Malcolm A. Smith, Lynn A. Gloeckler Ries, James G. Gurney, Julie A. Ross

HIGHLIGHTS

Incidence

- For the years from 1990-95, the leukemias represented 31% of all cancer cases occurring among children younger than 15 years of age and 25% of cancer cases occurring among those younger than 20 years of age. In the US there are approximately 3,250 children diagnosed each year with leukemia and 2,400 with acute lymphoblastic leukemia (ALL).
- The relative contribution of leukemia to the total childhood cancer burden varies markedly with age, being 17% in the first year of life, increasing to 46% for 2 and 3 year olds, and then decreasing to only 9% for 19 year olds (Figure I.1).
- The two major types of leukemia were ALL comprising nearly three-fourths and acute non-lymphocytic comprising 19%.
- There was a sharp peak in ALL incidence among 2-3 year olds (> 80 per million) which decreases to a rate of 20 per million for 8-10 year olds. The incidence of ALL among 2-3 year olds is approximately 4-fold greater than that for infants and is nearly 10-fold greater than that for 19 year olds (Figure I.2a).
- Leukemia rates are substantially higher for white children than for black children, with rates of 45.6 versus 27.8 per million for the period from 1986-95 for children 0-14 years old (Table I.4). This difference between white and black children is most apparent when examining rates of leukemia by single year of age (Figure I.3), with a nearly 3-fold higher incidence at 2-3 years of age for white children compared to black children.
- The incidence of leukemia among children younger than 15 years of age has shown a moderate increase in the past 20 years (Figure I.4) with the trend primarily reflecting an increase in ALL incidence during this period. The rates of leukemias other than ALL did not appear to increase from 1977 to 1995 (Figure I.5)

Survival

- Survival for children with ALL has markedly improved since the early 1970s, and overall survival for all children with ALL is now approximately 80% (Figure I.8). A number of improvements in treatment during this period have undoubtedly contributed to the improved survival.
- Survival for children with ALL is very dependent upon age at diagnosis, with the most favorable outcome observed for children older than 1 year of age and younger than 10 years of age.

Risk factors

- With the exception of prenatal exposure to x-rays and specific genetic syndromes, little is known about the causes of childhood ALL (Table I.5).
- Different risk factors are emerging for childhood AML that distinguish the disease from ALL, and this may provide avenues for future epidemiological studies (Table I.6).

INTRODUCTION

The leukemias of childhood are cancers of the hematopoietic system, involving in most cases, malignant transformation of lymphoid progenitor cells [1] and less commonly transformation of myeloid progenitor cells [2]. The leukemias account for the largest number of cases of childhood cancer and are the primary cause of cancer related mortality of children in the United States. Approximately 3,250 children and adolescents younger than 20 years of age are diagnosed with leukemia each year in the US, of which 2,400 are acute lymphoblastic leukemia. For the years from 1986-94, the leukemias represented 32% of all cancer cases occurring among children younger than 15 years of age and 26% of cancer cases occurring among those younger than 20 years of age. However, the relative contribution of leukemia to the total childhood cancer burden varied markedly with age, being 17% in the first year of life, increasing to 46% for 2 and 3 year olds, and then decreasing to only 9% for 19 year olds. To further illustrate the contribution Figure I.1 gives the incidence rates for both leukemia and total cancer (the sum of leukemia and non-leukemia) by single year of age.[1]

This chapter focuses on the following topics related to the incidence of leukemia among children in the United States: (1) the relative frequencies of the leukemia subtypes that occur among children; (2) variation in the incidence of the specific types of leukemia by age; (3) differences in incidence between males and females; (4) differences in incidence between white and black children; and (5) variation in leukemia incidence over time. In terms of survival for children with leukemia, the chapter focuses on three primary topics: (1) comparison of survival rates for children with ALL and AML; (2) the impact of age at diagnosis on survival; and (3) the remark-

[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.

Figure I.1: Total childhood cancer age-specific incidence rates by leukemia versus non-leukemia, all races, both sexes, SEER, 1986-94

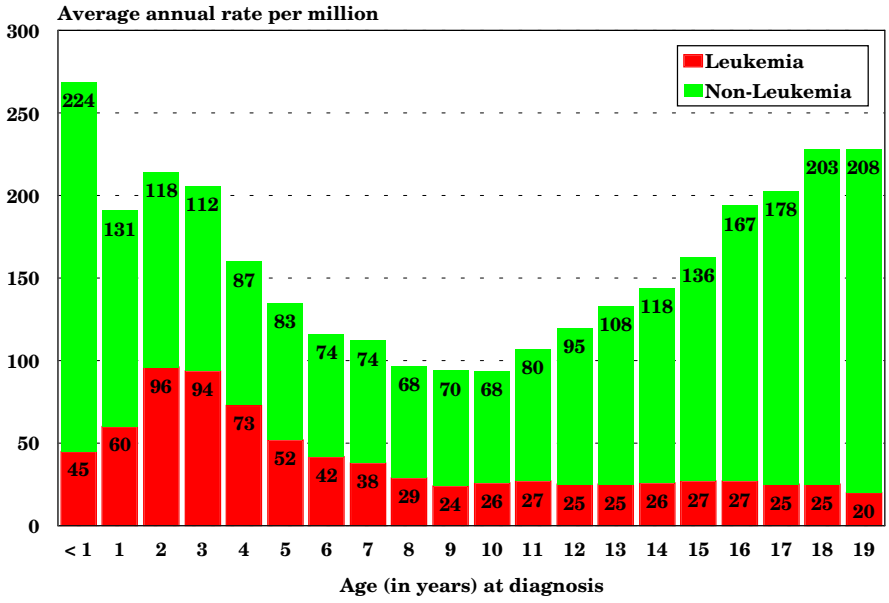


Table I.1: Percent distribution within ICCC subcategories for leukemia and age-adjusted* incidence rates for specific ICD-O codes, age <20, all races, both sexes, SEER, 1975-95

