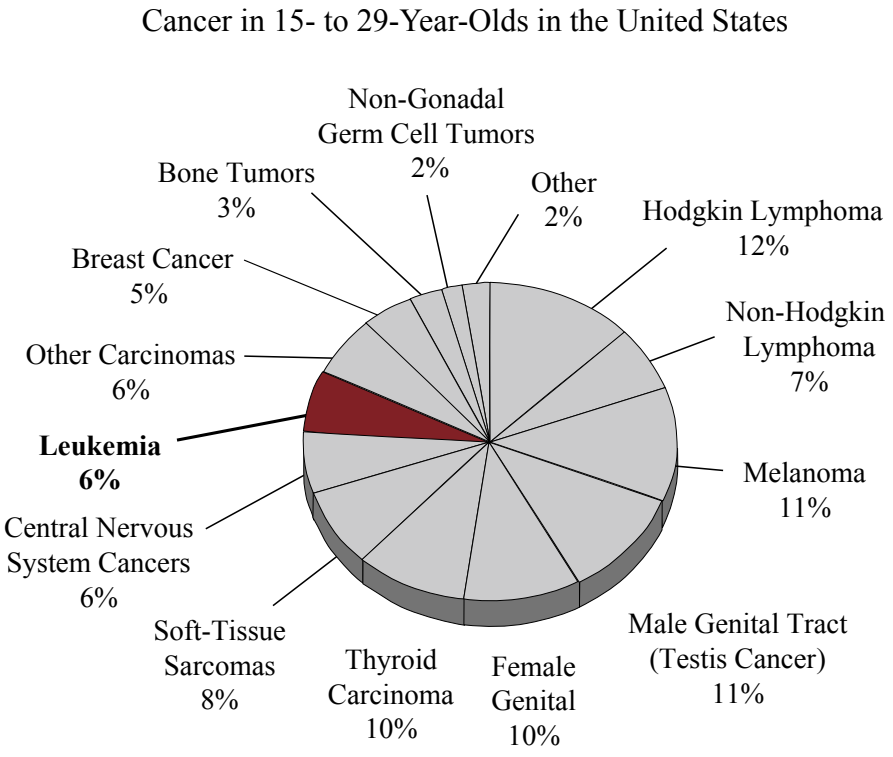
Chapter 4

Leukemias



Leonard Mattano, Jr., MD

James Nachman, MD

Julie Ross, PhD

Wendy Stock, MD

HIGHLIGHTS

Incidence

- The leukemias represented 6% of all cancers that occurred in 15- to 29-year-olds in the United States over the time period 1975 to 1999.
- Approximately 24 persons per million patients 15 to 29 years of age were diagnosed with leukemia in the U.S. during the year 2000.
- The incidence of leukemia was lower in the 15- to 29-year cohort than in any other age group.
- In the years between adolescence and older adulthood, the incidence of acute lymphoblastic leukemia (ALL) gradually decreased as the incidence of acute and chronic myeloid leukemias (AML and CML) increased.
- In the 15- to 19-year age group, ALL occurred at a rate twice that of AML; in the 20- to 24-year age group, both types of leukemia occurred at approximately equal rates; but in the 25- to 29-year age group, AML occurred at a rate 1.5 times that of ALL.
- Between 1975 and 1999, leukemia increased in incidence in 15- to 29-year-olds, with those in the 20- to 24-year age group experiencing the greatest increment, at an average rate of 1.2% per year.

Mortality & Survival

- During the period 1975 to 1999, the death rate for leukemias was higher for males than females in all age categories.
- Hispanics experienced the highest mortality for leukemias in those younger than 25 years, while African Americans/blacks had the highest mortality in those 25 years and older.
- Five-year survival rates for leukemia declined with advancing age.
- Survival rates for leukemia declined significantly as a function of age for those older than 15 years of age, and remained below 20% at 20 years for all age groups 20 years of age or older.
- An improvement in survival has occurred since 1975 in each category of leukemia, although the decrease in mortality among adolescent and young adult patients with ALL lags behind that of younger patients.
- Despite being a "chronic" leukemia, the ultimate survival of patients with CML was poor in all age groups, with a 20-year survival less than 20% regardless of age at diagnosis—including chronic myelogenous leukemias of childhood (juvenile myelomonocytic leukemia, etc.).

Risk Factors

- Risk factors for ALL include male gender, young age (2 to 5 years), Caucasian race/ethnicity, pre- and post-natal radiation exposure, and constitutional syndromes including trisomy 21, neurofibromatosis type 1, Bloom syndrome, Shwachman syndrome, and ataxia-telangiectasia.
- Risk factors for AML include Hispanic race/ethnicity, chemotherapeutic exposure to alkylating agents or topoisomerase II inhibitors, and constitutional syndromes including trisomy 21, Fanconi anemia, neurofibromatosis type 1, Bloom syndrome, Shwachman syndrome, familial monosomy 7, and Kostmann granuocytopenia.

INTRODUCTION

Leukemias represented approximately 6% of the cancers that occurred in adolescents and young adults over the time period 1975 to 2000. In the transition between childhood and older adulthood, the incidence of acute myeloid leukemia (AML) slowly rose while that of acute lymphoblastic leukemia (ALL) steadily decreased. In the 15- to 19-year age group, ALL occurred with an incidence approximately twice that of AML, whereas in the 25- to 29-year age group the incidence of AML was approximately 1.5 times that of ALL.

METHODS, CLASSIFICATION SYSTEM, AND BIOLOGICAL IMPLICATIONS

In the International Classification of Childhood Cancer (ICCC), leukemia is category I and in the International Classification of Diseases for Oncology, Second Edition (ICD-O-2) it spans categories 9800 to 9941. Leukemias coded under ICD-O-3 were converted to ICD-O-2 codes for inclusion in this chapter.

The ICCC leukemia class excludes the following ICD-O-3 histologies: myelodysplastic syndromes (refractory anemias with preleukemic manifestations) (9980-9989), and some chronic myeloproliferative disorders (9950, 9960-9962). The ICD-O-3 histologies of hypereosinophilic syndrome (9964) and chronic neutrophilic leukemia (9963) were included with I(e) unspecified leukemia. ICD-O-3 histologies of chronic myelomonocytic leukemia, NOS (9945) and juvenile myelomonocytic leukemia (9946) are reported under chronic myelomonocytic leukemia (ICD-O-2 9868) and ICCC I(c) and aggressive NK-cell leukemia (9948) is reported under ICD-O-2 code 9801 and ICCC I(e).

The ICCC I(a) has two subcategories of *lymphoid leukemia*, ALL and non-ALL lymphoid leukemia. ALL corresponds to ICD-O-2 9821, which has been expanded in ICD-O-3 as follows: precursor cell lymphoblastic leukemia, NOS (9835), precursor B-cell lymphoblastic leukemia (9836), and precursor T-cell lymphoblastic leukemia (9837). The "non-ALL" lymphoid leukemias are constituted by "lymphoid leukemia" (9820), acute, subacute, chronic, and aleukemic lymphocytic leukemia (9822-9824), prolymphocytic leukemia (9825), Burkitt cell leukemia (9826), and adult T-cell leukemia (9827).

