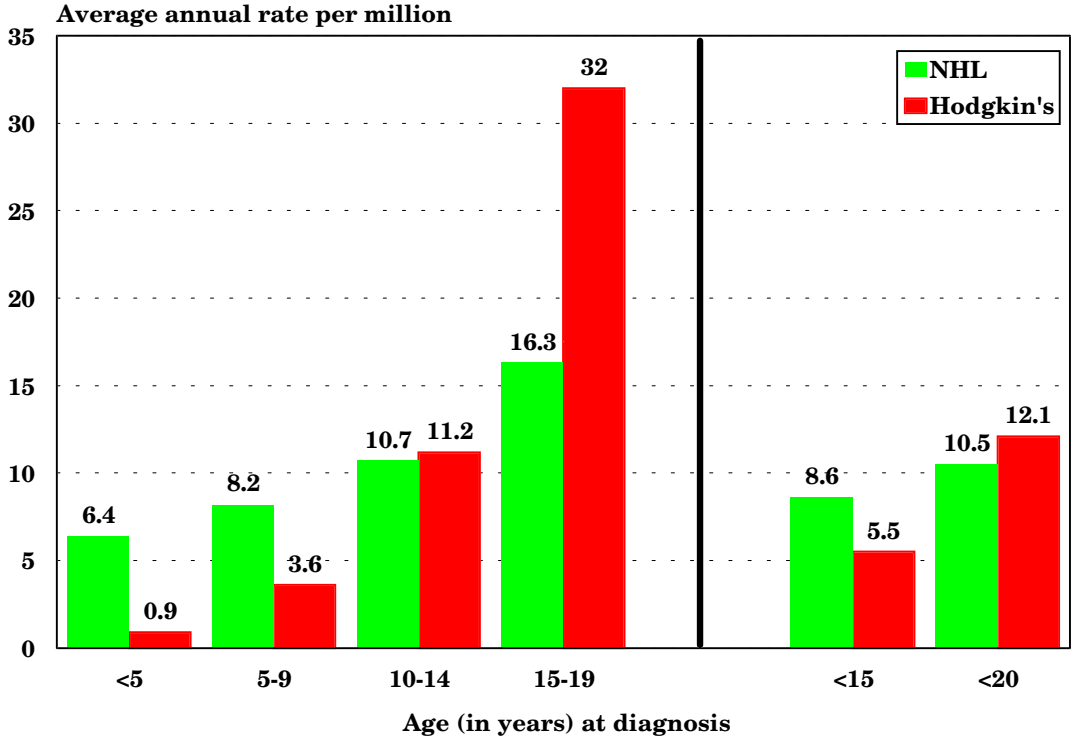
Age (in years) at diagnosis	<10			10-14			15-19		
	Both	M	F	Both	M	F	Both	M	F
Mixed Cellularity	32%	34%	25%	15%	21%	9%	13%	17%	10%
Nodular Sclerosis	46%	44%	51%	69%	59%	79%	74%	67%	81%
Lymphocytic Predominance	14%	15%	12%	7%	10%	3%	5%	7%	2%

Histologic subtype

Childhood Hodgkin's disease, similar to that arising in adults, is usually classified according to the Rye classification scheme, which includes four histologic subtypes: lymphocytic predominance, mixed cellularity, lymphocytic depletion, and nodular sclerosis [9]. The lymphocytic predominance subtype is now recognized as having a distinctive biological and clinical behavior from the other subtypes of Hodgkin's disease and is relatively uncommon among children [10,11]. Among children younger than 20 years of age diagnosed with Hodgkin's disease during 1975-95, the nodular sclerosis subtype was by far the most common and accounted for 70% of all cases. Mixed cellularity was the second most common subtype (16% of cases), followed by lymphocytic predominance (7% of cases), and cases not otherwise specified (NOS), (6% of cases). The lymphocytic depletion subtype was distinctly uncommon (<2% of cases) among Hodgkin's disease cases diagnosed in those younger than 20 years of age.

The relative frequencies of the mixed cellularity and nodular sclerosis subtypes were age and sex dependent. Mixed cellularity subtype was more common among children younger than 10 years of age (32% of all Hodgkin's cases) than among those diagnosed at 10-14 or 15-19 years of age (15% and 13% of Hodgkin's cases, respectively) (Table II.2 and Figure II.2). Mixed cellularity was also more common among males than females in each age group.

Figure II.3: Hodgkin's disease and NHL age-specific and age-adjusted* incidence rates by age, all races, both sexes SEER, 1990-95



*Adjusted to the 1970 US standard population

Nodular sclerosis subtype accounted for the vast majority (81%) of Hodgkin's disease among 15-19 year old females, and a somewhat lower percentage (approximately 67%) of Hodgkin's disease among 15-19 year old males (Table II.2).