Diagnostic Group	Specific Diagnosis:	Rate per million	% of Cases
Ia: Lymphoid leukemia		29.2	100.0%
	9820: Lymphoid leukemia, NOS		0.2%
	9821: Acute lymphoblastic		99.2%
	9822: Subacute lymphoid		0.0%
	9823: Chronic lymphocytic		0.1%
	9824: Aleukemic lymphoid		0.2%
	9825: Prolymphocytic leukemia		0.1%
	9826: Burkitt's cell leukemia		0.5%
	9827: Adult T-cell		0.0%
	9850: Lymphosarcoma cell		0.0%
Ib: Acute non-lymphocytic		7.6	100.0%
	9840: Erythroleukemia		0.4%
	9841: Acute erythremia		0.2%
	9861: Acute myeloid leukemia		68.7%
	9864: Aleukemic myeloid		0.0%
	9866: Acute promyelocytic		7.1%
	9867: Acute myelomonocytic		9.3%
	9891: Acute monocytic leukemia		9.1%
	9894: Aleukemic monocytic		0.0%
	9910: Acute megakaryoblastic		5.1%
Ic: Chronic myeloid leukemia		1.3	100.0%
	9863: Chronic myeloid leukemia		98.6%
	9868: Chronic myelomonocytic		1.4%
Id: Other specified leukemias		0.2	100.0%
	9830: Plasma cell leukemia		0.0%
	9842: Chronic erythremia		0.0%
	9860: Myeloid leukemia, NOS		33.3%
	9862: Subacute myeloid		0.0%
	9870: Basophilic leukemia		0.0%
	9880: Eosinophilic leukemia		0.0%
	9890: Monocytic leukemia, NOS		8.3%
	9892: Subacute monocytic		0.0%
	9893: Chronic monocytic		0.0%
	9900: Mast cell leukemia		0.0%
	9930: Myeloid sarcoma		58.3%
	9931: Acute panmyelosis		0.0%
	9932: Acute myelofibrosis		0.0%
	9940: Hairy cell leukemia		0.0%
	9941: Leukemia		0.0%
Ie: Unspecified leukemias		1.2	100.0%
	9800: Leukemia, NOS		20.5%
	9801: Acute leukemia, NOS		79.5%
	9802: Subacute leukemia, NOS		0.0%
	9803: Chronic leukemia, NOS		0.0%
	9804: Aleukemia leukemia, NOS		0.0%

*Adjusted to the 1970 US standard population

able improvements in survival rates for children with ALL during the past 20 years.

Classification system

Before discussing topics related to childhood leukemia incidence and outcome, it is necessary to describe the specific diagnoses that are included among the Diagnostic Groups for leukemia of the International Classification of Childhood Cancer (ICCC). Table I.1 illustrates that acute lymphoblastic leukemia (ALL) accounted for approximately 99% of cases among the lymphoid leukemia (Ia) diagnostic group, so that this ICCC diagnostic group is essentially synonymous with ALL. The "acute non-lymphocytic leukemia" diagnostic category Ib is henceforth referred to as the acute myeloid leukemia (AML) category since this is the preferred terminology [3], and it encompasses the various subtypes of AML that occur in children. The other three ICCC diagnostic categories combined accounted for only 6-7% of total leukemia cases in children. The chronic myeloid leukemias diagnostic group (Ic) included approximately 3% of leukemia cases occurring in the younger than 20 years of age group during the period from 1990-95, while the "other specified leukemia" diagnostic group (Id) included fewer than 1% of the leukemia cases. Approximately 3% of leukemia cases were included in the unspecified leukemia category (Ie) for the period from 1990-95.

INCIDENCE

Age-specific incidence

Table I.2 shows the incidence and relative proportion of specific diagnostic categories by 5-year age groups. For the younger than 15 years of age, ALL represented 78% of leukemia cases, while the AML subgroup (Ib) represented 16% of cases. The relative frequency of AML increased in the second decade of life as that of ALL decreased. While AML represented only 13-14% of leukemia cases in the first 10 years of life, it accounted for 36% of leukemia cases among 15-19 year olds. The incidence and relative contribution of the chronic myeloid leukemias also increased with age, representing about 9% of cases among 15-19 year olds.

As is apparent from Table I.2, the incidence of leukemia among children varied considerably with age. Figure I.2a illustrates that this variation was the result of a sharp peak in ALL incidence among 2-3 year old children (incidence over 80 per million), which returned to a rate of 20 per million for 8-10 year old children. The incidence of ALL among 2-3 year old

Table I.2: Age-adjusted incidence rates per million for specific leukemia by age groups all races, both sexes, SEER, 1990-95

Age (in years) at diagnosis	<5	5-9	10-14	15-19	<15*
Total leukemia	72.4 (100%)	38.0 (100%)	25.9 (100%)	26.0 (100%)	43.8 (100%)
ALL	58.1 (80%)	30.6 (81%)	17.4 (67%)	13.0 (50%)	34.0 (78%)
AML (Ib)	10.3 (14%)	5.0 (13%)	6.2 (24%)	9.3 (36%)	7.0 (16%)
CML (Ic)	1.1 (2%)	0.7 (2%)	1.1 (4%)	2.2 (9%)	1.0 (2%)
Other specified leukemias (Id)	0.3 (-)	0.3 (1%)	0.1 (-)	0.1 (-)	0.2 (1%)
Unspecified leukemias (Ie)	2.2 (3%)	1.0 (3%)	0.6 (2%)	1.1 (4%)	1.2 (3%)

* Rates are adjusted to the 1970 US standard population. Numbers in parentheses represent the percentage of the total cases for the specific age group.

children was approximately 4-fold greater than that for infants and was nearly 10-fold greater than that for 19 year olds. The distinctive shape of the age-incidence curve for ALL can be well-described by a mathematical model which assumes that childhood ALL results from two events required for full malignant transformation with the first of these events occurring *in utero* [4]. Experimental confirmation has been obtained for the initiation of childhood ALL *in utero* [5,6].

The incidence of AML in children also varied with age (Figure I.2b), but with a different pattern than that for ALL. AML rates were highest in the first 2 years of life, but subsequently decreased with a nadir at approximately 9 years of age, followed by slowly increasing rates during the adolescent years. The incidence of leukemia cases in the "chronic myeloid leukemia" category (Ic) likewise showed substantial variation with age. As shown in Figure I.2c, there was a peak in inci-

Figure I.2a: ALL (Ia): 1986-94, and AML (Ib): 1976-84 and 1986-94 age-specific incidence rates, all races both sexes, SEER