ICCC I(b) includes acute myeloid leukemias. ICCC I(b) has two subcategories: AML (9861) and non-AML acute leukemia [erythroleukemia (9840), acute erythemia (9841), aleukemic myeloid leukemia (9864), acute promyelocytic leukemia (9866), acute myelomonocytic leukemia (9867), acute monocytic leukemia (9891), aleukemic monocytic leukemia (9894), and acute megakaryocytic leukemia (9910). Included in AML are the following ICD-O-3 categories: acute myeloid leukemia with abnormal marrow eosinophils (9871), acute myeloid leukemia, minimal differentiation (9872), acute myeloid leukemia without maturation (9873), and acute myeloid leukemia with maturation (9874).

Chronic Myeloid Leukemia is category I(c) in the ICCC and applies to chronic myeloid leukemia (9863) and chronic myelomonocytic leukemia (9868) in the ICD-O-2. Additional ICD-O-3 groups included in I(c) are chronic myelogenous leukemia, BCR/ABL positive (9875) and atypical chronic myeloid leukemia, BCR/ABL negative (9876).

ICCC designates *Other Specified Leukemias* and *Unspecified Leukemias* in category I(d) and I(e), respectively. These two categories in ICCC apply to miscellaneous and unspecified types of leukemia (9800-9804, 9830, 9842, 9860, 9862, 9870-9890, 9892, 9893, 9900, 9930-9941).

For cases diagnosed in 2001 and forward, ICD-O-3 divides AML and CML into several different subtypes, but previous versions of the ICD-O did not. ICD-O-3 includes, in addition, data for lymphoproliferative syndromes, which are not included in this chapter.

As explained in the *Methods* chapter, data are presented for 15- to 29-year-olds with comparisons to the age groups 0 to 15 years and 30 to 44+ years, as appropriate. For some analyses the entire age range from birth to 85+ years is included. The absence of data in any figure or table within this chapter means that too few cases were available for analysis; it does not mean that the rate or change in rate was zero.

ALL in the 15- to 19-year age group is characterized by a higher proportion of T-cell immunophenotype, higher hemoglobin levels at diagnosis, and a lower frequency of lymphomatous features compared to younger children.[1] Cytogenetically, ALL in this age group is associated with a lower ratio of favorable features than is seen in younger children, including t(12;21) and hyperdyploidy (chromosome number > 51), and a higher incidence of Philadelphia-positive ALL,[1,2] although still low by comparison with older adults.

Adolescents with leukemia may receive care from either pediatric or medical oncologists. Four recent studies have suggested that young adult patients with ALL entered on

Table 4.1: *Incidence of Leukemia in Persons Younger Than 30 Years of Age, U.S., 1975-2000*

AGE AT DIAGNOSIS (YEARS)	<5	5-9	10-14	15-19	20-24	25-29
U.S. population, year 2000 census (in millions)	19.176	20.550	20.528	20.220	18.964	19.381
ALL LEUKEMIA						
Average annual incidence per million, 1975-2000, SEER	68.2	35.2	24.2	22.7	20.7	22.7
Average annual % change in incidence, 1975-2000, SEER	0.8%	2.2%	2.1%	1.5%	22.9%	0.2%
Estimated incidence per million, year 2000, U.S.	74.1	39.3	26.3	23.5	23.5	22.8
Estimated number of persons diagnosed, year 2000, U.S.	1,308	723	541	475	446	442
ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)						
Average annual incidence per million, 1975-2000, SEER	55.3	28.4	15.9	11.5	6.4	4.9
Average annual % change in incidence, 1975-2000, SEER	0.9%	3.3%	3.8%	2.8%	71.1%	17.6%
Estimated incidence of ALL per million, year 2000, U.S.	60.6	32.8	18.3	12.4	8.5	6.2
Estimated number of persons diagnosed, year 2000, U.S.	1.060	584	375	251	162	120.4
ACUTE MYELOGENOUS LEUKEMIA (AML)						
Average annual incidence per million, 1975-2000, SEER	5.4	3.4	4.2	5.8	6.7	7.5
Average annual % change in incidence, 1975-2000, SEER	1.7%	-9.4%	51.1%	8.5%	22.2%	38.5%
Estimated incidence of AML per million, year 2000, U.S.	6.3	3.0	3.4	5.3	5.9	4.8
Estimated number of persons diagnosed, year 2000, U.S.	103	69	70	108	112	94
CHRONIC MYELOID LEUKEMIA (CML)						
Average annual incidence per million, 1975-2000, SEER	1.0	0.6	1.0	2.1	3.1	5.2
Average annual % change in incidence, 1975-2000, SEER	na	na	na	-22.3%	29.1%	-13.6%
Estimated incidence per million, year 2000, U.S.	0.0	0.0	1.4	1.7	2.7	5.5
Estimated number of persons diagnosed, year 2000, U.S.	19	12	28	34	51	106

pediatric clinical trials have a significantly better event-free survival (EFS) and overall survival compared to adolescents treated on adult clinical trials.[3-6] The recently completed Children's Cancer Group study CCG-1961 for newly diagnosed patients with high-risk ALL had a 5-year EFS of 69.5% and a 5-year survival rate of 77%.[7] No difference in outcome has been observed for adolescents with AML treated on adult versus pediatric protocols.

INCIDENCE

Age-Specific Incidence

Table 4.1 shows age-adjusted incidence for ICCC subcategories, and Figures 4.1 and 4.2 illustrate the strong dependence on age of all leukemia and the individual subtypes. During the last quarter century, the incidence of leukemia peaked in early childhood and reached a nadir in late adolescence, and it was lower in the 15- to 29-year cohort than in any other younger or older age group except infants younger than 1 year of age.

The incidence of leukemia as a percentage of all cancers was inversely proportional to age, reflecting the rise in incidence of other cancers beginning at about 10 years of age (Figure 4.1). Within 5-year age groups there was a decrease in incidence from 11.5% in 15- to 19-year-olds to 6.4% and then to 4.2% in 20- to 24-year-olds and 25- to 29-year-olds, respectively. Leukemia represented 35.2% of all cancers in those younger than 5 years of age and 20.8% in those 10 to 14 years of age. In adults over 30 years the percentage was low, and gradually declined to just 2.3% of all cancers by age 40.

As shown in Figure 4.2 and Table 4.1, the incidence of different types of leukemia varied with age. Overall, ALL

decreased in incidence across all age groups, while AML and chronic myelogenous leukemia (CML) increased in incidence beyond age 5 years. ALL was the most common type in the 15- to 19-year group, occurring at an annual rate of 11.5 per million, twice that of AML. However, over the subsequent two 5-year age groups, ALL and AML incidence curves crossed: they were approximately equal in the 20- to 24-year age group, at about 6.6 per million; in the 25- to 29-year age group AML occurred at a rate of 7.5 per million, compared with a rate of 4.9 per million for ALL. The incidence of CML was 1.7 per million in children under 15 years of age and gradually increased over the 15- to 29-year age range, reaching a rate of 5.2 per million in those 25 to 29 years old, at which point it was more common than ALL.

Gender-Specific Incidence

Leukemia occurred with greater frequency in males of all ages, as shown in Figure 4.3. The male:female (M:F) ratio was relatively stable from birth through 44 years (M:F = 1.2 to 1.5) (Table 4.2). When examining gender incidence ratios in adolescents and young adults, differences emerge within the types of leukemia (Figures 4.4A-C; Table 4.2). ALL showed a male preponderance (1.9 to 2.1), whereas gender differences were marginal in AML, with M:F ratios of 1.0 in the 15- to 19- and 20- to 24-year groups, and 1.2 in the 25- to 29-year group. CML showed a male preponderance in all groups; as the overall incidence rose steadily with advancing age, the gender discrepancy widened to 2.1.

