

Epidemiology of Leukemia: Overview and Patterns of Occurrence

INTRODUCTION

Leukemia was first identified in 1845^{16, 293} and given its current designation in 1847.²⁹⁴ Since then, leukemia has been distinguished from other hematopoietic and lymphoproliferative neoplasms, although it was classified as a single entity until 1957.³⁰⁸ Then, lymphoid and myeloid leukemias were designated as separate forms in the seventh revision of the International Classification of Diseases (ICD).³⁰⁹ By 1967, the major cell-type categories (acute lymphoblastic leukemia [ALL], chronic lymphocytic leukemia [CLL], acute myeloid leukemia [AML], acute monocytic leukemia, and chronic myeloid leukemia [CML]) were distinguished in the eighth revision of the ICD.³¹⁰

Morphologic codes, developed for the International Classification of Diseases for Oncology (ICD-O),²¹⁴ were derived clinically from the French-American-British (FAB) Cooperative Group classification scheme. The FAB and other working group expert hematologists have identified morphologic and cytochemical features characterizing ALL,^{17, 49} AML,^{18, 20, 56} and chronic B- and T-lymphoid leukemias,^{55, 139} as well as distinct subtypes within each category. For example, the FAB-defined subtypes of AML include minimally differentiated (M0), myeloblastic (M1 and M2), promyelocytic (M3), myelomonocytic (M4), monocytic (M5), erythroid (M6), and megakaryoblastic leukemias (M7).^{18, 20} The FAB Cooperative Group has also described 14 distinct types of CLL,⁵⁵ most derived from mature B lymphocytes. Subtypes include the rare forms of prolymphocytic leukemia, hairy cell leukemia, and adult T-cell leukemia/lymphoma (ATLL), the latter two designated as forms of non-Hodgkin's lymphoma in the proposed third revision of the ICD-O (ICD-O-3).

The proposed ICD-O-3 uses immunophenotypic features as well as morphology to classify leukemia and lymphoma subtypes. Mounting evidence supports the need for cytogenetic and molecular as well as morphologic and immunophenotypic characterization of subtypes comprising ALL,^{111, 138, 236} CLL,^{171, 180, 181, 223, 238} AML,^{106, 198, 206} bilineage acute leukemias,¹⁸² and CML.²⁸⁰ But progress has lagged in systematically applying cyto-

netic, molecular, and immunophenotypic assessment within clinical settings. Thus, newly diagnosed leukemia cases reported to population-based cancer registries can frequently be classified by morphologic features only. For these reasons, leukemia incidence data reported by population-based cancer registries are still restricted to major cell types.^{207, 208} Leukemia mortality data are additionally complicated and difficult to interpret because at least 30% of death certificates do not report a specific leukemia cell type.²¹³

Therefore, the classification used in this chapter includes four specific leukemia cell types (ALL, CLL, AML, and CML), a combined category of other and not-other-wise-specified (NOS) leukemias, and the combination of these five categories that the authors designate as total leukemia. Based on the FAB system approach, monocytic leukemia is subsumed under the broader myeloid category of AML, which is interchangeable with acute non-lymphocytic leukemia (ANLL). The relative rarity of the leukemias, particularly for specific subtypes, requires evaluation of large populations and/or data compiled over many years from smaller populations to generate sufficiently stable rate estimates. Despite these problems, many descriptive and analytic studies have been carried out using data from population-based general cancer registries,^{207, 208, 224} specialized registries of hematopoietic disorders,⁴⁷ or pediatric tumor registries.²⁴

Earlier epidemiologic studies focused primarily on mortality outcomes. For leukemia subtypes characterized by poor survival, mortality and incidence rates are similar. In contrast, there is a growing divergence between mortality and incidence for childhood ALL, a substantial fraction of CLL, and a growing proportion of other leukemia types, due to improved survival. In the last two decades, therefore, incidence-based leukemia data have been reported increasingly, although mortality data are still valuable for assessing the public health burden and trend patterns.

DESCRIPTIVE EPIDEMIOLOGY

Comparison of Rates

Clues to etiology may be obtained by comparing rates for total leukemia and specific subtypes among populations.

Rates are calculated by dividing the number of cases (or deaths) by the product of the population at risk times years of observation, or by the sum of the annual population estimates. The resulting rate is usually expressed as cases (or deaths) per 100,000 person-years at risk. Because populations differ in age structure and leukemia rates vary considerably by age, one can compare rates for individuals in the same age group (age-specific rates) or weighted averages for all age groups among populations, using a common reference population to derive the weights (age-standardized rate). Age-standardized rate comparisons can also be made among population subgroups defined by gender, race, occupation, or other characteristics of interest.

Lack of accurate population census or leukemia occurrence data, particularly in developing countries, precludes meaningful population-based mortality and incidence rate estimates. In more developed regions, mortality data are generally available because of mandatory death certification. Regional or nationwide population-based cancer incidence data are increasingly available, but only the Connecticut, United States,^{52, 112} and Danish Cancer Registry^{33, 34} have been in operation for more than 50 years.

With these considerations, we have examined U.S. mortality data from the National Center for Health Statistics and the most recently published international incidence data.²⁰⁸ We generally selected cancer registries that operated for at least 15 years, reported incidence for the six leukemia categories, included at least 100 total leukemia cases during 1988-1992, and covered a wide geographic area and a range of ethnic groups. The U.S. incidence data are from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program, which includes information from five states and four cities (comprising approximately 10% of the U.S. population).²²⁴ Rates were age-standardized, using the world standard.

Mortality Patterns and Trends: Total Leukemia

Internationally, the highest age-standardized mortality rates for total leukemia occur in the populations of Western Europe, Oceania, and North America, where rates generally ranged from 4.8 to 7.4/100,000 person-years for males and from 3.2 to 4.6/100,000 for females.¹⁰ It is noteworthy that rates for both males and females in Israel and Costa Rica closely parallel those of the industrialized countries of Europe, Oceania, and North America. Lower rates (ranging from 3.7 to 4.5 for males and from 2.8 to 3.5 for females) characterize populations in Asia and Latin America.¹⁰

U.S. data from 1970-1994 reveal excess age-standardized leukemia mortality rates in the north and south-central regions for whites (Fig. 7-1), a pattern similar to that seen earlier (1950-1969) for both sexes.⁶⁸ Unfortunately, mortality data are too sparse in the north and south-central regions to evaluate patterns for African Americans.