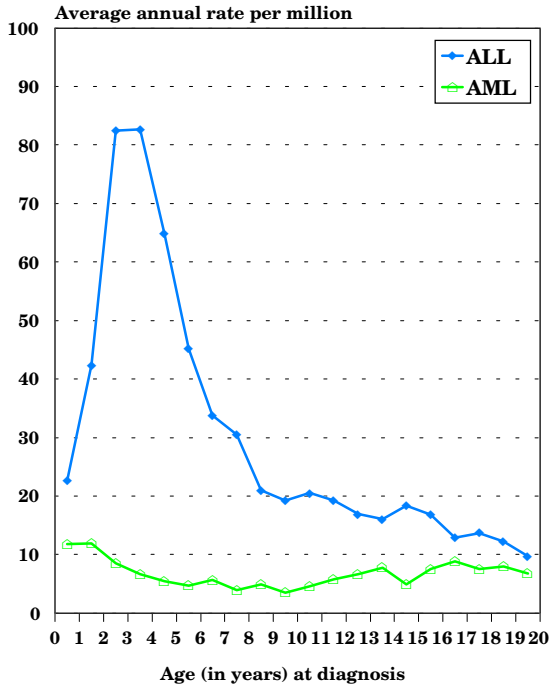
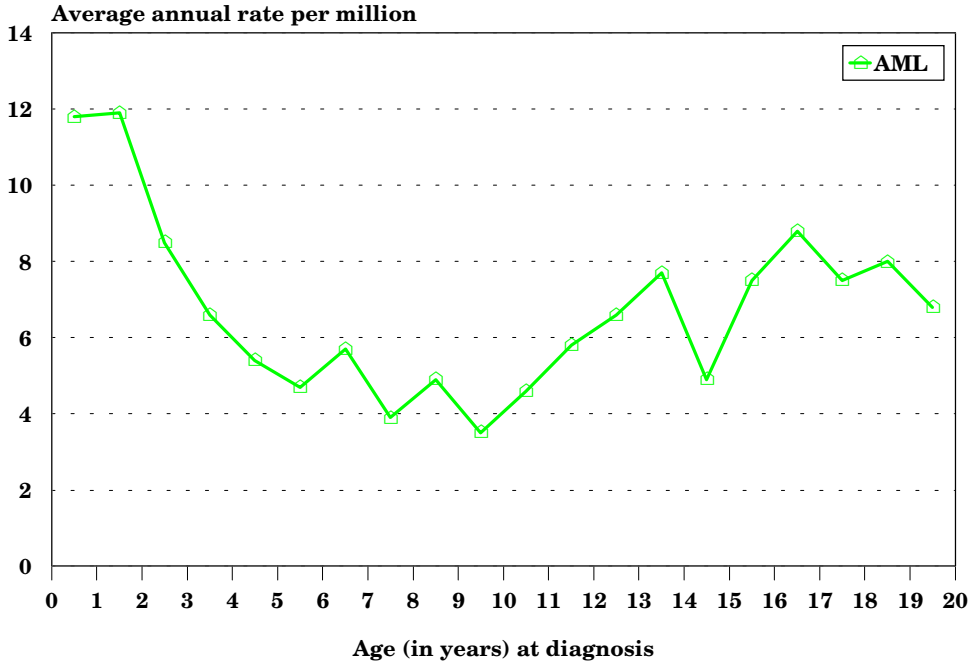
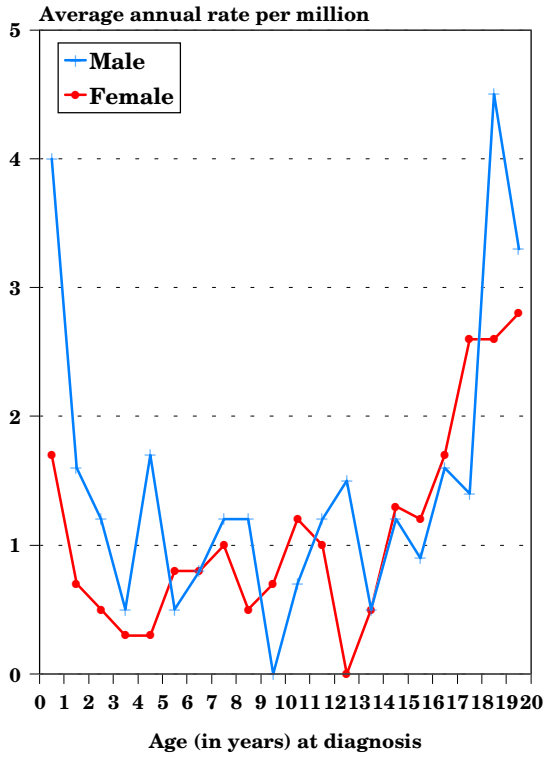


Figure I.2b: AML (Ib) age-specific incidence rates, all races both sexes, SEER, 1976-84 and 1986-94 combined



dence for males in the first year of life, with subsequent lower rates for both males and females until the late teen years. The increase in CML incidence in the later teen years appeared to represent the early portion of the increasing incidence curve for adult-type CML [7]. On the other hand, the cases coded as "chronic myeloid leukemia" in the first few years of life almost certainly reflect cases of juvenile myelomonocytic leukemia (previously termed juvenile chronic myeloid leukemia), a diagnosis associated primarily with young males [8,9].

Figure I.2c: Chronic myeloid leukemia age-specific incidence rates, all races, both sexes SEER, 1976-84 and 1986-94 combined



Sex-specific incidence

Table I.3 illustrates the incidence of the various leukemia types separately for males and females for the years 1990-95. The incidence of ALL among children younger than 15 years of age was consistently higher among males (approximately 20%) relative to females. For the 15-19 year olds, however, the male preponderance was greater, with males having a 2-fold higher ALL incidence than females. The incidence of AML was similar for males and females for all age groups. For the CML category, there was a 4-fold higher rate for males than females for the younger than 5-year age group, a difference that was not present for older age groups. As noted above, these cases likely represent juvenile myelomonocytic leukemia, which has a known male predominance [9].

Table I.3: Male to female ratios of age-adjusted leukemia incidence rates per million by type and age group, all races, SEER, 1990-95

	<5 Yrs Rate M/F Ratio	5-9 Yrs Rate M/F Ratio	10-14 Yrs Rate M/F Ratio	15-19 Yrs Rate M/F Ratio	<15 Yrs Rate* M/F Ratio	<20 Yrs Rate* M/F Ratio
Total leukemia	M = 78.5 F = 65.9 M/F = 1.2	M = 40.3 F = 35.7 M/F = 1.1	M = 28.4 F = 23.1 M/F = 1.2	M = 28.4 F = 23.4 M/F = 1.2	M = 47.4 F = 40.1 M/F = 1.2	M = 42.7 F = 36.0 M/F = 1.2
ALL	M = 63.7 F = 52.3 M/F = 1.2	M = 32.2 F = 29.0 M/F = 1.1	M = 18.8 F = 16.0 M/F = 1.2	M = 17.2 F = 8.6 M/F = 2.0	M = 36.7 F = 31.2 M/F = 1.2	M = 31.9 F = 25.6 M/F = 1.2
AML (Ib)	M = 10.0 F = 10.6 M/F = 0.9	M = 5.8 F = 4.3 M/F = 1.3	M = 6.7 F = 5.7 M/F = 1.2	M = 8.3 F = 10.4 M/F = 0.8	M = 7.4 F = 6.7 M/F = 1.1	M = 7.6 F = 7.6 M/F = 1.0
Chronic myeloid leukemia (Ic)	M = 1.7 F = 0.4 M/F = 4.3	M = 0.4 F = 1.0 M/F = 0.4	M = 1.4 F = 0.9 M/F = 1.6	M = 1.6 F = 2.9 M/F = 0.6	M = 1.1 F = 0.8 M/F = 1.4	M = 1.3 F = 1.3 M/F = 1.0