Racial/Ethnic Differences in Incidence

The incidence of leukemia in the 15- to 29-year age group varied by race/ethnicity (Figure 4.5; inset). Hispanics experienced the highest rate of leukemia—32.2 per million population—which was 1.3- to 1.7-fold higher than that of other racial/ethnic groups. The incidence in African Americans/blacks was lower, at 19.0 per million. The same ordering of incidence was seen in the 15- to 19- and 20- to 24-year age groups. In the 25- to 29-year age group, the incidence among African Americans/blacks increased to 25.7 per million, similar to the other racial/ethnic groups.

For ALL, the incidence order by race/ethnicity in 15- to 29-year-olds was similar to that of leukemias in general, with a slightly higher incidence in white non-Hispanics

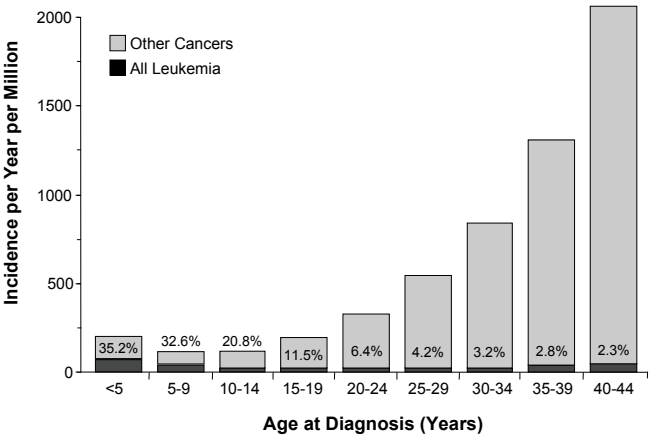


Figure 4.1: Incidence of Leukemia Relative to All Cancer, SEER, 1975-1999

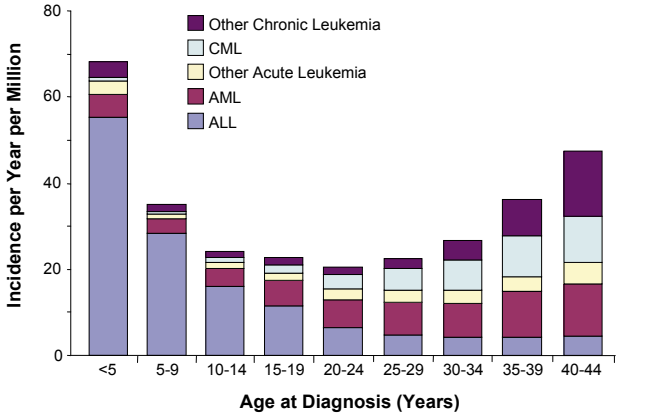


Figure 4.2: Incidence of Leukemia by Type, SEER 1975-1999

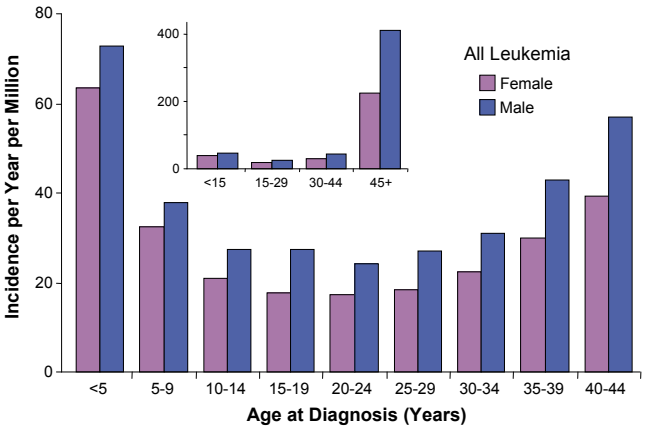


Figure 4.3: Incidence of All Leukemia by Gender, SEER 1975-1999

Table 4.2: *Investigated Risk Factors for ALL and AML*[8; modified]

DEGREE OF CERTAINTY	ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)	ACUTE MYELOID LEUKEMIA (AML)
GENERALLY ACCEPTED RISK FACTORS	Males	Race (Hispanic)
	Age (2-5 years)	Chemotherapeutic agents (alkylating agents, topoisomerase II inhibitors)
	High socioeconomic status	Down syndrome
	Race (whites>blacks)	Fanconi anemia
	In utero x-ray exposure	Neurofibromatosis type 1
	Postnatal radiation (therapeutic)	Bloom syndrome
	Down syndrome	Shwachman syndrome
	Neurofibromatosis type 1	Familial monosomy 7
	Bloom syndrome	Kostmann agranulocytosis
	Shwachman syndrome	
	Ataxia-telangiectasia	
SUGGESTIVE OF INCREASED RISK	Increased birth weight	Maternal alcohol consumption during pregnancy
	Maternal history of fetal loss	Parental and child exposure to pesticides Parental solvent exposure
LIMITED EVIDENCE	Parental smoking prior to or during pregnancy	Maternal marijuana use during pregnancy
	Parental occupational exposures	Indoor radon
	Postnatal infections	Postnatal use of chloramphenicol
	Diet	
	Vitamin K prophylaxis in newborns	
	Maternal alcohol consumption during pregnancy	
	Electric and magnetic fields	
	Postnatal use of chloramphenicol	
PROBABLY NOT ASSOCIATED	Ultrasound	
	Indoor radon	

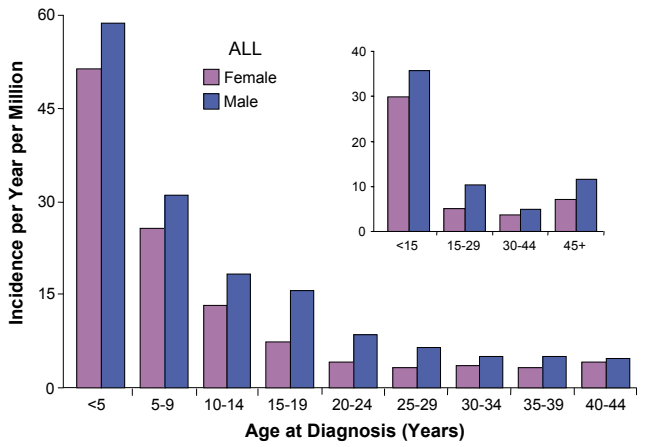


Figure 4.4A: Incidence of ALL by Gender, SEER, 1975-1999

as compared to Asians/Pacific Islanders and with a 2.1-fold excess incidence among Hispanics as compared to African Americans/blacks (Figure 4.6; inset).

The incidence of AML (Figure 4.7) was highest in Asians/Pacific Islanders, but the racial/ethnic variation was modest (range 5.9 to 7.7 per million). Due to the low incidence of CML among those 15 to 24 years of age, more comprehensive racial/ethnicity data were available for the 25- to 29-year age group, in which the incidence was highest for Asians/Pacific Islanders (6.7 per million), with lower—and virtually equivalent—incidence for the remaining racial/ethnic groups (approximately 5.3 per million) (Figure 4.8).