Age-specific incidence

The overall annual incidence rate for Hodgkin's disease among children younger than 20 years of age was 12.1 per million for the years 1990-95. For Hodgkin's disease, the contribution to overall childhood cancer incidence was less than 1% among children younger than 5 years of age, but increased to 16% for 15-19 year olds (Figure II.1). The incidence of Hodgkin's disease was markedly age dependent (Figures II.3 and II.4), with incidence increasing from less than one per million for children in the first 3 years of life, to

Figure II.4: Hodgkin's disease and NHL age-specific incidence rates, all races, both sexes SEER, 1976-84 and 1986-94

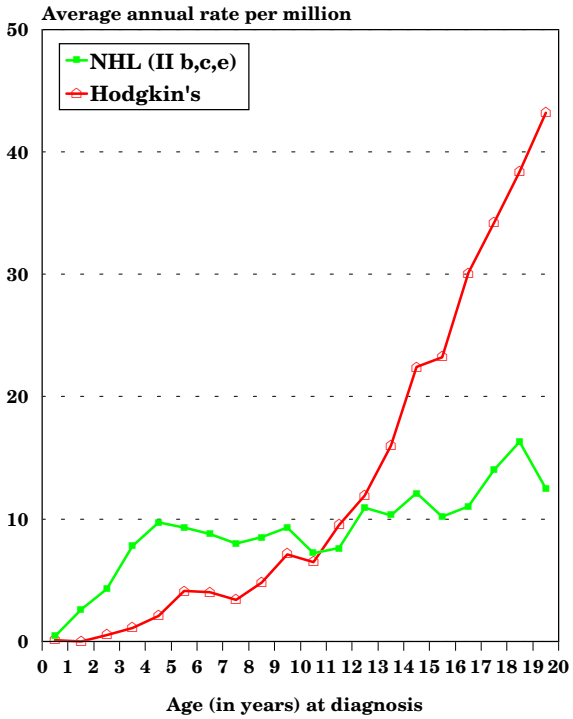
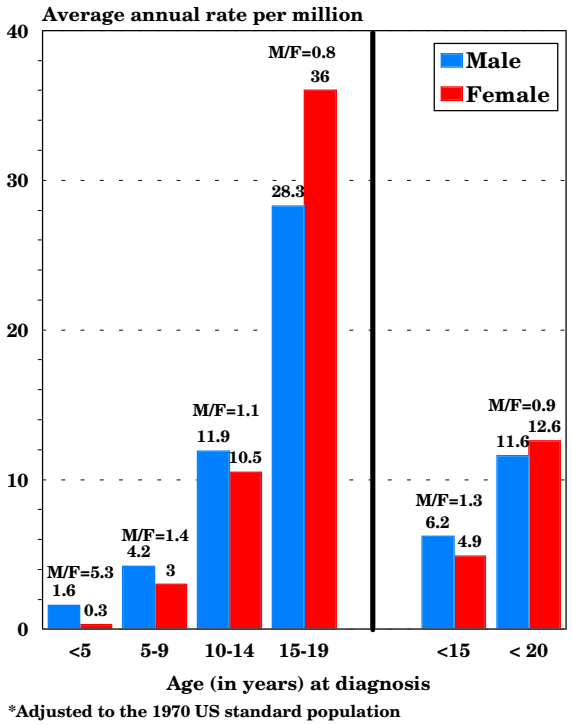


Figure II.5: Hodgkin's disease age-specific and age-adjusted* incidence rates by age and sex with male to female ratios (M/F) all races, SEER, 1990-95



*Adjusted to the 1970 US standard population

43.2 per million for 19 year olds (Figure II.4).[1] While the overall incidence of Hodgkin's disease for children younger than 20 years of age was similar to that for NHL (12.1 versus 10.5 per million, respectively) (Figure II.3), the incidence of Hodgkin's disease was 2-3 fold higher than NHL among 15-19 year olds, while the incidence of NHL was higher among those younger than 10 years of age (Figure II.4).

Sex-specific incidence

The incidence of Hodgkin's disease was slightly higher among females than males for children younger than 20 years of age during 1990-95 (M/F = 0.9) (Figure II.5).

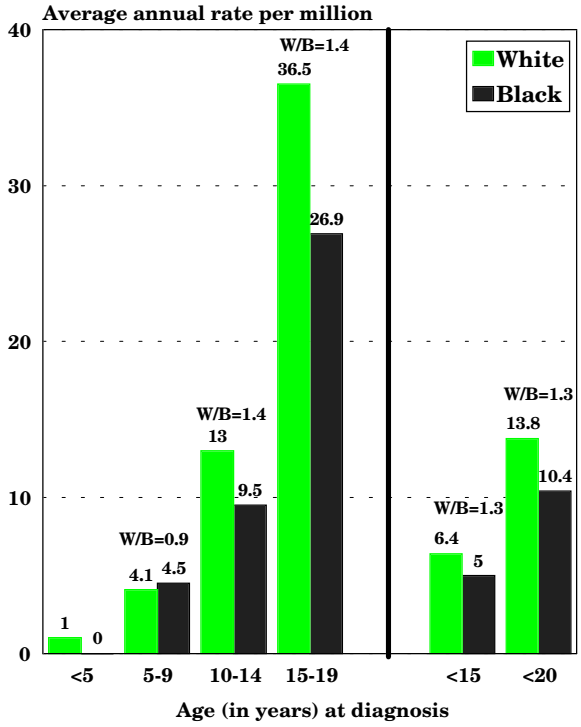
[1] Enumeration of the population at risk by single years of age was available only for the census years 1980 and 1990. The US Bureau of the Census provides intercensal population estimates by 5-year age groups, but not by single years of age. Therefore, the population estimates for 1980 were used in rate calculations for cases diagnosed from 1976-84 and the 1990 estimates were used for cases diagnosed from 1986-94.