*Adjusted to the 1970 US standard population

Table I.4: White to black ratios of age-adjusted leukemia incidence rates per million by type and age group, both sexes, SEER, 1986-95

	<5 Yrs Rate* W/B Ratio	5-9 Yrs Rate W/B Ratio	10-14 Yrs Rate W/B Ratio	15-19 Yrs Rate W/B Ratio	<15 Yrs Rate* W/B Ratio	<20 Yrs Rate* W/B Ratio
Total Leukemia	W = 77.2 B = 38.4 W/B = 2.0	W = 37.5 B = 28.6 W/B = 1.3	W = 27.4 B = 18.4 W/B = 1.5	W = 26.5 B = 15.2 W/B = 1.7	W = 45.6 B = 27.8 W/B = 1.6	W = 40.9 B = 24.7 W/B = 1.7
ALL	W = 63.2 B = 26.9 W/B = 2.4	W = 31.8 B = 1.8 W/B = 1.8	W = 19.8 B = 11.6 W/B = 1.7	W = 14.3 B = 6.4 W/B = 2.2	W = 36.8 B = 18.3 W/B = 2.0	W = 31.2 B = 15.4 W/B = 2.0
AML (Ib)	W = 10 B = 7.7 W/B = 1.3	W = 3.8 B = 6.1 W/B = 0.6	W = 5.3 B = 5.1 W/B = 1.0	W = 8.3 B = 7.1 W/B = 1.2	W = 6.2 B = 6.2 W/B = 1.0	W = 6.7 B = 6.4 W/B = 1.1

*Adjusted to the 1970 U.S. standard population

Black-white differences in incidence

Leukemia rates were substantially higher for white children younger than 15 years of age compared to black children, with rates of 45.6 versus 27.8 per million for the period from 1986-95 (Table I.4). This difference between white children and black children was most apparent when examining rates of leukemia by single year of age (Figure I.3), with a nearly 3-fold higher incidence at 2-3 years of age for white children compared to black children.

The difference in leukemia incidence was primarily the result of lower ALL rates among black children (Table I.4), with ALL incidence for white children younger than 5 years of age being more than twice that for black children (63.2 versus 26.9 per million). A lower ALL incidence for black children was observed for each 5-year age group up to 20 years of age. The incidence of AML, unlike that for ALL, was similar for white and black children for all age groups (Table I.4).

Figure I.3: Leukemia age-specific incidence rates for white (1986-94) and black (1976-84 and 1986-94) children, SEER

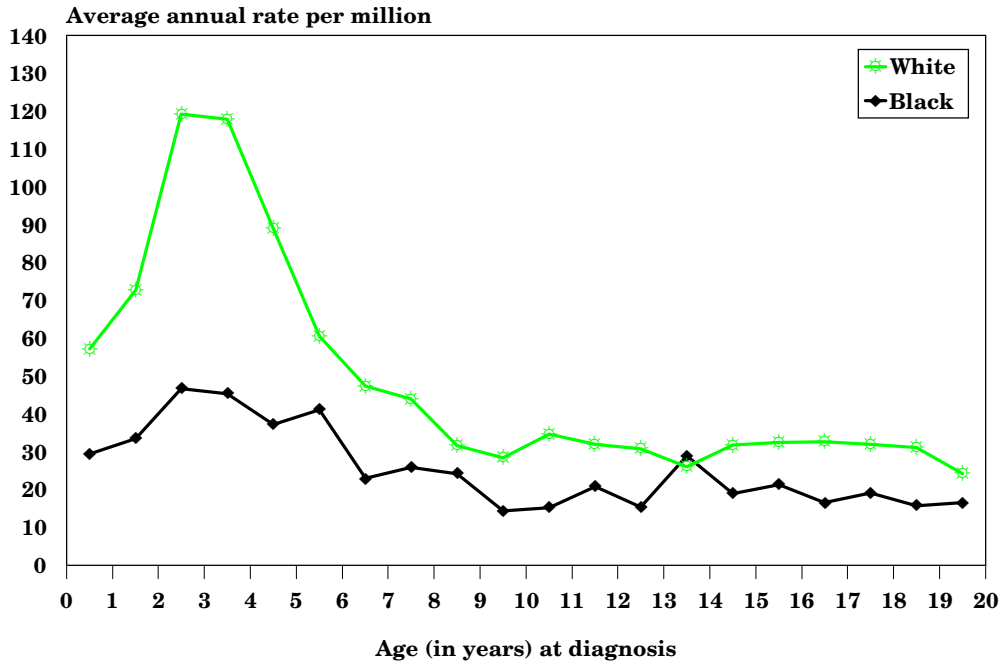
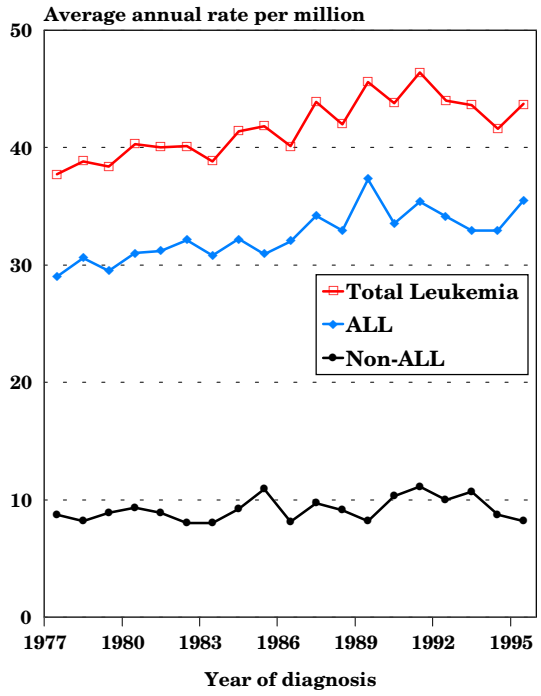


Figure I.4a: Trends in leukemia and ALL age-adjusted* incidence rates, age <15 all races, both sexes, SEER, 1977-95



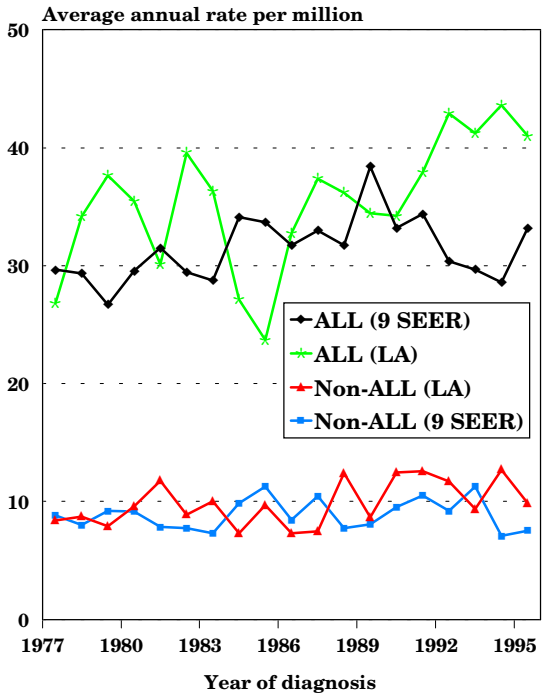
*Adjusted to the 1970 US standard population