Incidence Trends

Between 1975 and 1999, the incidence of leukemia in children younger than 15 years of age increased annually at a statistically-significant average of 0.8% per year (Figure 4.9). In 15- to 29-year-olds the annual rate of increase was 0.6%. The highest rate of increase occurred in 20- to 24-year-olds, at an average of 1.2% per year. Adults 30 years and older experienced a modest decrease in annual incidence, which was statistically significant in those over 45 years of age when diagnosed.

From 1975 to 1999, the incidence of leukemias in females 15 to 29 years old increased annually at an average rate two-fold that of males (0.8 versus 0.4%) (Figure 4.10). For children younger than 15 years of age the rate of increase was similar for both genders. In older age groups the annual incidence of leukemia decreased for both genders, with the greatest decrease among women in the 30- to 44-year subset and among men 45 years old and older.

The annual incidence of ALL has increased for all age groups (Figure 4.11). Between 1975 and 1999, the incidence of ALL increased by an average of 1.5% per year for those 15 to 29 years of age and by 1.0% per year for those younger than 15 years and for those 30 years of age and older. AML has shown an annual decline in incidence in all age groups 15 years of age or younger—on average, a decrease of 1.4% per year for 15- to 29-year-olds, 1.9% for those 30- to 44 years, and 0.5% for those 45 years of age and older. Trend data for AML are not

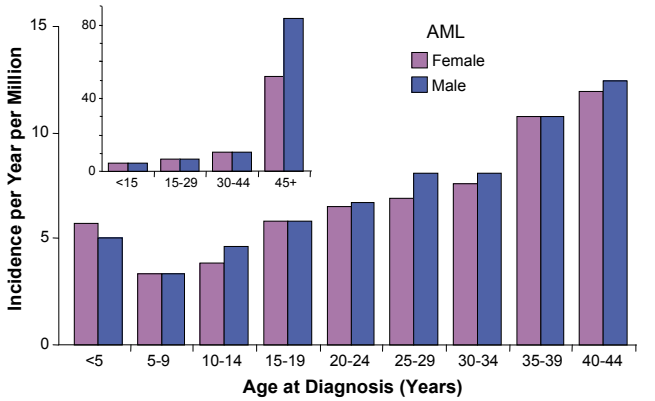


Figure 4.4B: Incidence of AML by Gender, SEER 1975-1999

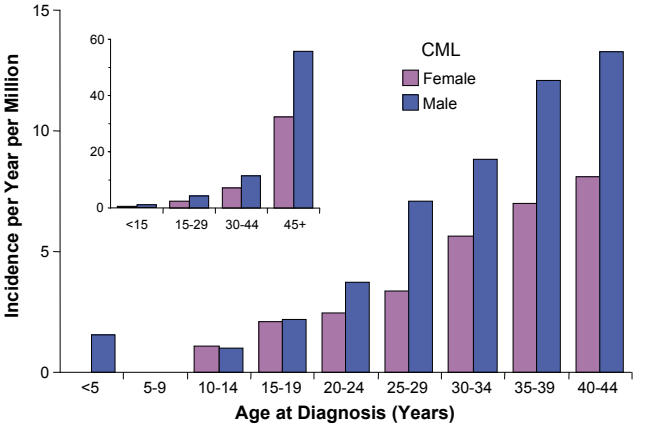


Figure 4.4C: Incidence of CML by Gender, SEER 1975-1999

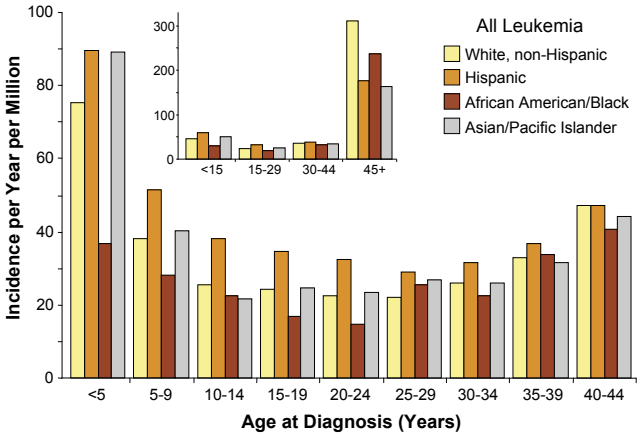


Figure 4.5: Incidence of All Leukemia by Race/Ethnicity, SEER 1990-1999

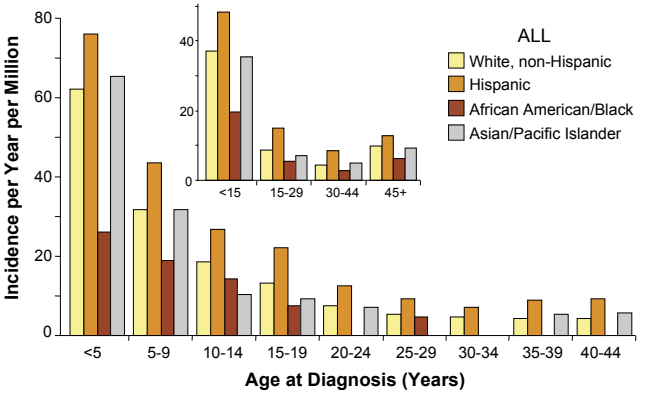


Figure 4.6: Incidence of ALL by Race/Ethnicity, SEER 1990-1999

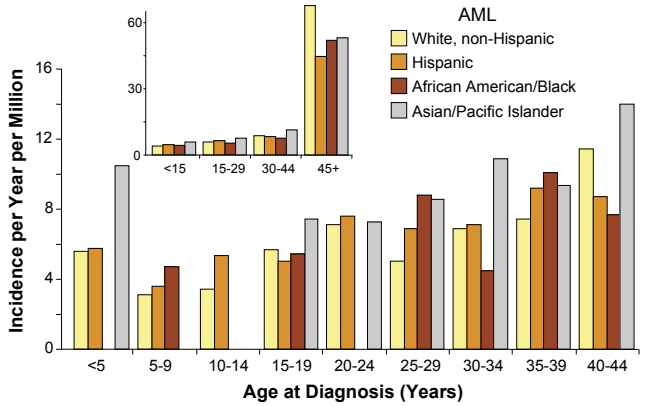


Figure 4.7: Incidence of AML by Race/Ethnicity, SEER 1990-1999

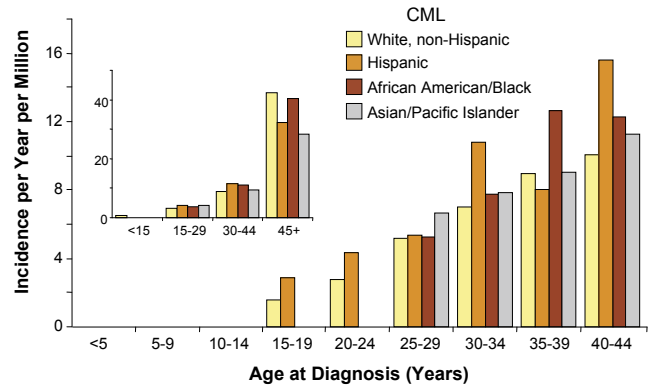


Figure 4.8: Incidence of CML by Race/Ethnicity, SEER 1990-1999

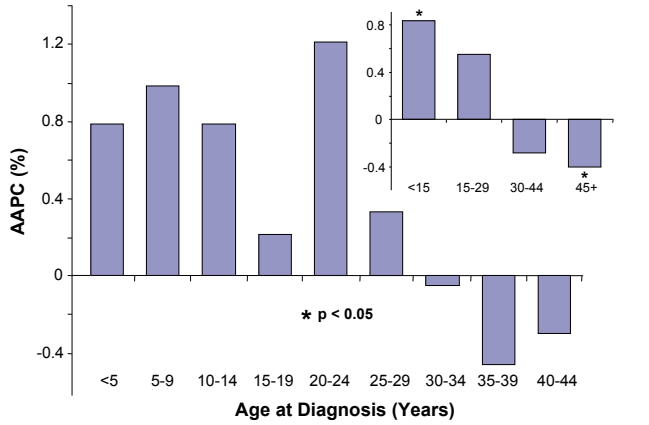


Figure 4.9: Average Annual Percent Change (AAPC) in Incidence of All Leukemia, SEER 1975-1999