U.S. age-standardized mortality trends since 1950 have shown a modest decline among whites and a slight increase among nonwhites (the latter comprising African

Americans, Asian-Pacific Islanders, and Native Americans). Overall, the mortality trends demonstrate a convergence of rates within gender, although rates have been consistently higher among males than females. Age-specific mortality patterns reveal dramatic declines for white and nonwhite children and adolescents (ages 0-19 years) since the early 1960s, whereas a less rapid decline characterizes young adults (ages 20-44 years) (Fig. 7-2). There was little change in mortality during 1950-1996 among middle-aged persons. Rates rose among the elderly of both racial groups, although the rate of increase slowed substantially after 1960 among whites. The great decline among children and the increase in the elderly were similarly evident in other populations, although mortality rates leveled off in the 1960s and 1970s among whites in most developed countries.¹⁴³

Survival: U.S. Population-Based Data

Total Leukemia. Overall, 5-year relative survival (adjusted for general population mortality) from all forms of leukemia combined has improved significantly (rising from 34.4% to 43.1%) in regions covered by the U.S. SEER Program registries (Table 7-1). In general, for total leukemia and subtypes occurring at all ages, white patients survive longer than African-American patients, but survival is similar for males and females.^{217, 224}

Leukemia Subtypes. Based on SEER Program data, survival improved from 1974-1976 to 1989-1995 for patients with each form of leukemia (see Table 7-1). When survival data for 1989-1995 are evaluated according to age at diagnosis, ALL patients show the largest gradient, with 5-year relative survival ranging from 81.1% among children ages 0-14 years to 5.8% among those age 65 years and older. Progressive worsening in survival with increasing age has also been found in ALL patients in the United Kingdom.⁵³ Particularly notable has been the dramatic improvement in 5-year relative survival for childhood leukemia that began in the 1960s.^{35, 54, 262} Between 1973-1974 and 1989-1995 SEER data demonstrate an increase in 5-year relative survival from 53.2% to 81.1% for children with ALL and from 13.7% to 42.6% for those with AML.²²⁴ Survival for children with ALL depends heavily on age at diagnosis, with highest survival among those ages 1-4 years (85%) and 5-9 years (80%) and lowest survival among infants (37%).²⁶⁴ For childhood ALL overall, 5-year survival rates were slightly better for females than males and notably better for whites than African Americans.²⁶⁴ Survival is also poorer for other racial groups in the United States than for whites, particularly African American Indians, due to worse prognostic features and problems with treatment compliance.⁸⁷

The patterns for childhood AML patients demonstrate higher survival in those ages 5-9 years at diagnosis than for either younger or older children, better survival in females than males, but similar survival outcome in white and African-American children. For patients with either form of childhood leukemia, differences in survival by age, gender, and race mostly reflect underlying biologic factors, although socioeconomic factors and health care access may also contribute. The treatment-related improvements in survival of children diagnosed with ALL