TRENDS

The incidence of leukemia among children younger than 15 years of age increased in the past 20 years, as shown in Figure I.4a. The estimated annual percentage change (EAPC) for total leukemia for the period from 1977 to 1995 was 0.9% per year, with the trend primarily reflecting an increase in ALL incidence during this period (EAPC for ALL, 0.9%). The rates of leukemias, other than ALL, did not increase significantly from 1977 to 1995 (Figure I.5), although the small number of cases diagnosed each year for the less common leukemia types results in considerable scatter in year to year rates, which makes interpretations of trends difficult. The higher rate of nonspecific classification of leukemia cases (ICCC Category Ie) in the years prior to 1977 (greater than 5 per million in 1973 and 1974, but 1-2 per million after 1977), is the reason for restricting examinations of trends over time for specific leukemia diagnoses to the period from 1977 to 1995 [10].

While a model based on a constantly increasing rate can be applied to the ALL and the leukemia incidence data to estimate an EAPC, visual inspection of the incidence of ALL and total leukemia from 1977 to 1995 suggests that reality is more complicated (Figure I.4a). For example, ALL incidence for the 9 SEER areas and the Los Angeles area combined peaked in 1989, and rates have been 5-10% below this peak value in subsequent years. The situation is further complicated by different time trend patterns for ALL for the 9 SEER areas compared with the Los Angeles area. For the 9 SEER areas, ALL incidence has been more or less stable since 1984. On the other hand, ALL incidence for the Los Angeles area showed more variability, being higher in the late 1970s and early

Figure I.4b: Trends in ALL and non-ALL age-adjusted* incidence rates, age <15 all races, both sexes, SEER, 1977-95

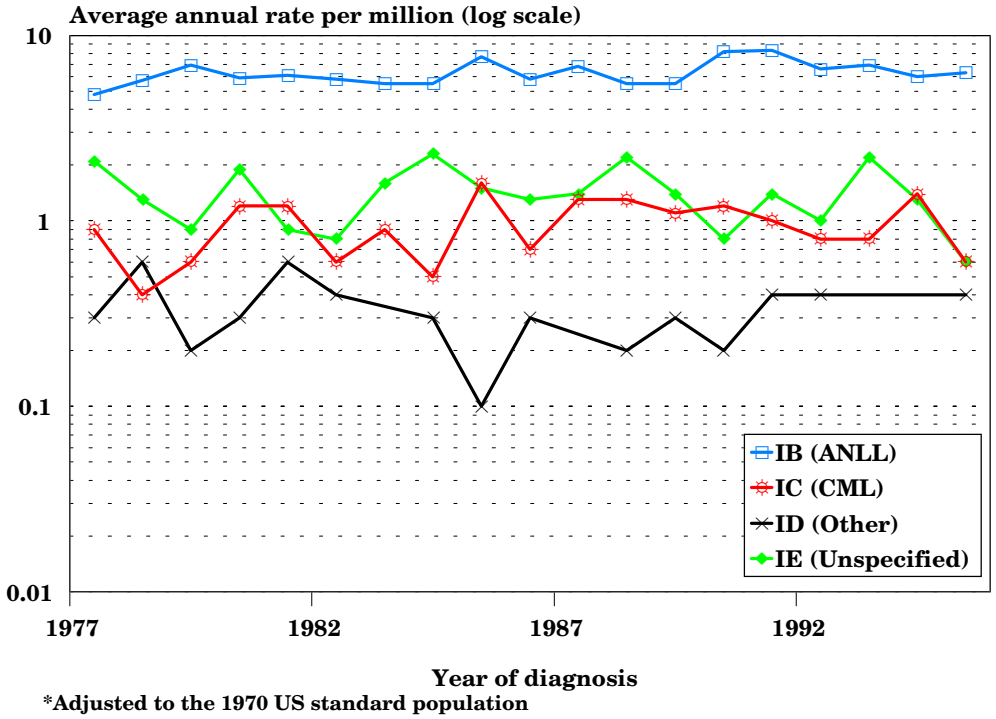


*Adjusted to the 1970 US standard population

1980s, then decreasing to a nadir in 1984-85, and subsequently increasing to rates higher than those for the 9 SEER areas (Figure I.4b). For 1990 to 1995, ALL rates can be calculated for Hispanic and non-Hispanic children. For non-Hispanic children, the ALL rates were similar between Los Angeles (LA) and the 9 SEER areas. However, the ALL rates for Hispanic children were higher than those for non-Hispanic children. Since over one-half of the children younger than 15 residing in Los Angeles were Hispanic, a much higher proportion than for the 9 SEER areas, the overall higher ALL rates in Los Angeles can be explained by the higher proportion of Hispanic children living in LA. In addition, between 1990 and 1995, there were increases in the population of Hispanic children under 15 and decreases in the population of non-Hispanic children under 15 in LA. This change in population characteristics would tend to produce increased rates of ALL due to the higher rates of ALL among Hispanic children. Therefore, the higher ALL rates in LA can be explained by the higher proportion of Hispanic children in LA, and the increase in ALL rates for LA can be at least partially explained by increases in the percentage of Hispanic children in LA. Ongoing monitoring of childhood leukemia trends, as well as epidemiologic and basic laboratory studies, are needed to develop a better understanding of the pathogenesis of childhood leukemia and an enhanced ability to explain changes in leukemia incidence over time.