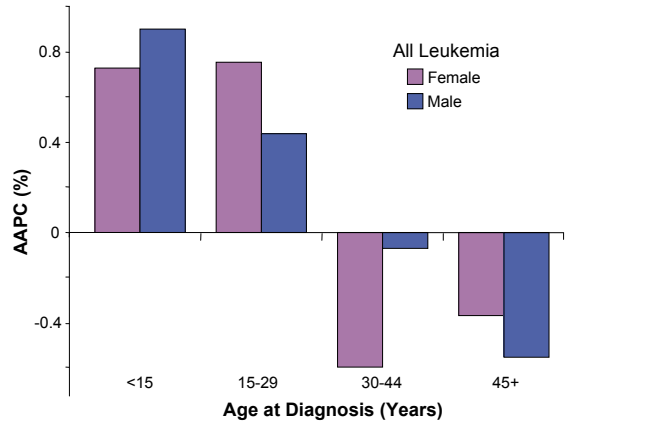


Figure 4.10: Average Annual Percent Change (AAPC) in Incidence for all Leukemia by Gender, SEER 1975-1999

available for those younger than 15 years of age due to the low baseline incidence.

OUTCOME

Mortality

During the period 1975 to 1999, mortality (deaths per year per million) for leukemias was higher for males than females in all age categories (Figure 4.12). The discrepancy was smallest for those younger than 5 years of age, with a M:F mortality ratio of 1.1, and remained in the 1.3 to 1.6 range through age 44; thereafter mortality for males was 1.8-fold that of females. Figure 4.13 shows mortality as a function of SEER incidence, thus normalized for the higher incidence of leukemias in males. These data reveal equivalent death rates for males and females in those younger than 5 and those 10 to 34 years old. The death rate was slightly higher for males in the 5- to 14-year age range, and was slightly higher for females 35 years and older.

Race/ethnicity data from 1990 to 1999 (Figure 4.14) reveal that Hispanics experienced the highest mortality in those younger than 25 years of age with leukemia, while African Americans/blacks had the highest mortality of those 25 years and older. The lowest mortality was consistently seen among American Indians/Alaska Natives in all age groups except those 20 to 24 years old; Asians/Pacific Islanders had a slightly lower mortality in this age group (9.2 versus 9.7 per million per year).

Survival

For the population in general and for both genders, 5-year survival rates for all leukemia declined with advancing age. For the 1975 to 1998 era, the 20-year survival rates were highest among those younger than 10 years of age, at 62% and 59% for the 0- to 5-year-olds and the 5- to 9-year-olds, respectively (Figure 4.15). The 20-year rates decreased dramatically for the next two age groups (10 to 14 years, 42%; 15 to 19 years, 30%, and remained below 22% for all groups 20 years of age and older.

As shown in Figures 4.16 and 4.17, long-term survival rates for each gender were twice as high among those younger than 15 years than in those 15 to 29 years, and even lower for those 30 years of age and older.

The same inverse relationship between survival and age at diagnosis was observed for ALL (Figures 4.18, 4.19, and 4.20), with the 15- to 29-year age groups having 20-year survival rates that were 5% to 10% better than for all leukemia (Figure 4.15).

Among those with AML (Figure 4.21), the 5- to 9-year age group had the highest 20-year survival rate (39%), followed by those under 5 years (30%). Individuals 15 to 29 years of age had 20-year survival rates between 20% and 27%, while survival for those 30 years and older was below 20%. Patients over 45 years of age had only a 5% 20-year survival.

Figure 4.22 shows 20-year survival rates for CML patients over the period 1975 to 1998. Despite being a "chronic"

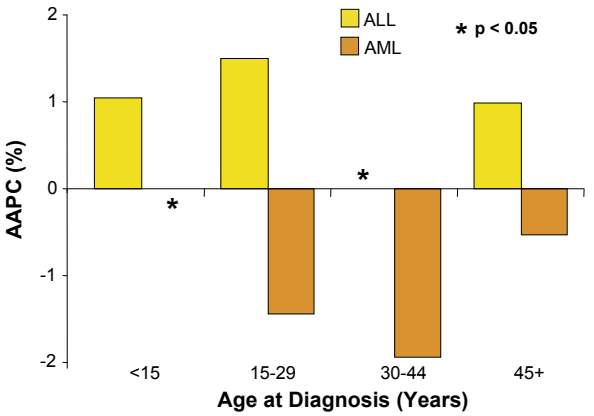


Figure 4.11: Average Annual Percent Change (AAPC) in Incidence for AML and ALL, SEER 1975-1999

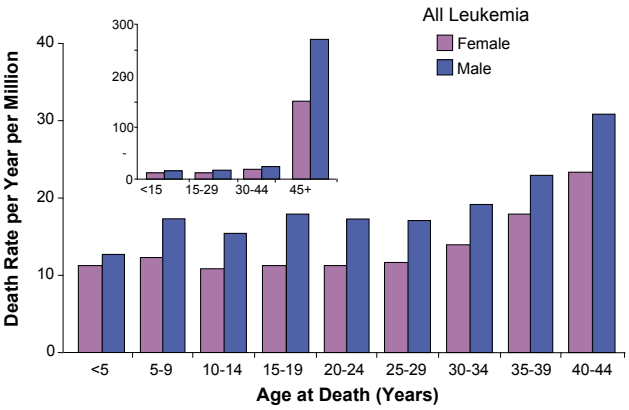


Figure 4.12: National Mortality for All Leukemia by Gender, 1975-1999

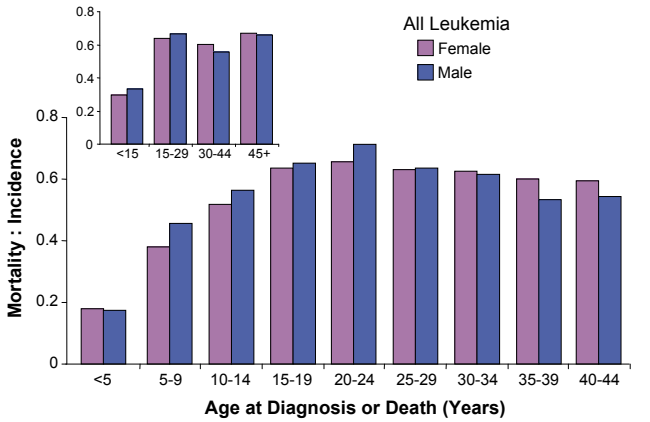


Figure 4.13: Ratio of National Mortality to SEER Incidence for All Leukemia, 1975-1999