However, the differential by sex was age dependent. Among children younger than 15 years of age, Hodgkin's disease was more common among males (M/F = 1.3), with the differential greatest for children younger than 5 years of age (M/F = 5.3). However, for children diagnosed with Hodgkin's disease at ages 15-19 years, Hodgkin's disease incidence was higher among females (M/F = 0.8).

Black-white differences in incidence

When considering children younger than 20 years of age, black children had a lower incidence of Hodgkin's disease than white children (Figure II.6). However, the incidence was very similar for black and white children younger than 10 years of age. For those over 10 years of age, the ratio of white to black incidence was approximately 1.4:1.

Figure II.6: Hodgkin's disease age-specific and age-adjusted* incidence rates by age with white to black ratios (W/B) both sexes, SEER, 1990-95



*Adjusted to the 1970 US standard population

TRENDS

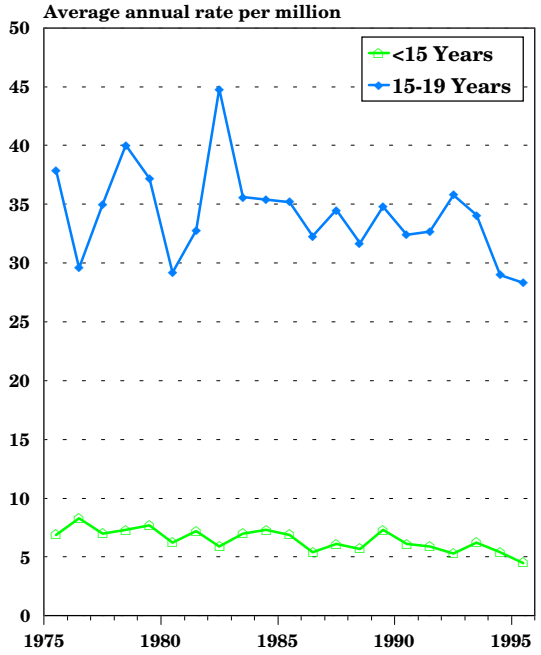
The age-adjusted incidence rate for Hodgkin's disease for children younger than 20 years of age decreased from 14.5 per million in 1975-79 to 12.1 per million in 1990-95 (Table II.3). The incidence for children younger than 15 years of age declined during this period from approximately 7.4 per million to 5.5 per million. The incidence for 15-19 year olds declined from 35.9 per million (1975-79) to 32.0 per million (1990-95) (Figure II.7). The decline in Hodgkin's incidence rates for the younger than 15 year age group occurred for both males and females [estimated annual percentage change (EAPC) of -2.0% and -1.4%, respectively]. The decline in incidence for 15-19 year olds appeared to be greater for males (EAPC = -1.4%) than for females (EAPC = -0.1%). A similar pattern of declining rates for males and stable rates for females was observed in regions of the United Kingdom for the years 1984-93 [12]. Another report described little change or slight decline in the occurrence of Hodgkin's disease among 20 populations from around the world for the period from the early 1970s to the 1980s [13]. In contrast to these reports, increasing incidence rates for the 15-24 year olds were reported for males and females in four geographical areas of the US for the period from 1947-50 to 1984-88 [13].

Table II.3: Hodgkin's and NHL age-adjusted* incidence rates all races, both sexes, SEER, 1975-79 through 1990-95

	1975-79	1980-84	1985-89	1990-95
Hodgkin's <15 years	7.4	6.7	6.3	5.5
Males	8.4	8.0	7.5	6.2
Females	6.4	5.3	5.1	4.9
Hodgkin's <20 years	14.5	13.8	13.1	12.1
Males	14.8	14.8	13.4	11.6
Females	14.2	12.8	12.8	12.6
NHL <15 years	8.5	8.1	8.6	8.5
Males	11.7	12.6	11.7	12.7
Females	5.2	3.4	5.3	4.2
NHL <20 years	9.1	9.7	10.0	10.5
Males	12.1	14.0	13.4	14.6
Females	5.9	5.2	6.5	6.1

*Adjusted to the 1970 US standard population

Figure II.7: Trends in Hodgkin's disease age-adjusted* incidence rates by age, all races, both sexes, SEER, 1975-95



*Adjusted to the 1970 US standard population

SURVIVAL

For cases diagnosed from 1985-94, the 5-year survival rate for Hodgkin's disease was 91% for children younger than 20 years of age (Figure II.8). White children had a slight survival advantage over black children (92% versus 84% 5-year survival), and males and females had similar outcome (90% versus 92% 5-year survival). Outcomes were also similar for children diagnosed younger than 15 years of age compared to 15-19 year olds (92% versus 90% 5-year survival).