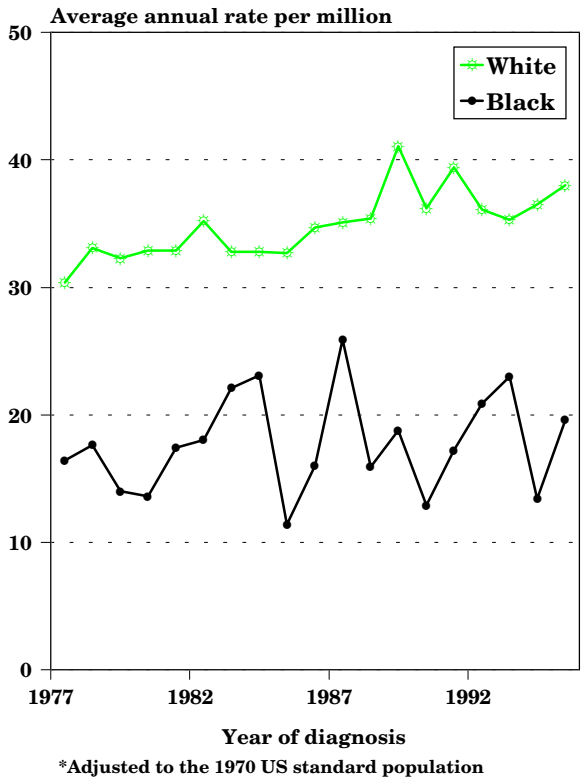
Figure I.6 illustrates the incidence of ALL for white and black children for the period from 1977 to 1995. While the incidence of ALL for white children increased at an overall rate of approximately 1% per year since 1977, there was no apparent increase in ALL rates for black children during this same period.

Figure I.5: Trends in non-ALL leukemia age-adjusted* incidence rates age <15, all races, both sexes, SEER, 1977-95



*Adjusted to the 1970 US standard population

Figure I.6: Trends in ALL age-adjusted* incidencerates by race, age <15 both sexes, SEER, 1977-95



*Adjusted to the 1970 US standard population

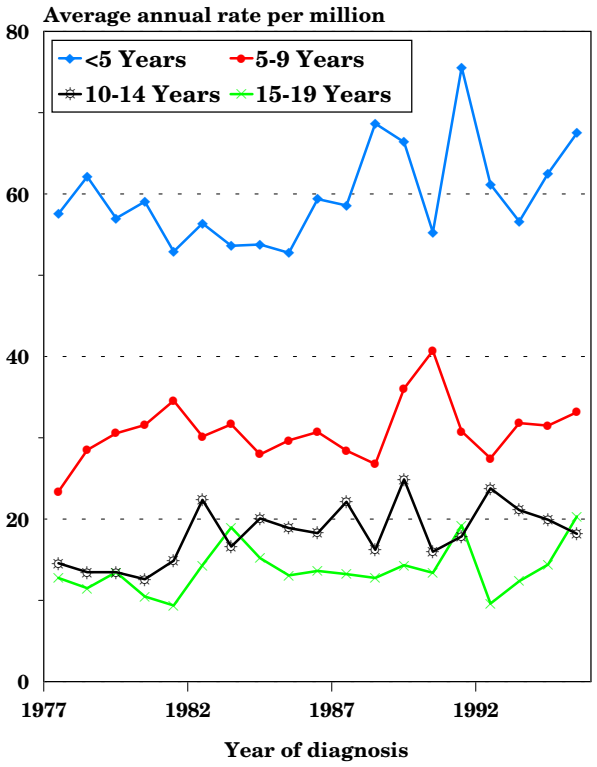
Figure I.7 illustrates the variation in ALL incidence for white children for specific 5-year age groups. Incidence rates for white children 0-4, 5-9, 10-14, and 15-19 years of age demonstrated modest increases when the entire time period was considered. Because the incidence of ALL was greater for those younger than 5 years of age than for the older age groups, the increasing rates for those younger than 5 years of age accounted for the largest proportion of the overall increase in ALL rates for white children.

SURVIVAL

Survival for children with ALL markedly improved from 1975-84 to 1985-94, with 5-year survival rates for children younger than 20 years of age increasing from 61% to 77% (Figure I.8). A number of improvements in treatment during this period have undoubtedly contributed to the improved survival rate, including: a) identification of increasingly effective methods of central nervous system prophylaxis [1]; b) identification of the contribution of treatment intensification to improved outcome for selected groups of patients [27-29]. Examples of effective methods of treatment intensification include use of post-induction consolidation with high-dose methotrexate [28, 29] and use of post-remission re-induction/re-consolidation regimens ("delayed intensification") [27].

Survival for children with ALL is very dependent upon age at diagnosis. For the years 1985-94, 5-year survival rates were highest for the 1-4 year age group and the 5-9 year age group (85% and 80%, respectively) (Figure I.8). Infants had the poorest outcome (37% 5-year survival rate), fol-

Figure I.7: Trends in ALL age-specific incidence rates by year of diagnosis, white children both sexes, SEER, 1977-95

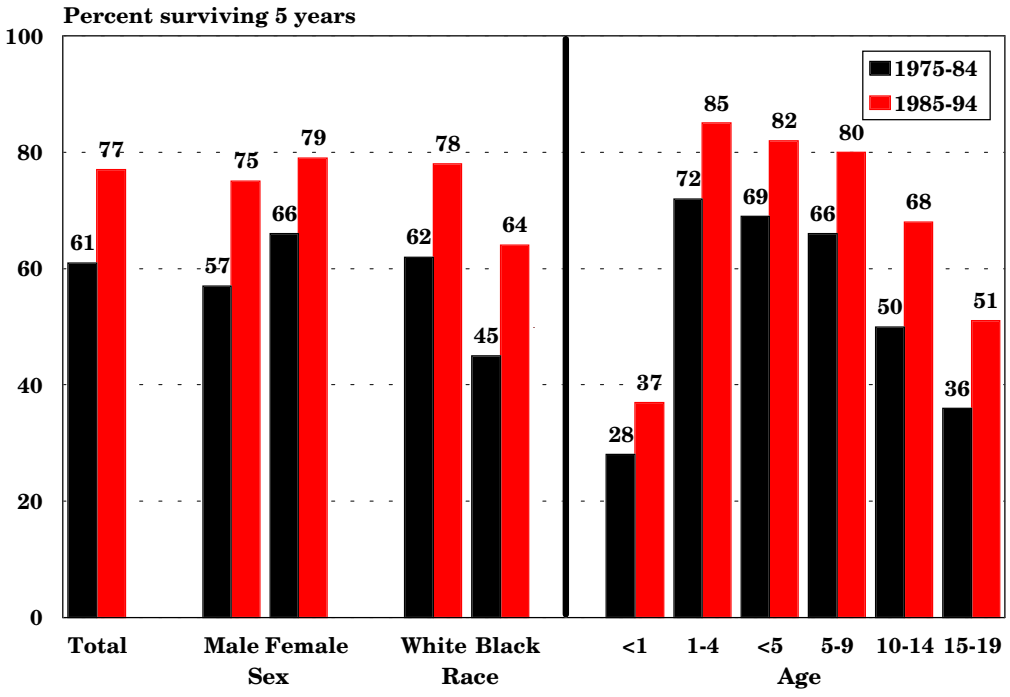


lowed by the 15-19 year age group (51% 5-year survival rate). The favorable prognosis of 1-9 year old children is likely related to the relatively high proportion of cases in this age range with favorable biological subtypes (e.g., cases with hyperdiploid DNA content or with the TEL-AML1 gene rearrangement) [30-32]. The poor prognosis for infants with ALL reflects the high frequency of cases with rearrangements of the MLL gene on chromosome band 11q23 [33,34]. The less favorable outcome for adolescents and young adults is likely due in part to the increased relative frequency of higher risk ALL subtypes (e.g., Philadelphia chromosome positive ALL and T-cell ALL).