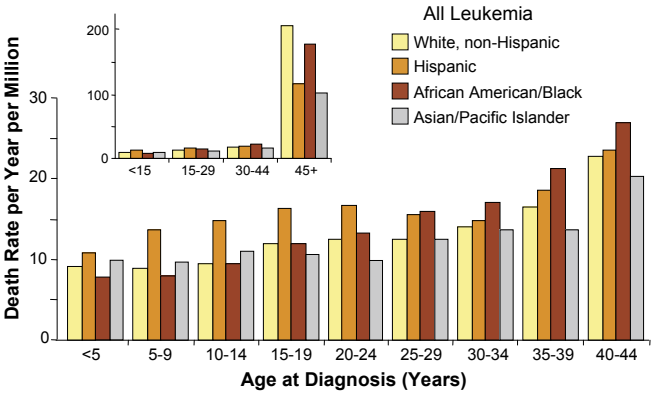


Figure 4.14: National Mortality by Race/Ethnicity for All Leukemia, 1990-1999

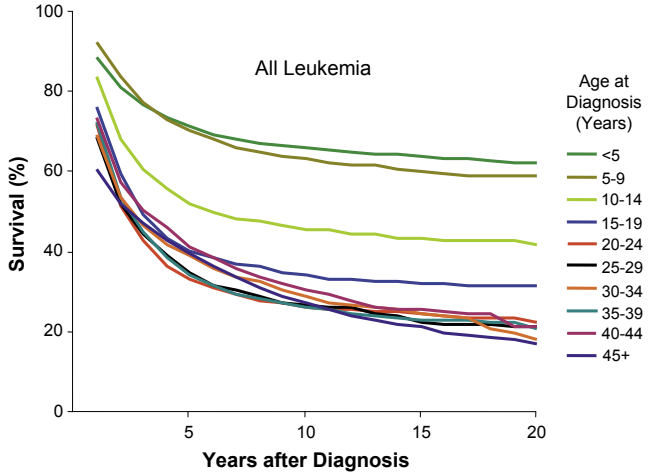


Figure 4.15: Survival Rates for All Leukemia by Age, SEER 1975-1998

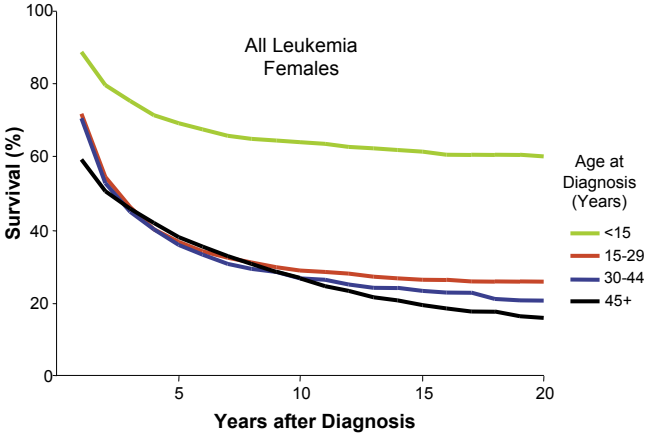


Figure 4.16: Survival Rates for All Leukemia in Females by Age, SEER 1975-1998

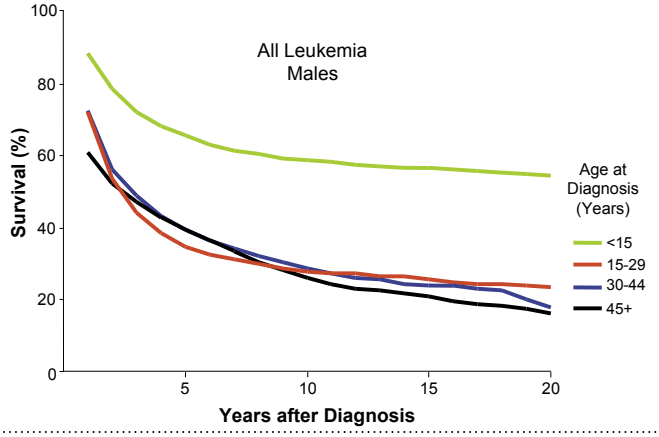


Figure 4.17: Survival Rates for All Leukemia in Males, by Age, SEER 1975-1998

leukemia, the ultimate survival was poor in all age groups, with 12-year survival rates less than 20% in all patients older than 15 years when diagnosed. The best survival was in the <5 and 15- to 19-year age groups (about 30 % at 15 years) and the worst survival occurred in those older than 45, of whom 85% died within two years.

Figures 4.23, 4.24, and 4.25 illustrate the 5-year survival rates for all leukemia, for ALL, and for AML by age according to era (four equal 6-year intervals from 1975 to 1998). While improvements in survival in each disease and age category occurred during this period, survival for the acute leukemias remained inversely correlated with age (Figs. 4.24 and 4.25). There was less of an age-dependent difference for all leukemia in those older than 15 years (Fig. 4.23), in large part due to an increasing proportion of chronic leukemias across this age span. In ALL, steady progress was made across the eras in all age groups. During the late 1980s and 1990s, progress in AML therapy in those under 30 years of age was negligible and considerably less than in older patients.

RISK FACTORS

Numerous risk factors have been investigated as to their potential association with the development of leukemia in children and adolescents, although little is known about such factors for older adolescents and young adults. These have been summarized recently into categories, based on the degree of certainty of the association, and include demographic, environmental, genetic, and exposure-related factors (Table 4.2). Age, gender, race/ethni-

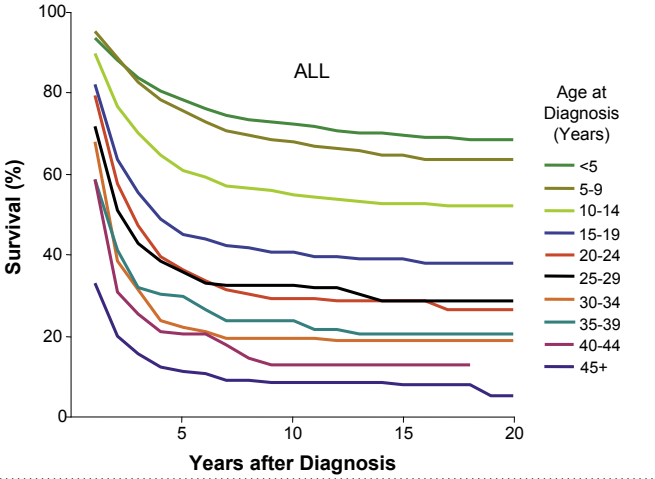


Figure 4.18: Survival Rates for ALL by Age, SEER 1975-1998

city, socioeconomic status, genetic syndromes, and radiation exposure (in-utero and/or therapeutic) are known risk factors for leukemias in younger age groups.[8]

Genetic syndromes have been reported in an estimated 2.6% of British children diagnosed with leukemia, 90% of these attributable to Down syndrome (DS, constitutional trisomy 21).[9] Whereas the pathogenic basis for the 10- to 20-fold increased risk of ALL in individuals with DS has not been elucidated, somatic mutations of the GATA1 gene are seen in virtually all cases of DS-associated AML and may be implicated in the 500-fold increased risk of megakaryoblastic AML seen in these patients.[10,11] Such mutations may also confer enhanced leukemic sensitivity to cytarabine via dysregulation of cytidine deaminase gene expression.[12]