RISK FACTORS (TABLE II.4)

Available epidemiological and molecular biological data suggest that Hodgkin's disease among children and adolescents represents at least two distinctive conditions [14-16]. In one condition, EBV genomic sequences are typically present in the Reed-Sternberg cells. This form of Hodgkin's disease is more common for

Figure II.8: Hodgkin's disease 5 year-relative survival rates by sex, race, age and time period SEER (9 areas), 1975-84 and 1985-94

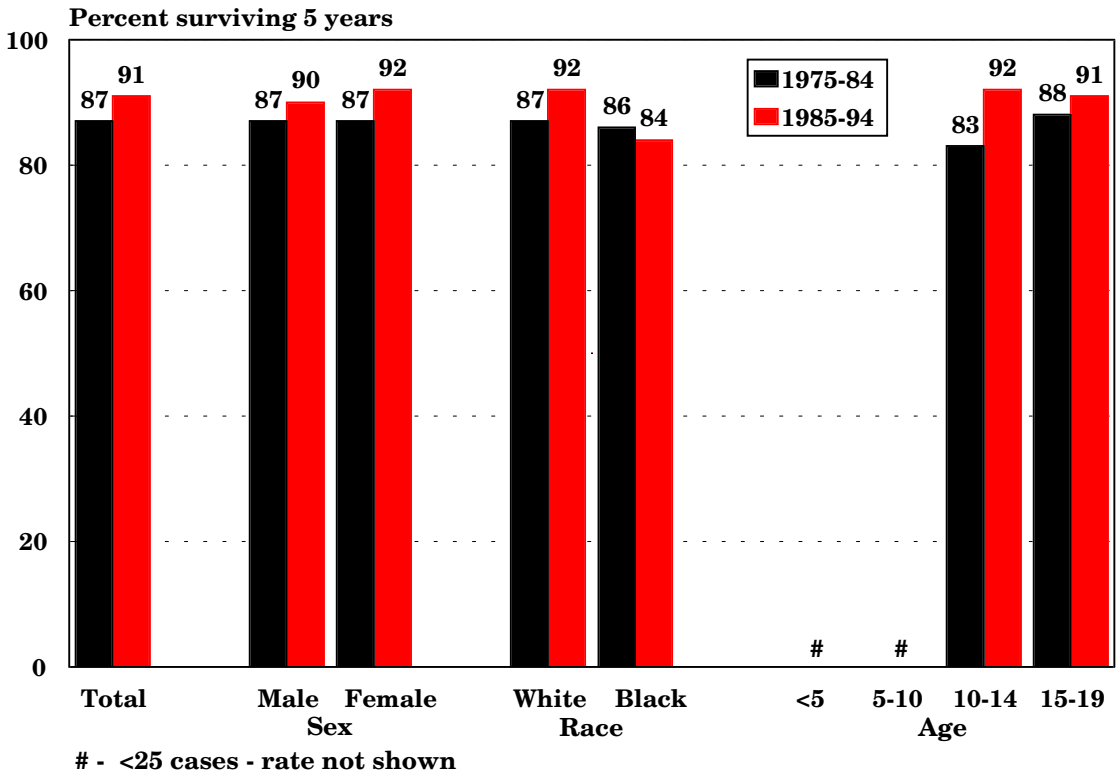


Table II.4: Current knowledge on causes of Hodgkin's disease in children

Exposure or Characteristic	Comments	References
Known to increase risk		
Family history of Hodgkin's disease	Monozygotic twins of young adult patients have a 99-fold increased risk. Other siblings have a 7-fold increased risk.	22,33,34
Epstein-Barr virus infection	EBV-associated HD is associated with mixed cellularity vs. nodular sclerosis histologic subtypes, children from economically less-developed vs. more-developed regions and young adult males vs. females. Additionally, history of infectious mononucleosis and high titer antibodies to EBV are associated with HD among young adults, although paradoxically HD cases among the young adult population typically do not have detectable EBV genomic sequences in tumor tissue.	7,8,16-18,20,21,35-37
Socioeconomic status	For young adult disease (ages 16-44), risk increases with socioeconomic status and with related characteristics such as small family size and single family housing. In children younger than 10 years of age, risk appears higher for lower socioeconomic status.	15,38-40
Social contacts	For young adult disease, having fewer siblings and childhood playmates is associated with higher risk. These findings suggest that infections in early childhood may reduce risk of young adult disease.	19,33
Factors for which evidence is inconsistent or limited		
Clustering	Young adult cases (age 16-45 years) tend to cluster more than older cases (age 46-70).	41

childhood cases occurring in developing countries compared to cases occurring in countries with higher socioeconomic status [7,8]. EBV involvement is also associated with male sex, mixed cellularity subtype, and young age at diagnosis [7,8,16-18]. However, the associated environmental and/or genetic factors that cause EBV infection, which is common among young children (particularly in developing countries), to result in Hodgkin's disease in a very small percentage of children are not understood. A second form of Hodgkin's disease is primarily of the nodular sclerosis subtype, arising in older adolescents and young adults living in more affluent societies [15,16]. In spite of observations suggesting a relationship between Hodgkin's disease among older adolescents/young adults and infectious mononucleosis and high titers of antibodies against EBV [19-21], cases of Hodgkin's disease in this population typically do not have EBV genomic sequences detectable in tumor tissue [7,8].