For the younger than 20 year old population, 5-year survival rates were slightly higher for females than for males (79% versus 75%) (Figure I.8). Five-year survival rates for black children younger than 20 years of age with ALL were lower than for white children (64% versus 78%). While the poorer outcome for black children with ALL could represent differences between black and white children in the pharmacokinetics or pharmacodynamics of the drugs used for ALL treatment or differences in access to health care, the relative paucity among black children of the most curable ALL subtypes that occur at higher incidence among white children younger than 10 years of age may also contribute to the poorer outcome observed for black children.

Survival for children with AML was substantially lower than that for children with ALL (Figure I.9). While outcome for children with AML improved significantly from 1975-84 to 1985-94, 5-year survival rates were only 41% for the period 1985-94 for the younger than 20 year old age group. In contrast to ALL, older children and adolescents with AML had outcome that was similar to that observed for the

Figure I.8: ALL 5-year relative survival rates by sex, race, age and time period, SEER (9 areas), 1975-84 and 1985-94



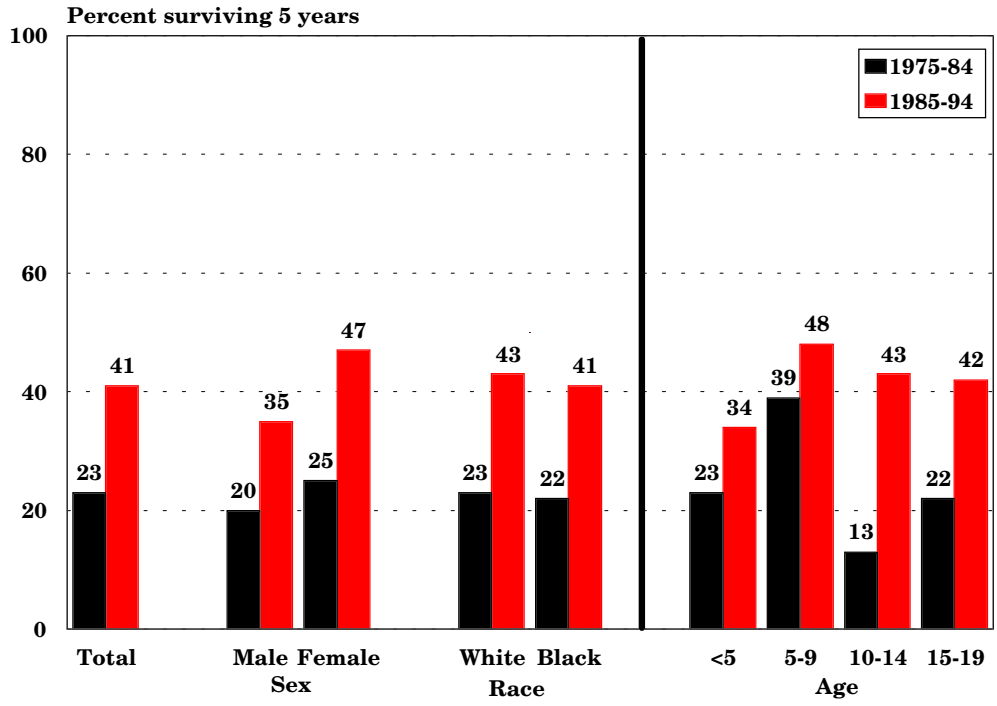
younger than 5-year age group, with the younger than 5-year age group having somewhat lower outcome than for the older age groups. As was the case for ALL, outcome for females with AML was somewhat better than outcome for males. In contrast to the poorer outcome for black children with ALL, for AML outcome was similar for white and for black children younger than 20 years of age.

RISK FACTORS

Tables I.5 and I.6 summarize current knowledge of the causes of childhood ALL and AML. With the exception of prenatal exposure to x-rays and specific genetic syndromes, little is known about the causes of and risk factors for childhood ALL [13]. It is important to note that ALL is a heterogeneous grouping of biological subtypes of leukemia, and smaller studies of the past may have lacked sufficient statistical power to examine potential risk factors. Thus, one emerging theme concerning the etiology of childhood ALL is the need to separately study different biological groups of ALL. For example, the cases of ALL that arise in infants and that have rearrangements of the MLL gene on chromosome 11 appear to have different epidemiological associations than cases that arise in young children that typically have B-precursor ALL immunophenotype and hyperdiploid DNA content [14-16]. Recognition of the need to study these different ALL subtypes independently has been one impetus for larger studies of the etiology of ALL. In these larger studies some intriguing associations have emerged that can be followed up further in more focused investigations. For example, high birth weight and maternal history of fetal loss have been associated primarily with ALL occurring in children younger than 2 years of age [17-19].

From a global perspective, childhood ALL appears to be much more common in

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



countries of the developed world than in those of the developing world, a difference that has been attributed to different patterns of exposure of children in these populations to infectious agents [20,21]. A delayed pattern of infections, as found in countries such as the United States, is hypothesized to somehow cause (or allow) ALL to occasionally develop, possibly through alterations in immune function. However, in the absence of an understanding of specific infectious agents or specific immune perturbations associated with the pathogenesis of ALL, it is not possible to apply these theories to explain the trends in incidence for childhood ALL observed in the United States since the 1970s.

Table I.5: Current knowledge on causes of acute lymphoblastic leukemia (ALL)

Exposure or Characteristic	Comments	References
Known risk factors		
Sex	Overall, there is about a 30% higher incidence in males compared to females.	16,22,36
Age	There is a peak in the incidence between the ages of about 2 and 5.	16,22,36
Race	There is an approximate 2-fold higher risk in white children compared to black children.	16,22,36
Higher socioeconomic status	Increased risk has been fairly consistently associated with the most common ALL (diagnosed at ages 2 - 5 years). It is unknown what aspect of higher SES is relevant but higher age of exposure to infectious agents has been hypothesized.	16,22,36,37
Ionizing radiation (in utero)	In past studies, there was a consistent, increased risk (about 1.5 fold) of leukemia associated with prenatal diagnostic x-ray exposure. However, this is unlikely to be an important risk factor for childhood leukemia today due to fewer x-rays, increased shielding, and lower radiation levels.	16,22,36,38,39
Ionizing radiation postnatal (therapeutic)	Therapeutic radiation for such conditions as tinea capitis and thymus enlargement has been associated with an increased risk.	16,22,36,40
Down syndrome, neurofibromatosis, Shwachman syndrome, Bloom syndrome, ataxia telangiectasia, Langerhans cell histiocytosis, and Klinefelter syndrome	Increased occurrence is associated with these genetic conditions and is particularly apparent in children with Down syndrome for whom there is a reported 20-fold increased risk of leukemia.	16,22,26,36
Factors for which evidence is suggestive but not conclusive		
High birth weight (> 4000 grams)	Several studies have reported an elevated risk (approximately 2-fold) in larger babies, particularly for children diagnosed younger than two years of age.	16,22,36,41
Maternal history of fetal loss prior to the birth of the index child	Approximately 2-5 fold increased risk of leukemia has been noted in a few studies; particularly in children diagnosed younger than two years of age.	16,18,22,36,42
Maternal age > 35 at pregnancy	A slight increased risk has been somewhat inconsistently associated with older maternal age.	16,22,36
First born or only child	Slight increased risk reported but birth order may be surrogate marker for exposure to infectious agent.	16,22,36