Among individuals with neurofibromatosis type 1, homozygous mutations in the neurofibromin tumor-suppressor gene are associated with myeloid leukemias.[13] Characteristic to the chromosome breakage syndromes is DNA instability resulting in aberrant pathways of DNA repair. Mutations associated with leukemic and lymphomatous malignancy have been identified in genes associated with ataxia-telangiectasia (ATM, ATR), Fanconi anemia (FANC family), and Bloom syndrome (BLM).[14,15] Causative factors in the development of leukemias in those with congenital neutropenia (Kostmann agranulocytosis, Shwachman syndrome) have not been identified. The autosomal dominant form of severe congenital neutropenia is associated with heterozygous mutations in the neutrophil elastase gene (ELA2) and consequent alterations in the

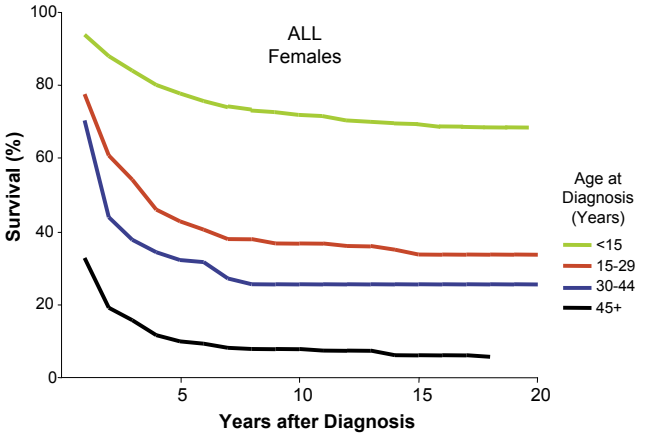


Figure 4.19: Survival Rates for ALL in Females by Age, SEER 1975-1998

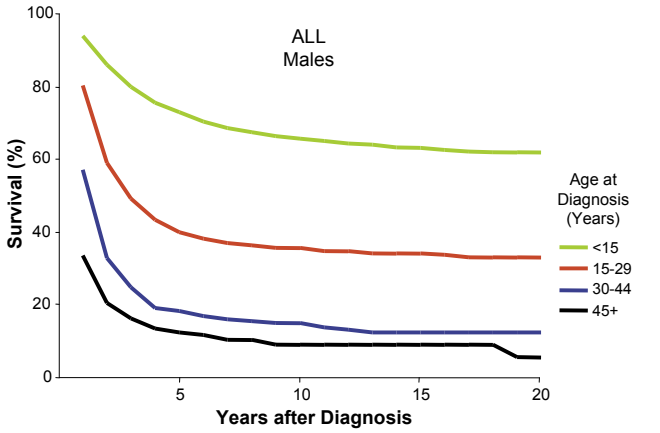


Figure 4.20: Survival Rates for ALL in Males by Age, SEER 1975-1998

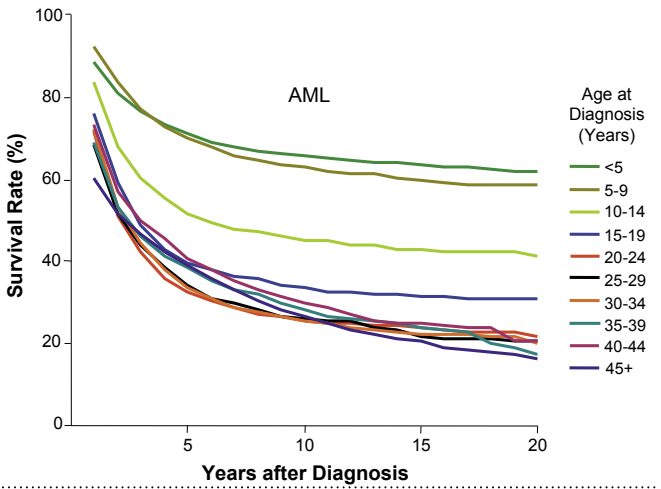


Figure 4.21: Survival Rates for AML by Age, SEER 1975-1998

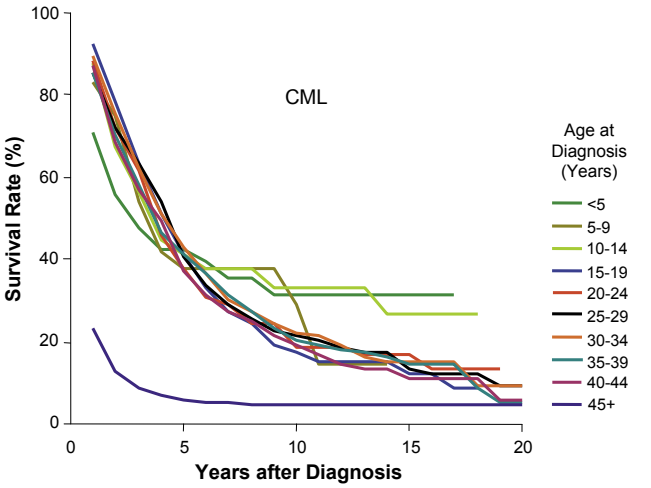


Figure 4.22: Survival Rates for CML by Age, SEER 1975-1998

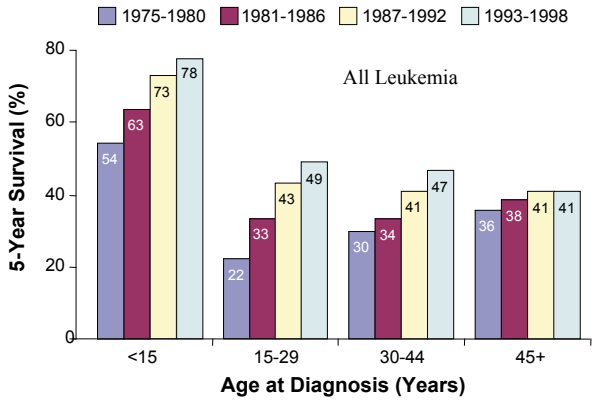


Figure 4.23: 5-Year Survival Rate for All Leukemia by Era, SEER

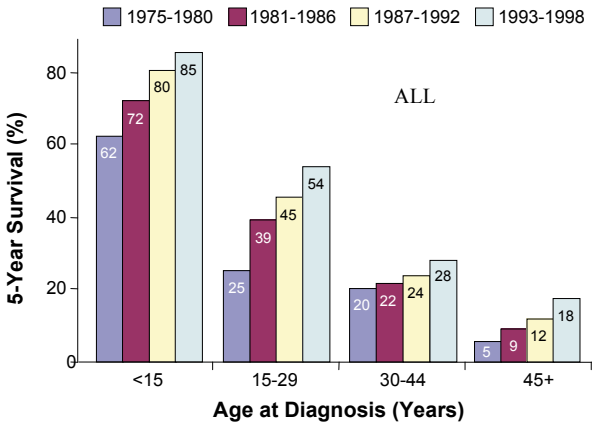


Figure 4.24: 5-Year Survival Rate for ALL by Era, SEER

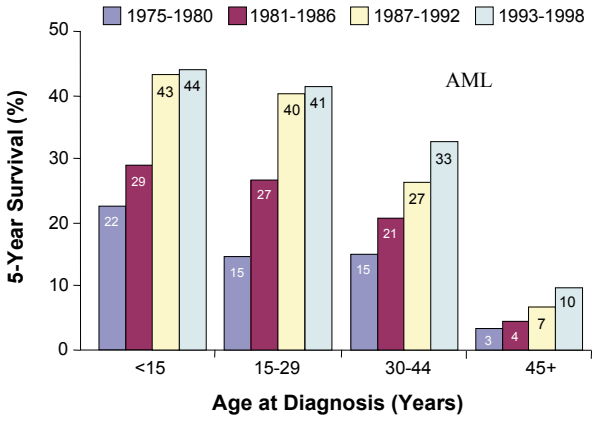


Figure 4.25: 5-Year Survival Rate for AML by Era, SEER

serine protease neutrophil elastase. Proteolytic regulation of hematopoiesis may be affected.[16]