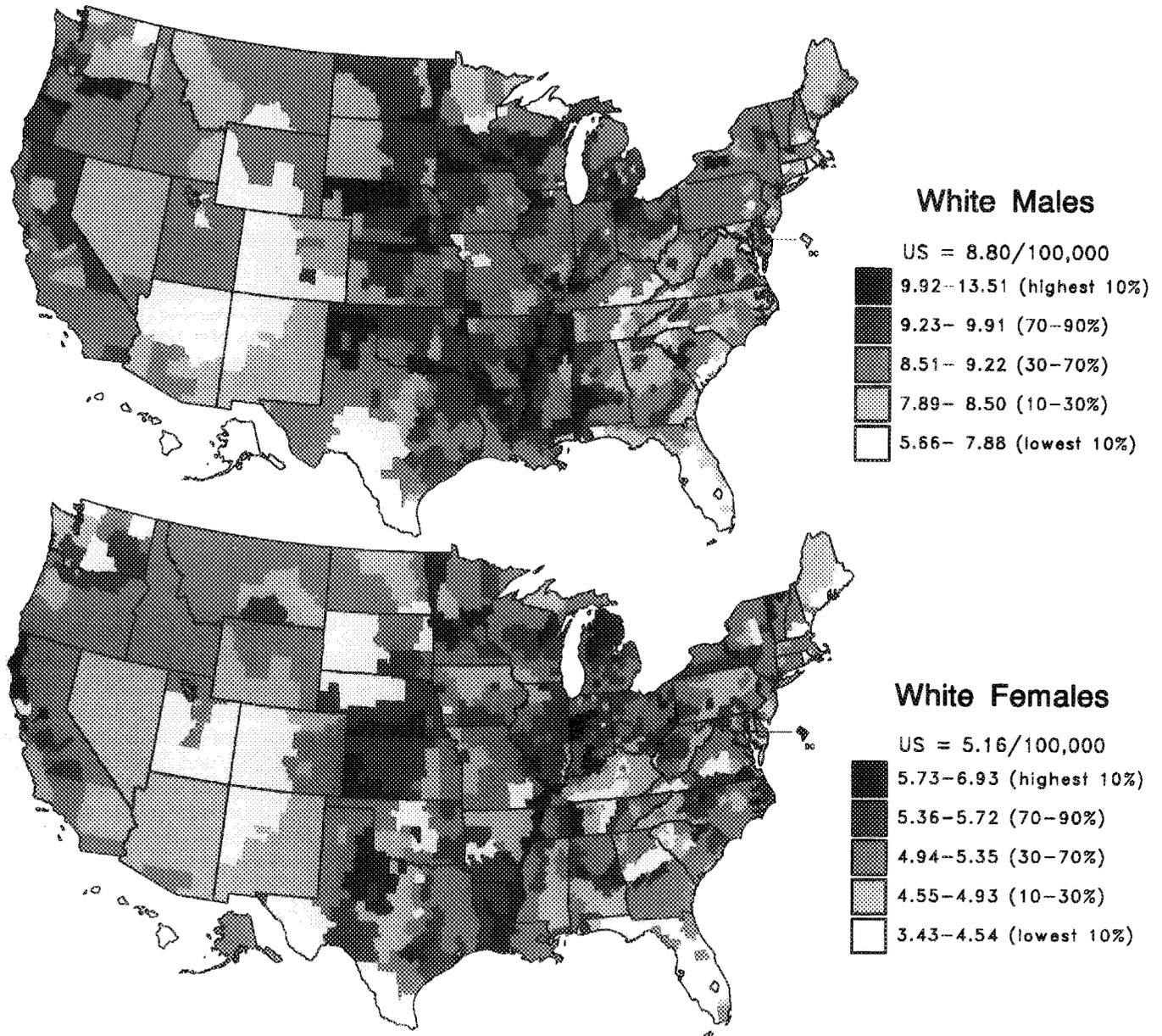


FIGURE 7-1. US leukemia mortality rates by state economic area (age-adjusted 1970 US population), 1970-1994. (Data from Devesa SS, Grauman DJ, Blot WJ, et al: Atlas of Cancer Mortality in the United States, 1950-94. Bethesda, Maryland: National Institutes of Health, National Cancer Institute, NIH Publication No. 99-4564, 1999.)

and AML have been responsible for the big declines in leukemia mortality among young people (see Fig. 7-2)²⁶¹; some long-term survivors can be regarded as cured.³⁵

CLL patients experienced a modest, although statistically significant, increase in 5-year relative survival between 1974-1976 and 1989-1995. Five-year relative survival was higher and similar among U.S. whites than among African Americans with CLL and higher in those younger than age 65 at diagnosis than older persons (see Table 7-1). Clinical trials, however, have shown little survival advantage for chemotherapy treatment of patients with indolent or early-stage CLL.^{69, 139}

Among the four major leukemia cell types, prognosis is poorest for patients diagnosed with AML as adults; overall, 5-year relative survival is 14.5% in AML patients

of all ages combined during 1989-1995 (see Table 7-1). Unfortunately, results of clinical trials do not consistently support a survival advantage following treatment with autologous or allogeneic bone marrow transplantation compared with standard chemotherapy regimens.^{48, 319} However, improved survival has been seen following response to early treatment with chemotherapy plus all-transretinoic acid among patients with acute promyelocytic leukemia (M3).⁸⁰

CML is often indolent initially, with rising blood cell counts, sometimes resulting in early mortality from congestive heart failure or stroke (due to hyperviscosity associated with high blood cell counts). Between 1974-1976 and 1989-1995, 5-year relative survival rose significantly from 22.5% to 31.9%. African-American males have nota-

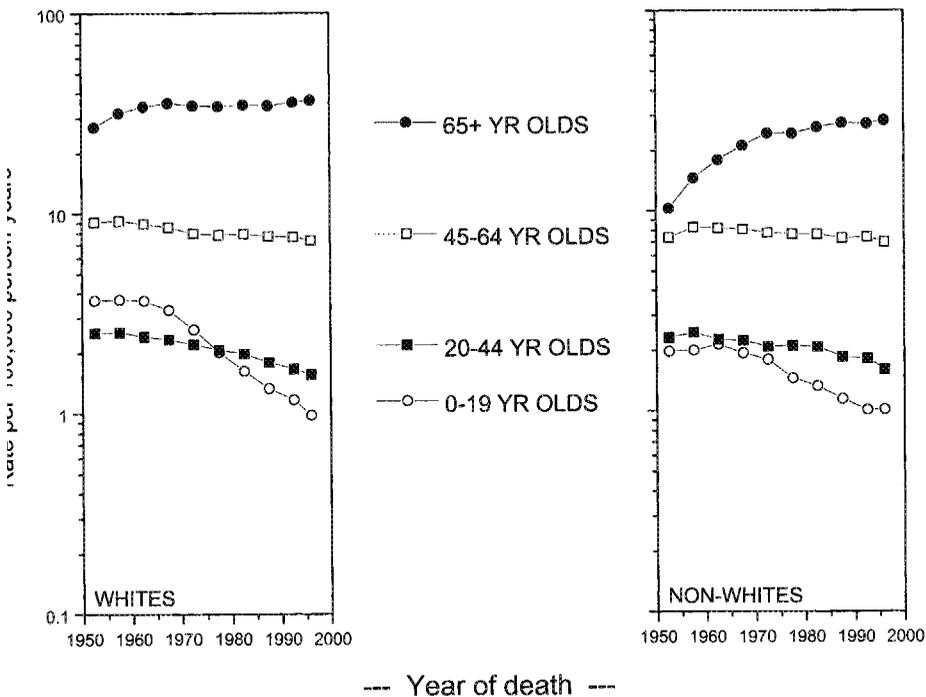


FIGURE 7-2. US trends in leukemia mortality (age-adjusted, world standard) by age group among whites and nonwhites 1950-1996.

ly lower survival (21.4%) than the 31% to 33% typical survival of white males and females; the small numbers of African-American women preclude meaningful comparisons (see Table 7-1). Early treatment with interferon α -2b (alone or in combination with other agents) may halt the progression,¹¹³ but prognosis becomes grave subsequent to blast transformation.

Incidence Patterns and Trends

International Racial and Geographic Patterns

Total Leukemia. Within virtually all populations, total leukemia age-adjusted incidence rates are higher for

males than for females (Fig. 7-3).²⁰⁸ For leukemia patients of both sexes, there is a distinct racial and geographic gradient, with highest rates among white populations in North America, Australia, and New Zealand, followed by rates in populations in northern and western Europe, African Americans, and Hispanics in Los Angeles. Mid-level rates are observed for persons in southern Europe and Israeli Jews. Lowest rates occur (in descending order) in Japanese in Osaka, Chinese in Shanghai, and Indians in Bombay (see Fig. 7-3).