Table I.5 (cont'd): Current knowledge on causes of acute lymphoblastic leukemia (ALL)

Factors for which evidence is inconsistent or limited		
Smoking prior to and during pregnancy	Some studies have reported an increased risk associated with maternal smoking during pregnancy but others have not. A few recent studies have suggested a modest increased risk (about 1.5 fold) associated with paternal smoking prior to pregnancy.	16,22,36,43-48
Parental occupations and occupational exposures	Isolated reports associated with parental exposure to motor vehicle exhaust, hydrocarbons, and paints. This is the subject of several current epidemiologic studies.	16,22,36
Postnatal infections	Evidence is very inconsistent.	16,22
Diet	A few reports have suggested that meat consumption (particularly, cured meats) is associated with an increased risk. Maternal diet and childhood leukemia has not been explored in any detail and further study is warranted.	49,50
Electromagnetic fields	A few studies have reported a slight increased risk for children living near high voltage power lines; others have reported no association. A recent large study of U.S. children with ALL found little or no association between risk of ALL and electromagnetic field exposure. Other large epidemiologic studies evaluating this exposure are ongoing.	16,22,51-54
Vitamin K prophylaxis in newborns	Although an increased risk of ALL was first reported in the early 1990's, several large studies since then have found no association.	16,22,55-60
Maternal alcohol consumption during pregnancy	Unlikely to be an important risk factor for ALL (but see AML).	16,22
Postnatal use of chloramphenicol	One study reported quite substantial increased risks (approximately 10-fold) with postnatal use of this broad-spectrum antibiotic.	61
Factors unrelated to risk		
Ultrasound		16,22

*Note that the majority of these risk factors have been reviewed recently in references 16,22,36; only selected references are presented for additional reading.

Different risk factors are emerging for childhood AML that distinguish the disease from ALL, and this may provide avenues for future epidemiological studies. For example, exposure to specific chemotherapy agents has been associated with an increased risk of childhood AML, in contrast to the rarity of treatment-related ALL [22-24]. With this information, it may be possible to design epidemiological studies to examine exposures to environmental agents that have a biologic nature that is similar to these chemotherapy agents [14]. Further, associations with factors such as benzene and pesticides that have emerged in a few studies suggest that childhood AML may share risk factors with adult AML, and this is being investigated in several large epidemiological studies [25]. Finally, as for ALL, the associations of AML with genetic syndromes are compelling, as illustrated by the magnitude of risk of AML in Down syndrome [26].

SUMMARY

ALL is by far the most common type of leukemia occurring in children and shows a distinctive age-distribution pattern, with a marked incidence peak at 2-3 years of age.

Table I.6: Current knowledge on causes of acute myeloid leukemia (AML)

Exposure or Characteristic	Comments	References
Known risk factors		
Race	The highest incidence rates are reported in the Hispanic children.	16,22,36
Chemotherapeutic agents	Increased risk is associated with prior exposure to alkylating agents or epipodophyllotoxins.	16,22,36,62,63
Ionizing radiation (*in utero*)	In past studies, there was a consistent, increased risk (about 1.5 fold) of leukemia associated with prenatal diagnostic x-ray exposure. However, this is unlikely to be an important risk factor for childhood leukemia today due to fewer x-rays, increased shielding, and lower radiation levels.	16,22,36
Down syndrome, neurofibromatosis, Shwachman syndrome, Bloom syndrome, familial monosomy 7, Kostmann granulocytopenia, Fanconi anemia	Increased occurrence associated with these genetic conditions, particularly with Down syndrome. One report suggests as high as a 500-fold increased risk of a specific type of AML in Down syndrome.	16,22,26,36
Factors for which evidence is suggestive but not conclusive		
Maternal alcohol consumption during pregnancy	Three studies have reported an increased risk (approximately 1.5-2 fold) in mothers who drank alcoholic beverages during pregnancy. These associations have been particularly apparent in children diagnosed younger than three years of age.	16,22,36,64
Parental and child exposure to pesticides	Increased risk has been noted in a few studies and in adult AML data; subject of several current investigations.	16,22,25,36,45
Parental exposure to benzene	Exposure has been associated with an increased risk in several studies; again follows adult AML data; also subject of several current investigations.	16,22,36,45
Factors for which evidence is inconsistent or limited		
Maternal use of recreational drugs during pregnancy	One report suggested that maternal marijuana use during pregnancy was associated with increased risk.	65
Radon	A few correlational studies have suggested an increased risk of childhood and adult AML in areas with high radon concentrations; this is a subject of several current epidemiologic studies of AML.	16,22,36
Postnatal use of chloramphenicol	As in ALL, one study found quite substantial increased risks of AML (approximately 10-fold) with postnatal use of this broad-spectrum antibiotic.	61

*Note that the majority of these risk factors have been reviewed recently in references [16,22,36]; only elected references are presented for additional reading.

The peak at 2-3 years of age is much less apparent for black children than for white children, with this difference accounting for the substantially lower incidence of ALL observed for black children. By contrast with ALL, the age-distribution pattern for AML shows highest rates in the first two years of life, with decreasing incidence until 10 years of age followed by increasing rates thereafter. Again in contrast to ALL, the incidence of AML in black children and white children is similar.

The improvement in survival for children with ALL over the past 35 years is one of the great success stories of clinical oncology. Survival rates for childhood ALL were below 5% in the early 1960s, but are now approaching 80% [35]. Outcome for children with AML has also improved, but 5-year survival rates have increased to only the 40% range. Black children with ALL have poorer outcome than do white children, but for AML there is similar outcome for black children and white children. Since the peak in ALL incidence at 2-3 years of age is much lower for black children than for white children and since these ALL cases in young children are known to have the most favorable prognosis, the poorer outcome for black children may reflect in part a different distribution of biological subtypes of ALL in black children compared to white children.

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