For Hodgkin's disease arising in young adults, genetic susceptibility may be a factor for some cases, based on the greatly increased relative risk for Hodgkin's disease occurring in both members of monozygotic twin pairs compared to the risk of occurrence in dizygotic twin pairs [22]. Further support for genetic predisposition to Hodgkin's disease is the consistently low incidence of Hodgkin's disease (especially of the nodular sclerosis subtype) among populations of East Asian ethnic origin and the high incidence (especially of mixed cellularity subtype) among some populations of South Asian origin, with these differences appearing to be independent of socioeconomic status [15].

NON-HODGKIN'S LYMPHOMA

The non-Hodgkin's lymphomas that develop in children are distinct from the more common forms of lymphomas in adults. While the lymphomas in adults are more commonly of low or intermediate grade, almost all of those that occur in children can be classified into one of four high-grade categories: 1) the Burkitt's and Burkitt-like lymphomas (small noncleaved cell lymphomas); 2) lymphoblastic lymphomas; 3) diffuse large B-cell lymphomas; and 4) anaplastic large cell lymphomas. Each of these types of childhood NHL is associated with distinctive molecular biological characteristics, with translocations resulting in activation of the C-MYC gene occurring in the Burkitt's and Burkitt-like lymphomas, translocations involving the TAL1 gene and the T-cell receptor genes typifying the lymphoblastic lymphomas, and translocations involving the NPM gene at chromosome band 5q35 in the anaplastic large cell lymphomas. These NHL categories are also associated with characteristic clinical presentations, with the Burkitt's and Burkitt-like lymphomas commonly present in the abdomen among US children (but in the jaws of young children in Africa), and with lymphoblastic lymphomas commonly present as large mediastinal masses. The lymphoblastic lymphomas of children are indistinguishable histologically from T-cell acute lymphoblastic leukemia (ALL). The clinical and biological characteristics of each of these categories of childhood NHL are summarized in Table II.5.

Histologic subtype

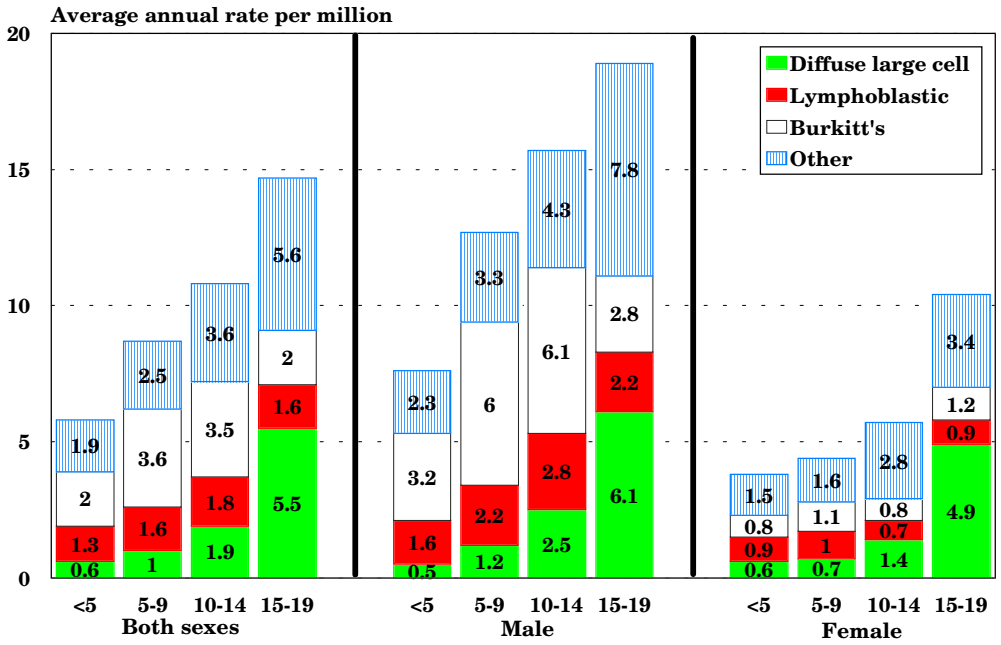
Figure II.9 illustrates the distinctive distributions by age and by sex of the NHL subtypes that predominate in US children in the geographic areas covered by the SEER Program. For Burkitt's and Burkitt's-like lymphoma, the incidence was much higher for males than for females. Five to fourteen year olds had higher rates than children younger than 5 years of age and adolescents 15-19 years of age. For children younger than 20 years of age, the incidence for the Burkitt's lymphomas was nearly 5.0-fold higher for males (3.2 per million) than for females (0.7 per million).

Table II.5: Major histopathological categories of non-Hodgkin's lymphoma in children*

Category (REAL)	Category (Working Formulation)	Clinical Presentation	Chromosomal Translocation	Genes Affected
Burkitt's and Burkitt-like lymphomas	ML small noncleaved cell	Intraabdominal (sporadic), jaw (endemic)	t(8;14)(q24;q32) t(2;8)(p11;q24) t(8;22)(q24;q11)	C-MYC, IgH IgK,Igλ
Lymphoblastic lymphoma, precursor T	Lymphoblastic convoluted and nonconvoluted	Mediastinal	MTS1/p16ink4a Deletion TAL1 t(1;14)(p34;q11) t(11;14)(p13;q11)	TAL1, TCRαδ, RHOMB1, HOX11
Anaplastic large cell lymphoma	ML immunoblastic or ML large cell	Variable	t(2;5)(p23;q35)	ALK, NMP
Diffuse large cell lymphoma	ML large cell	Variable	t(8;14)(q24;q32) in adults, but not well characterized in children	BCL2, IgH (in adults)

* Adapted from Shad and Magrath [31], and from Goldsby and Carroll [6].