Leukemia Subtypes. For the worldwide registries shown in Fig. 7-3, other and NOS represents between 5% and 25% of total leukemia. Other and NOS comprise 10% or less of the total for both sexes in (ascending order or increasing proportion of other and NOS for males)

TABLE 7-1. 5-Year Relative Survival Rates for Leukemia in the U.S. Surveillance Epidemiology and End Results Program by Time Period, Race, Sex, Age, and Cell Type

| Period, Age, and Race/Sex Group | Leukemia Cell Type | | | | |
|---------------------------------------|--------------------|---------|-----------|---------|---------|
| | CLL (%) | ALL (%) | Total (%) | CML (%) | AML (%) |
| 1974-1976, all ages, races, and sexes | 68.2 | 38.4 | 34.4 | 22.5 | 5.7 |
| 1989-1995, all ages, races, and sexes | 70.5* | 58.8* | 43.1* | 31.9* | 14.5* |
| White males | 72.5* | 57.7* | 45.5* | 31.2* | 13.2* |
| White females | 71.8 | 60.9* | 43.0* | 32.6 | 15.2* |
| A-A males | 43.6 | 48.5 | 29.7 | 21.4 | 10.9 |
| A-A females | 53.7 | 54.6 | 37.5 | 47.6 | 15.6 |
| Ages 0-14 | N/C | 81.1 | 74.0 | N/C | 42/6 |
| Ages 0-64 | 78.8 | 63.4 | 51.2 | 40.9 | 25.1 |
| Ages 65+ | 65.9 | 5.8 | 33.9 | 21.7 | 2.8 |

*p<.05 for 1989-1995 versus 1974-1976.

A-A = African-American; N/C = not calculated.

From Ries LAG, Kosary CL, Hankey BF, et al (eds): Cancer Statistics Review, 1973-96 Bethesda, Maryland, National Cancer Institute, NIH Publication Number 99-1789, 1999.

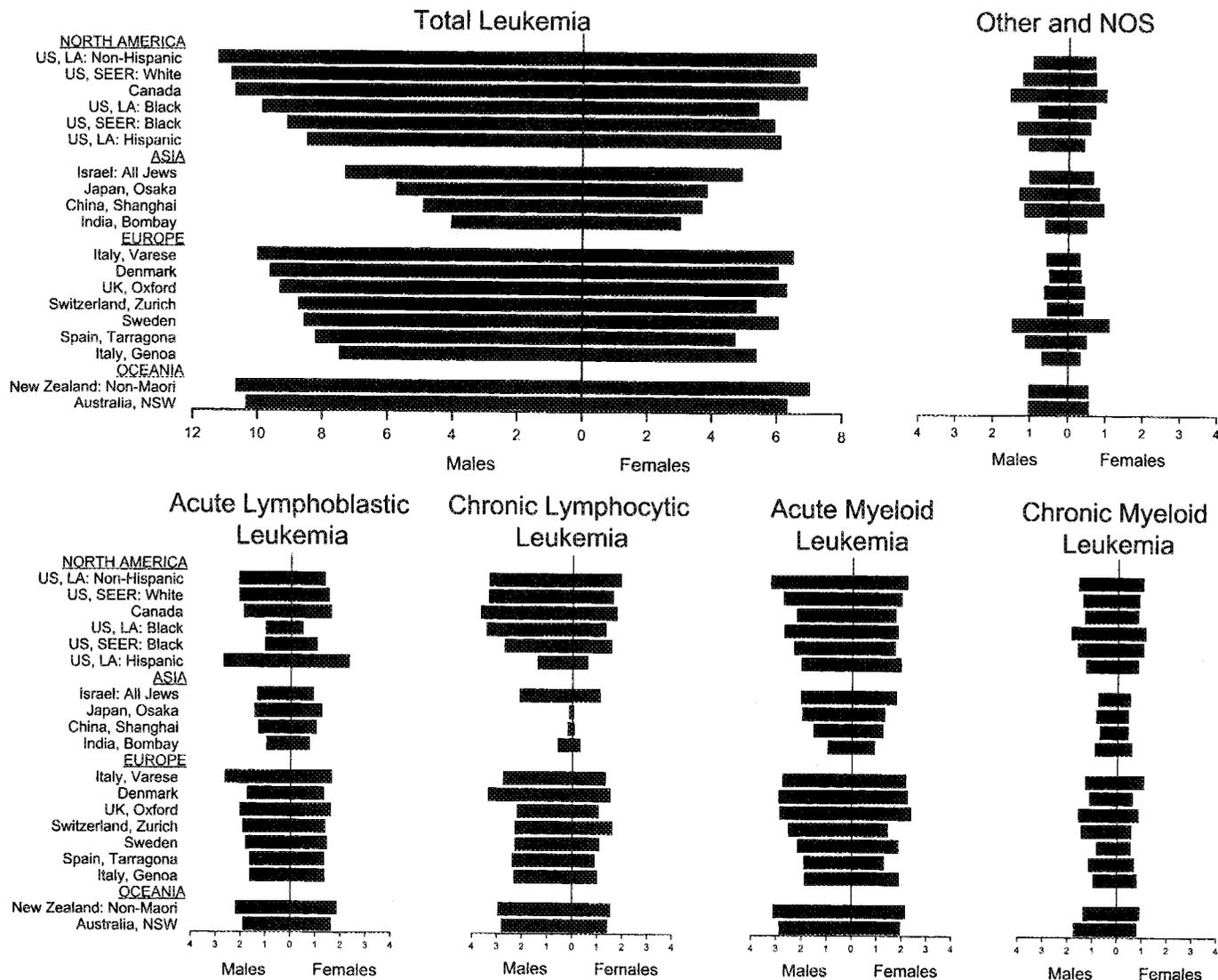


FIGURE 7-3. International variation in leukemia incidence (age-adjusted, world standard) by sex for total leukemia and by cell type. (Data from Parkin DM, Muir CS, Whelan SL, et al: Cancer Incidence in Five Continents, vol 7. Lyon, France, IARC Scientific Publication No. 143, 1997.)