Originally proposed in 1988, the so-called Greaves' hypothesis has attempted to correlate patterns of infection during infancy with the development of B-precursor ALL in early childhood.[17] Specifically, reduced exposure to infection during the first year of life purportedly results in immunologic naiveté, a biologically abnormal response to later infection and, rarely, leukemic transformation of a susceptible clone.[18,19] Support for the hypothesis has been derived mainly from proxy measures of delayed infectious exposure during infancy, including higher socioeconomic status (improved hygiene), social isolation (avoidance of daycare), breast-feeding (passive immunity), and birth order (higher rank equated with reduced exposure).[20,21] Studies assessing history of infections during infancy have drawn conflicting conclusions.[21,22]

SUMMARY

Leukemias in the AYA cohort reflect a transition from a childhood pattern, represented by a preponderance of ALL with favorable prognostic features, to an adult pattern, dominated by AML and a rising incidence of CML. Between 1975 and 1999, leukemia increased in incidence in 15- to 29-year-olds, with those in the 20- to 24-year age group experiencing the greatest increment at an average rate of 1.2% per year. Risk factors for ALL include male gender, young age (2 to 5 years), Caucasian race/ethnicity, pre- and post-natal radiation exposure, and constitutional syndromes including trisomy 21, neurofibromatosis type 1, Bloom syndrome, Shwachman syndrome, and ataxia-telangiectasia. Risk factors for AML include Hispanic race/ethnicity, chemotherapeutic exposure to alkylating agents or topoisomerase II inhibitors, and constitutional syndromes including trisomy 21, Fanconi anemia, neurofibromatosis type 1, Bloom syndrome, Shwachman syndrome, familial monosomy 7, and Kostmann granuocytopenia.

An improvement in survival has occurred since 1975 in each category of leukemia, although the decrease in mortality among adolescent and young adult patients with ALL lags behind that of younger patients. Despite being a "chronic" leukemia, the ultimate survival of patients with CML was poor in all age groups, with a 15-year survival

less than 20% regardless of age at diagnosis. During the period 1975 to 1999, the death rate for leukemias was higher for males than females in all age categories. Hispanics experienced the highest mortality for leukemias in those younger than 25 years, while African Americans/blacks had the highest mortality in those 25 years and older.

Broader participation in cooperative clinical group trials by adolescents and young adults is needed to further define the unique features of leukemia in these patients and to better assess and optimize therapies.

REFERENCES

1. Chessells JM, Hall E, Prentice HG, et al.: The impact of age on outcome in lymphoblastic leukaemia; MRC UKALL X and XA compared: a report from the MRC Paediatric and Adult Working Parties. Leukemia 1998;12:463-73.
2. Plasschaert SL, Kamps WA, Vellenga E, et al.: Prognosis in childhood and adult acute lymphoblastic leukaemia: a question of maturation? Cancer Treat Rev 2004;30:37-51.
3. Stock W, Sather H, Dodge RK, et al.: Outcome of adolescents and young adults with ALL: a comparison of Children's cancer group (CCG) and Cancer and Leukemia Group B (CALGB) regimens. Blood 2000;96:467a.
4. Boissel N, Auclerc MF, Lheritier V, et al.: Should adolescents with acute lymphoblastic leukemia be treated as old children or young adults? Comparison of the French FRALLE-93 and LALA-94 trials. J Clin Oncol 2003;21:774-80.
5. Testi AM, Valsecchi MG, Conter V, et al.: Difference in outcome of adolescents with acute lymphoblastic leukemia (ALL) enrolled in pediatric (AIEOP) and adult (GIMEMA) protocols. Blood 2004;104:539a.
6. de Bont JM, van der Holt B, Dekker AW, et al.: Significant difference in outcome for adolescents with acute lymphoblastic leukemia (ALL) treated on pediatric versus adult ALL protocols. Blood 2003;102:222a.
7. Nachman J, Siebel N, Sather H, et al.: Outcome for adolescent and young adults 16-21 years of age (AYA) with acute lymphoblastic leukemia (ALL) treated on the Children's Cancer Group (CCG) 1961 study. Blood 2004;104:196a.
8. Bhatia S, Ross JA, Greaves MF, Robison LL: Epidemiology and etiology. In: Pui CH (ed): Childhood Leukemias. Cambridge, UK: Cambridge University Press, 1999, p. 41.
9. Narod SA, Stiller C, Lenoir GM: An estimate of the heritable fraction of childhood cancer. Br J Cancer 1991;63:993-9.
10. Crispino JD: GATA1 in normal and malignant hematopoiesis. Semin Cell Dev Biol 2005;16:137-47.
11. Hitzler JK, Zipursky A: Origins of leukaemia in children with Down syndrome. Nat Rev Cancer 2005;5:11-20.
12. Ge Y, Stout ML, Tatman DA, et al.: GATA1, cytidine deaminase, and the high cure rate of Down syndrome children with acute megakaryocytic leukemia. J Natl Cancer Inst 2005;97:226-31.
13. Side L, Taylor B, Cayouette M, et al.: Homozygous inactivation of the NF1 gene in bone marrow cells from children with neurofibromatosis type 1 and malignant myeloid disorders. N Engl J Med 1997;336:1713-20.
14. Duker NJ: Chromosome breakage syndromes and cancer. Am J Med Genet 2002;115:125-9.
15. Eyfjord JE, Bodvarsdottir SK: Genomic instability and cancer: networks involved in response to DNA damage. Mutat Res 2005;592:18-28.
16. Horwitz M, Li FQ, Albani D, et al.: Leukemia in severe congenital neutropenia: defective proteolysis suggests new pathways to malignancy and opportunities for therapy. Cancer Invest 2003;21:579-87.
17. Greaves MF: Speculations on the cause of childhood acute lymphoblastic leukemia. Leukemia 1988;2:120-5.
18. Greaves MF, Alexander FE: An infectious etiology for common acute lymphoblastic leukemia in childhood? Leukemia 1993;7:349-60.
19. Greaves MF: Aetiology of acute leukaemia. Lancet 1997;349:344-9.
20. Gilham C, Peto J, Simpson J, et al.: Day care in infancy and risk of childhood acute lymphoblastic leukaemia: findings from UK case-control study. BMJ 2005;330:1294-9.
21. Jourdan-Da Silva N, Perel Y, Méchinaud F, et al.: Infectious diseases in the first year of life, perinatal characteristics and childhood acute leukaemia. Br J Cancer 2004;90:139-45.
22. Neglia JP, Linet MS, Shu XO, et al.: Patterns of infection and day care utilization and risk of childhood acute lymphoblastic leukemia. Br J Cancer 2000;82:234-40.