Figure II.9: NHL age-specific incidence rates by histologic group sex, and age, all races, SEER (9 areas), 1977-95



In contrast to the Burkitt's lymphomas, the incidence of diffuse large cell lymphoma rose steadily with increasing age, with males showing somewhat higher incidence than females for the population younger than 20 year age group (M/F = 1.4). Lymphoblastic lymphoma occurred at similar frequency across all 5-year age groups, and like the other lymphoma subtypes for children younger than 20 years of age was more common in males than females (M/F = 2.5).

Age-specific incidence

The contribution of the non-Hodgkin's lymphomas to the overall cancer incidence increased from 3% for children younger than 5 years of age to 8-9% for 10-14 and 15-19 year olds (Figure II.1). Figure II.3 illustrates that the incidence of NHL varied much less by age than did Hodgkin's disease. The incidence of NHL rapidly increased in the first three years of life, before reaching a plateau rate of approximately 10 per million at around 4 years of age (Figure II.4). A similar age-incidence

Figure II.10: NHL age-specific incidence rates by sex, all races, SEER 1976-84 and 1986-94 combined

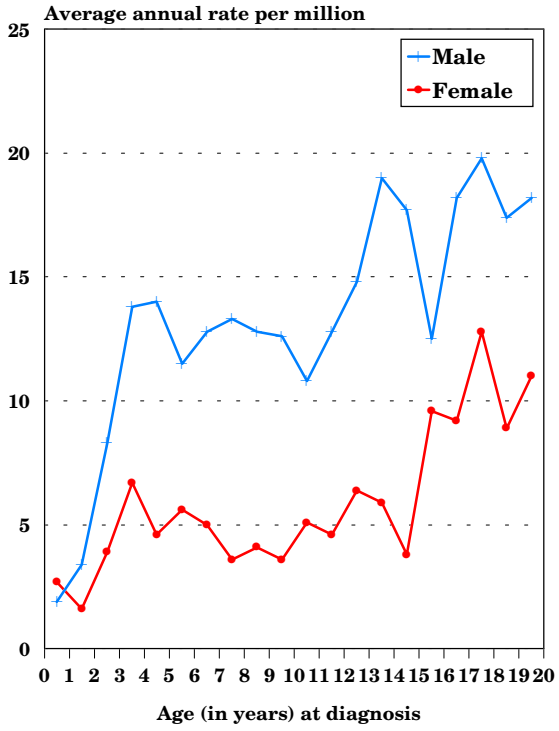
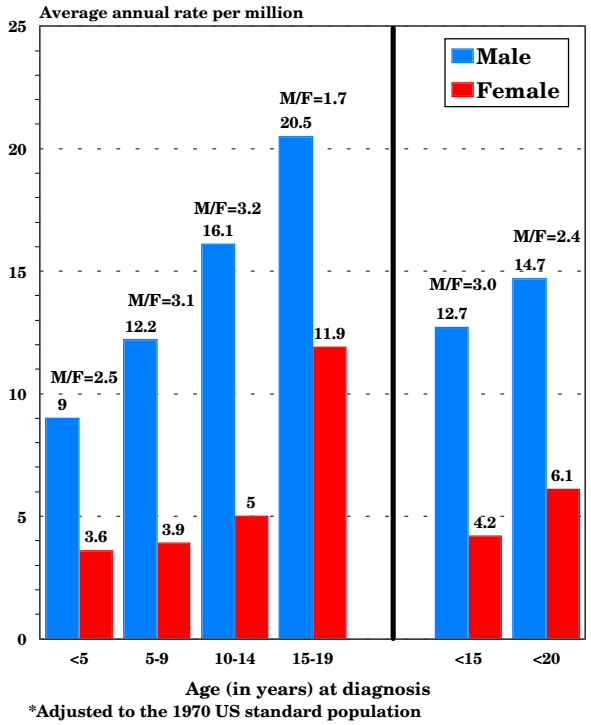


Figure II.11: NHL age-specific and age-adjusted* incidence rates by age and sex with male to female ratios (M/F), all races, SEER, 1990-95