Denmark, Switzerland, Italy (Varese), the United Kingdom, Los Angeles whites and African Americans (males only for the latter), Italy (Genoa), Australia, and New Zealand. Approximately 10% to 19% of total leukemia consists of other and NOS in (ascending order for men) SEER whites, Los Angeles Hispanics (less than 10% for women), Canada, Israel, Spain, SEER African Americans, India, and Sweden. Other and NOS comprise 20% or more of total leukemia (ascending for men) in Japan and China.

Similar to total leukemia, higher ALL age-standardized rates occur among populations in Northern and Western Europe, North America, and Oceania, and rates in Asian and black populations are lower. In contrast to international patterns for total leukemia, highest rates in Europe are reported from Varese, Italy, and the highest U.S. rates are described for Hispanics of both sexes in Los Angeles. Compared with other populations on the Asian landmass, Israeli Jews of both sexes have the highest total leukemia rates but lower ALL rates than those of other populations,

except for Indians in Bombay. Although common ALL accounts for virtually all of the early childhood incidence peak among most populations,⁹⁷ the distribution of ALL subtypes varies among populations.^{97, 98}

Internationally, racial and geographic variation is greater for CLL than for any other form of leukemia, with the highest age-standardized rates in North American whites, followed by U.S. blacks and white populations in Oceania and northern and southern Europe. Lower rates occur among U.S. Hispanics, and significantly low rates occur among Asian populations (see Fig. 7-3).^{102, 208} On the North American continent, there is a zone of high CLL incidence in the north-central United States (e.g., Iowa and Detroit) and also in the contiguous southern Canadian provinces (e.g., Saskatchewan, Quebec, Ontario, Alberta, and Manitoba).

ATLL, a mature T-cell neoplasm, is rare in most populations, except for endemic regions for human T-lymphotropic virus type I, which include southwestern parts of Japan, Jamaica and Trinidad, parts of West and Central

Africa, some regions in South America, and other restricted geographic areas.^{81, 173} After a long latent period, ATLL is estimated to occur in 1 per 1000 carriers per year, for a total of an estimated 2500-3000 cases worldwide.²⁷ The age-standardized incidence rate of ATLL is estimated to range from 1.9 to 2.9 per 100,000 person-years, based on data from Jamaica and Trinidad,⁵⁷ and 2.6 to 4.0 based on data from Kyushu,²⁷⁸ with highest risk among individuals who acquire the retrovirus during childhood. Those infected before age 20 years are estimated to have a cumulative lifetime risk of 4.0% for males and 4.2% for females.¹⁹⁷

The international pattern for AML resembles that for total leukemia, with highest age-standardized incidence rates in Denmark, North American whites, Oceania, and African Americans (see Fig. 7-3). Midlevel rates are seen in Japanese, Israeli Jews, southern Europeans, and Hispanics in Los Angeles. Lowest rates occur in China and India. In most populations, AML incidence is higher for males than for females.

There is substantially less international variation for CML than is seen for any other cell type (see Fig. 7-3). For both males and females, rates are highest among the African-American population in Los Angeles, followed by whites in Australia and then by African Americans in the regions covered by the SEER registries. African Americans in Detroit and Los Angeles have the highest rates among females (see Fig. 7-3).¹⁰² As with other leukemias, CML is more common among males than females.

U.S. Age-Standardized Rates and Time Trends

Total Leukemia. Age-standardized rates for total leukemia are higher for males of both races than for females and within each gender higher for whites than for African Americans (Fig. 7-4). Among whites, incidence changed little between 1973-1978 and 1985-1990, but declined somewhat thereafter. Incidence among African Americans rose between 1973-1978 and 1979-1984 and then declined slowly. Age-specific trends in the geographic regions covered by the U.S. SEER Program showed a slight increase in rates for children under age 15 years, mostly due to an abrupt jump up in rates between 1983 and 1984.¹⁶² For leukemia patients younger than age 65 years at diagnosis, there was little overall change for whites during 1973-1996 and a small decline for African Americans (the latter greater for females than males). Declines were seen during 1973-1996 among leukemia patients diagnosed at age 65 years or older.²²⁴ Internationally, leukemia incidence rates have been relatively stable since the 1960s for children, adolescents, young adults, and middle-aged persons, but rose among the elderly from the 1960s to the early 1970s.^{75, 143}

Leukemia Subtypes. Other and NOS leukemias in the United States include acute NOS (ranging from 35% to 70% of all other and NOS leukemias), chronic NOS, lymphoid NOS, myeloid NOS, other NOS, and unspecified NOS (with either unspecified or myeloid NOS as the second largest contributor and generally ranging from 1%

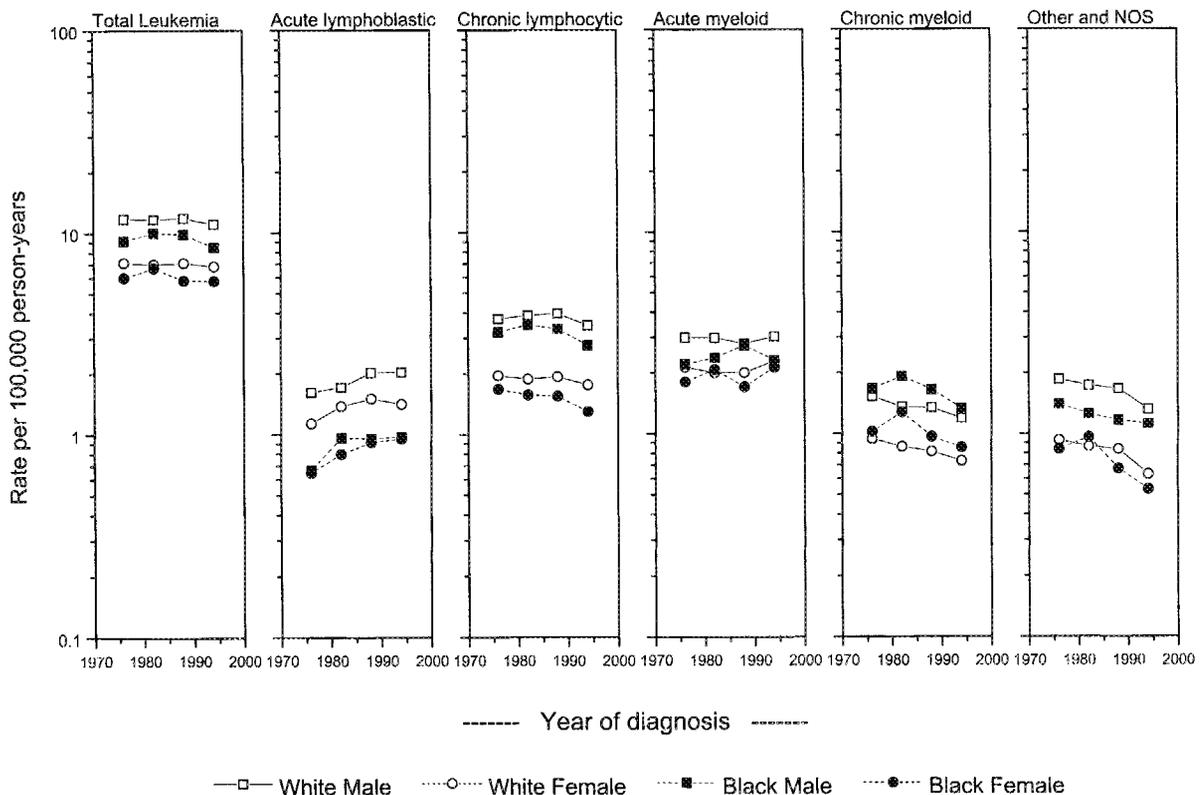


FIGURE 7-4. United States trends in leukemia incidence (age-adjusted, world standard) by race and sex for total leukemia and by cell type in the nine SEER areas. (Data from Ries LAG, Kosary CL, Hankey BF, et al: Cancer Statistics Review, 1973-96. Bethesda, Maryland: National Cancer Institute, NIH Publication No. 99-2789, 1999.)

to 40%). Other and NOS age-standardized rates, similar to that for total leukemia, are higher for males of both races than for females and higher for whites than African Americans within each gender. Rates for other and NOS in the United States declined for all four race-gender groups during the interval from 1973-1978 and 1991-1996. There was an acceleration of the rate of decline between 1985-1990 and 1991-1996 for whites and a steeper decline between 1979-1984 and 1991-1996 for African-American females (see Fig. 7-4).

For ALL, age-standardized incidence is higher for whites of both sexes than for African Americans. Incidence of ALL rose between 1973-1978 and 1985-1990 and then leveled off in all four race-sex groups (see Fig. 7-4).

Age-standardized CLL incidence rates are notably higher in males of both races than females; within each gender, rates are higher for whites than for African Americans (see Fig. 7-4), followed by Hispanics and American Indians, with very low and similar rates among Chinese Americans, Japanese Americans, and Filipinos.^{84, 103} CLL age-standardized incidence in regions covered by SEER Program registries has declined in all four gender-race groups, commencing in 1973-1978 for females and in 1979-1984 for males (see Fig. 7-4).

For AML, age-standardized rates are modestly higher in males of both races than in females and within gender are higher in whites than in African Americans for males but similar for females of both races (see Fig. 7-4). Incidence was fairly stable during 1973-1978 through 1991-1996. A similar stable incidence trend pattern was seen for adults ages 15-64 years in the regions covered by a population-based specialist registry of hematologic diseases in the United Kingdom; however, significant decreases, estimated at 3% per year, occurred among the elderly.⁴⁷ This decline in AML among the elderly paralleled a highly significant increase of 6% per year for myelodysplastic syndromes among older persons. It is likely that the increasing recognition of myelodysplastic syndromes during the same period may have resulted in less misclassification of these disorders as AML.

Age-standardized incidence for CML is higher in males than in females of both races, with rates higher in African Americans than in whites within each gender, unique among the leukemias (see Fig. 7-4). Midlevel rates occur in Hispanics followed by progressively lower rates in Japanese Americans, Chinese Americans, Filipinos, and American Indians.^{84, 103} Age-standardized incidence among whites declined steadily but slowly over time (see Fig. 7-4). Among African Americans, age-standardized incidence rose between 1973-1978 and 1979-1984 and then declined steadily thereafter at a more rapid rate than the decline observed in whites.

U.S. Age-Specific Rates and Racial/Ethnic Patterns

Total Leukemia. Approximately 1.5% of white males, 1.1% of white females, 0.8% of African-American males, and 0.7% of African-American females in the SEER populations will eventually develop some form of leukemia.²²⁴ The racial and ethnic pattern for total leukemia in the United States parallels the findings observed in interna-

tional comparisons. For men, highest rates are found among white non-Hispanics (14.1 per 100,000 person-years, age-adjusted according to the 1970 U.S. population), followed by African Americans (10.7), and then white Hispanics (10.3). Progressively lower rates occur in Asian and Pacific Islanders (8.5) and American Indians (3.6).²²⁴ For women, the pattern is similar, although rates are generally lower and differences less striking than those for males; high to midlevel rates were seen in female non-Hispanic whites (8.3) followed by African-American (6.9) and Hispanic whites (6.9), whereas low rates were seen in Asian/Pacific Islanders (5.8) and American Indians (3.1).

Leukemia Subtypes. Based on U.S. SEER Program data (1973-1996) for both genders and all races combined, lymphoid leukemias account for 47% of all leukemias (17.3% acute; 28.5% chronic; 1.2% lymphoid NOS); myeloid leukemias comprise 41.4% (25.3% acute; 13.2% chronic; 2.9% myeloid NOS); and other or unspecified types represent 11.7% (4.8% acute NOS, 0.3% chronic NOS, 6.6% other and NOS).²²⁴ ALL is the predominant type before the age of 15 years (comprising 77.1% of total leukemia), and CLL is the most common type at age 65 years and older (40.2% of total leukemia).