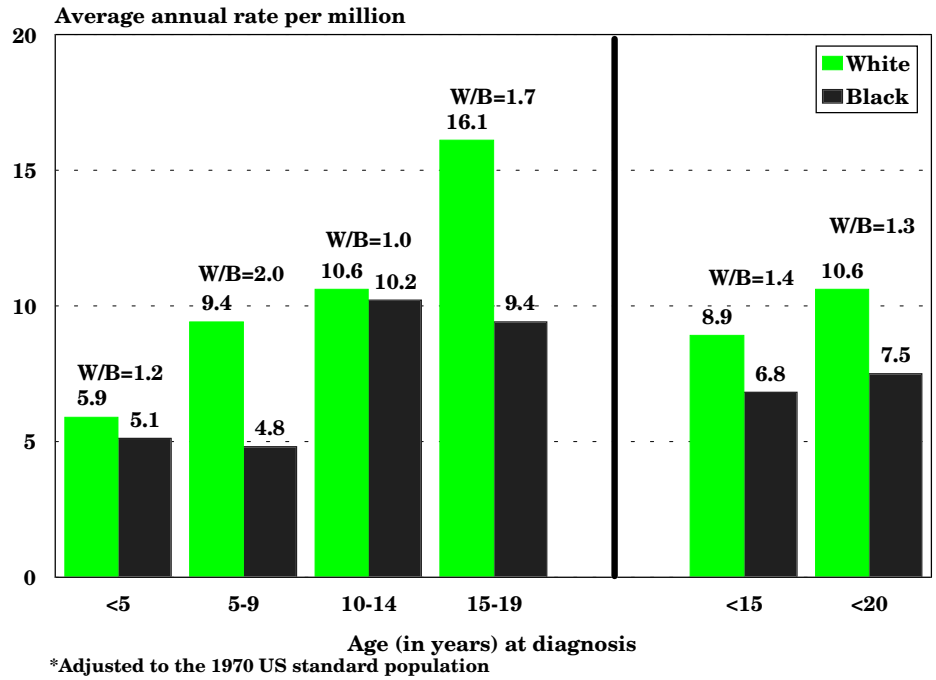


pattern was observed for males and females (Figure II.10), but the incidence rate among children older than 4 years of age was much higher for males than for females. While incidence rates for NHL remained fairly stable through the remainder of the first decade, the incidence began increasing after age 10 (Figures II.4 and II.10). Part of this increase in incidence among adolescents was due to higher rates for diffuse large cell lymphomas compared to rates for this subtype in younger children (Figure II.9).

Sex-specific incidence

There was a notable male predominance for NHL in children, with 70% of the cases occurring in males (Table II.1). The male predominance was seen for all age groups (Figures II.10 and II.11), although it was more pronounced for children younger than 15 years of age (M/F = 3.0)

Figure II.12: NHL age-specific and age-adjusted* incidence rates by age and race with white to black ratios (W/B) both sexes, SEER, 1990-95



compared to 15-19 year olds (M/F = 1.7). As noted in the preceding paragraph, the age-incidence pattern is similar for males and females, although incidence is higher at all age groups for males than females (Figure II.10).

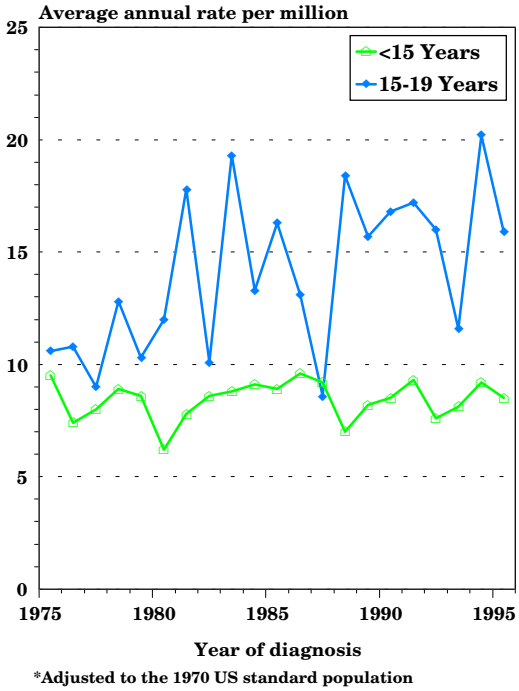
Black-white difference in incidence

The incidence of NHL among white children was 1.4-fold and 1.3-fold higher than that for black children for the younger than 15 years of age group and younger than 20 years of age group, respectively (Figure II.12). The difference in incidence between white and black children appeared greatest for children 5-9 years of age and 15-19 years of age (Figure II.12).

Trends in incidence rates

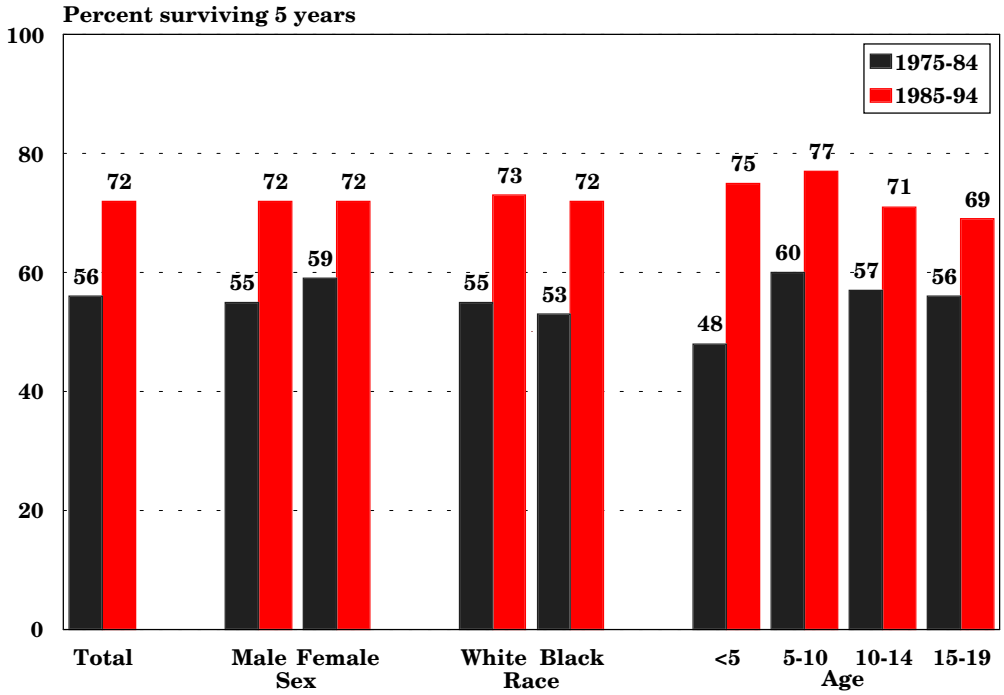
The incidence of NHL remained stable for children younger than 15 years of age from 1975 through 1995 (Table II.3). How-