For ALL, age-specific rates demonstrate a U-shaped pattern and are generally higher for whites of both sexes than for African Americans (Fig. 7-5). There is a notable peak in incidence between the ages of 2 and 3 years, which is also observed in most populations internationally,^{159, 207} followed by declining rates during later childhood, adolescence, and young adulthood (see Fig. 7-5). Rates then rise, beginning in midlife, to reach a second peak (slightly lower than the peak in early childhood) among the elderly. Beginning in adolescence and continuing among all age groups, incidence among white males is consistently higher than among white females. A similar pattern is suggested in African Americans, although based on small numbers of cases (see Fig. 7-5).¹⁰²

CLL incidence rates are consistently higher in males of both races than in females (sex ratios approach or exceed 2:1, the highest for any leukemia cell type), with little difference within gender until age 70, when rates for whites become somewhat higher than rates for African Americans (see Fig. 7-5). CLL almost never occurs before the age of 30 years and is predominantly a disease of the elderly (see Fig. 7-5). After age 30 years, CLL incidence rises exponentially and with a steeper slope than that for any leukemia cell type, achieving the highest incidence level among the elderly. Hairy cell leukemia is close to five times more common in males than in females, with higher rates in whites than in nonwhites.²² Similar to CLL, hairy cell leukemia is unknown in childhood, but then rises in incidence beginning at age 30 years. Unlike CLL, hairy cell leukemia reaches a plateau at about age 60 years.

AML rates in infancy are higher among whites of both sexes than among African Americans, whereas in childhood there is some suggestion of higher rates in African Americans than in whites (see Fig. 7-5). Thereafter, rates are similar by sex and race in most age groups until late middle age, when incidence is higher in males of both races than among females, with rates within gender

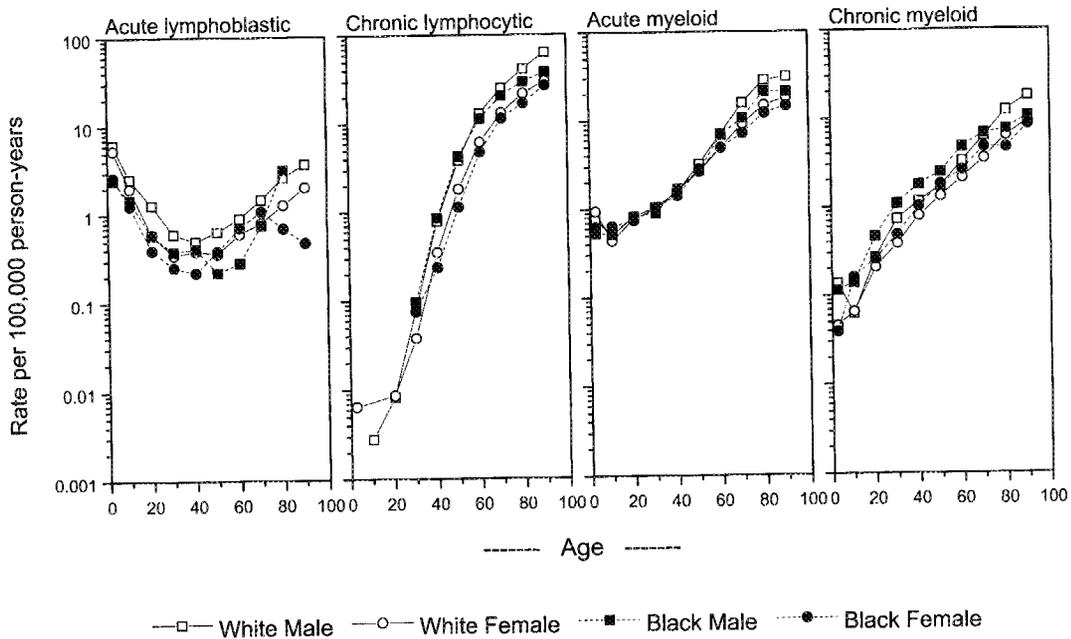


FIGURE 7-5. United States age-specific leukemia incidence rates according to leukemia cell type by race and sex in the nine SEER areas. (Data from Ries IAG, Kosary CL, Hankey BF, et al: Cancer Statistics Review, 1973-96. Bethesda, Maryland: National Cancer Institute, NIH Publication No. 99-2789, 1999.)

higher among whites than among African Americans (see Fig. 7-5). In one study from Los Angeles, Hispanics had a higher frequency of acute promyelocytic leukemia than non-Hispanics; this finding was observed among two series of patients with AML.⁷⁴ Among children, AML comprises about 15% to 25% of leukemia in most Western populations, with highest rates in infancy, followed by a decline in incidence until age 10 years when incidence begins to rise.^{159, 264} After age 40 years, incidence rates increase at a more rapid rate until ages 70 to 80 years, after which the rates increase more slowly (see Fig. 7-5).

CML is the only leukemia subtype for which rates among African Americans are consistently higher than for those among whites in most age groups, except among the very young (see Fig. 7-5).²⁶⁴ CML rarely occurs in children younger than 5 years of age, except for juvenile myelomonocytic leukemia in white males, who experience fourfold higher rates than females.^{11, 202, 264} After age 5 years, rates are somewhat higher for males of both races than females. Between the ages of 5 and 65 years, incidence is higher in African-American males than in white males, whereas at age 75 years and older, the highest rates occur in white males. For females older than 5 years, rates are slightly higher in African Americans than in whites until age 80 years and older, when rates are slightly higher in whites than in African Americans. After early childhood, the rates rise log-linearly with increasing age (see Fig. 7-5).

Thus, ALL rates are notably higher among whites than among African Americans and have a distinct bimodal age distribution; CLL rates are notably higher among males than among females and rise more rapidly with age compared with other forms of leukemia; and CML is unique among the leukemias because of higher rates among African Americans than among whites.

ANALYTIC EPIDEMIOLOGY

Following the detailed consideration of the descriptive epidemiology of the leukemias, we now turn our attention to a brief overview of known and suspected risk factors. Although established and postulated risk factors are discussed individually, it must be recognized that etiology is clearly multifactorial. There are also likely to be different factors that induce or promote initial versus subsequent events in leukemogenesis. Given current limited understanding about the epidemiology of leukemia occurrence, there is little discussion of the role or timing of known or suspected risk factors acting at the specific steps.