Figure II.13: Trends in NHL age-adjusted* incidence rates, all races both sexes, SEER, 1975-95



*Adjusted to the 1970 US standard population

Figure II.14: NHL 5-year relative survival rates by sex, race, age and time period, SEER (9 areas), 1975-84 and 1985-94



ever, the incidence among 15-19 year olds increased from 10.7 per million (1975-79) to 16.3 per million (1990-95) (Figure II.13). This increase among the older adolescents/ young adults is similar to that reported for young adults older than 20 years of age [13,23].

SURVIVAL

The 5-year survival rate for children younger than 20 years of age with NHL was 72% for the years 1985-94, a substantial improvement from the 56% survival rate for the years 1975-84 (Figure II.14). For the most recent 10-year period, survival was similar for white and black children and was similar for males and females. During this 10-year period, children younger than 10 years of age had slightly better 5-year survival rates than did those 10-19 years of age (approximately 76% versus 70%).

RISK FACTORS (TABLE II.6)

The etiology of most cases of childhood NHL is unknown. In a small proportion of cases, childhood NHL is linked with various disorders of immune dysfunction. Congenital immunodeficiency syndromes (e.g., Wiskott-Aldrich, ataxia-telangiectasia, X-linked lymphoproliferative syndrome, and severe combined immunodeficiency) and acquired immunodeficiency syndrome (AIDS) from human immunodeficiency virus (HIV) infection are associated with an increased risk of NHL [24-26]. Persons who are immuno-compromised as a result of organ and bone marrow transplantation are also at increased risk of NHL [24,27,28]. EBV is associated with the endemic or 'African-type' Burkitt's lymphomas, but much less commonly with the sporadic Burkitt's lymphomas in the US [29-31]. Few epidemiologic studies of childhood cancer have focused exclusively on NHL, and most prenatal and perinatal exposures evaluated to date were not associated with increased or decreased risk [32].

SUMMARY

Overall, age-adjusted incidence rates for Hodgkin's disease and NHL were similar for children and adolescents younger than 20 years of age, although the age-specific incidence patterns are markedly different. Among young children, Hodgkin's disease is more common among males than females, whereas for older adolescents Hodgkin's disease is more common among females. Hodgkin's disease has a high 5-year relative survival rate, currently greater than 90%. For unknown reasons,

Table II.6: Current knowledge on causes of non-Hodgkin's lymphoma (NHL) in children

Exposure or Characteristic	Comments	References
Known risk factors		
Immunodeficiency	Immunosuppressive therapy, congenital immunodeficiency syndromes (e.g., ataxia telangiectasia), acquired immunodeficiency syndrome (AIDS) all predispose to NHL.	24-27,42,43
Substantial evidence implicating factor		
Epstein-Barr virus	EBV is associated with 'African-type' Burkitt's lymphoma, and chronic immune suppression due to malaria may be a co-factor in this situation. EBV is also associated with NHL in patients with immunodeficiency.	27,29-31,44,45
Factors for which evidence is inconsistent or limited		
Radiation	While a few studies report increased NHL risk in adults or children with ionizing or electromagnetic field (EMF) radiation, others report no association.	46-50

the incidence of Hodgkin's disease appears to be slowly decreasing for both younger children and for older adolescents. Substantial evidence implicates EBV in the etiology of a subset of Hodgkin's disease (primarily mixed cellularity subtype), but the mechanism by which EBV results in development of Hodgkin's disease and the potential role of co-factors are not understood.

The non-Hodgkin's lymphomas of children are a heterogeneous group of tumors, with Burkitt's and Burkitt-like tumors predominating among 5-14 year olds, and with diffuse large cell lymphomas being the most common subtype among 15-19 year olds. Particularly for the Burkitt's lymphomas, there is a marked sex differential, with males having a much higher incidence than females. Survival rates have improved substantially for NHL between the late 1970s and the late 1980s are now over 70%, with similar rates for both sexes and for whites and blacks. The incidence of NHL among children younger than 15 years of age appears fairly constant over the past 21 years, while there appears to have been a slight increase in incidence for the 15-19 year old age group. The etiology of childhood NHL is poorly understood, although a small proportion of cases arise in children with congenital or acquired severe immune dysfunction.

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