Except for ionizing radiation, a few occupational and environmental chemical exposures, HTLV-I as the cause of ATLL, and a few genetic disorders, the risk factors for the leukemias are as yet poorly understood. Knowledge of leukemia risk factors is insufficient to explain the observed international variation in leukemia rates. Only during the last two decades have etiologic studies increasingly distinguished among the various forms of leukemia.

Radiation Exposure

Ionizing Radiation

Ionizing radiation is perhaps the best known and most studied risk factor for the leukemias, given the detailed prospective studies of populations exposed to environmental, occupational, military, and medically related sources of radiation. The relationship of this exposure to leukemia is described in more detail in Chapter 8.

Japanese Atomic Bomb Survivors. CLL has been the

only major leukemia cell type not linked with radiation exposure.^{30, 229} Long-term follow-up studies of survivors of the bombing of Hiroshima and Nagasaki have provided much of the current understanding of the relation of estimated doses and dose-response function of ionizing radiation to mortality and incidence risks for ALL, AML, and CML.^{216, 220, 254, 289} Leukemia was the first radiation-induced cancer reported among atomic bomb survivors. The dose-response pattern for total leukemia was consistent with a linear-quadratic relationship, with risks steadily increasing with dose up to approximately 3 to 4 Gy (1 gray or Gy = 100 rad), and then flattening somewhat at doses above this level. Based on mortality data, the summary excess relative risk estimate for leukemia among the atomic bomb survivors was 6.21 per Gy, and the absolute excess per 10⁴ PY-Gy was 2.94.²⁵⁴ Males had relative risks similar to those of females, but the former demonstrated absolute excess risks about twofold higher than the latter. For both forms of acute leukemia, persons younger than 20 years at exposure were characterized by absolute risks peaking within 10 years, and then falling rapidly. Population members ages 20 to 35 years at the time of the bomb had less pronounced peaks, followed by more gradual declines, whereas individuals older than 35 years demonstrated little variation in risk with time since exposure. CML was much less common among exposed survivors in Nagasaki than among those in Hiroshima (lower absolute risks), but there was no difference between the two cities in relative risks. For CML, those younger than 15 years at exposure experienced a sharp incidence peak and older persons a smaller peak at 5 years following exposure.^{30, 289}

Workers Exposed to Ionizing Radiation. Workers in the medical fields of radiologic technology and diagnostic radiology comprise the largest category of persons exposed occupationally to ionizing radiation. Radiologists and x-ray technicians employed in the first half of the 20th century were reported to be at increased risk for leukemia. Physicians who were members of a professional radiologic society in Britain during 1897-1921 were characterized by a sixfold excess risk of mortality from leukemia, whereas there was no significant increase in leukemia among those joining the society after 1921.²⁶⁸ U.S. radiologists who entered a professional specialty society during 1920-1929 had an 8.8-fold excess; those joining during 1930-1939 had a 3.4-fold excess (of primarily acute and myeloid leukemia); and those joining in 1940 or later had no significant excess mortality from leukemia.¹⁷⁸ Leukemia (except CLL) was significantly increased among 27,911 Chinese x-ray technicians who were monitored during 1950-1985.²⁹⁵ However, leukemia was not significantly elevated among U.S. Army x-ray technicians monitored during 1946-1974¹³¹ nor among U.S. civilian x-ray technologists who belonged to the American Registry of Radiation Technologists.⁷¹

Findings from many epidemiologic studies of cancer risk among nuclear energy workers have been reviewed extensively.^{30, 158} A combined analysis of 95,673 U.S., U.K., and Canadian nuclear workers employed for 6 months or longer yielded a relative risk of 1.2 for leukemia mortality (excluding CLL), for a cumulative protracted dose of 100 mSv (1 sievert [Sv] = 100 rem) compared with 9 mSv

and an excess relative risk of 2.2 per Sv for leukemia.⁴⁵ Among 124,743 U.K. workers in industries with ionizing radiation exposure, a small, borderline significant excess relative risk was found for leukemia (excluding CLL), with 90% confidence limits (following adjustment for potential confounding factors) ranging from 0 to just under 4 times the risk estimated at low doses for Japanese atomic bomb survivors.¹⁹⁶ No significant excess risks for childhood leukemia were found among children of nuclear workers (39,557 male and 8,883 female workers) in nuclear plants in the United Kingdom although risks were significantly higher among children (based on three exposed childhood cases) whose fathers had a cumulative preconception dose of 100 mSv or more.²²⁸ No excess risk of leukemia was found among children of parents residing in proximity to nuclear plants in Ontario, Canada, nor was there evidence of an elevated risk among offspring of those male residents who were radiation workers (based on linkage with the Canadian National Dose Registry).¹⁸⁵ Leukemia was not found in excess among cohorts of U.S.^{270, 272} or U.K.¹⁴ radium dial workers nor among uranium miners.²⁰⁰ A borderline significant increase was reported among U.K. tin miners who had worked at least 10 to 20 years underground.¹¹⁶ Whereas a 2.5-fold increase in leukemia (primarily AML and CML) was found among 3741 U.S. servicemen exposed to one aboveground nuclear detonation in 1957,⁴⁴ no increase was observed among 46,186 U.S. military participants in other nuclear atmospheric tests during 1951-1958.²²⁶ However, leukemia mortality and incidence were elevated among 528 New Zealand military participants in British atomic weapons tests,²¹² and excess mortality from leukemia and multiple myeloma (but not other radiation-related cancers) was found among 22,347 British military participants in nuclear tests.⁶⁴ It was noted, however, that the latter excess may have reflected a substantially lower rate of these two major categories of hematopoietic neoplasms among the unexposed comparison group when the comparison subjects were evaluated in relation to national mortality rates.³⁰

Radiation Therapy: Malignant Conditions. Based on the findings of studies of atomic bomb survivors and other populations exposed at low to moderate doses of ionizing radiation, it is not surprising that acute leukemia and CML occur as second primary cancers in persons treated with radiation therapy for malignant¹²⁴ and benign conditions.^{30, 158} Leukemia risks that are approximately two- to threefold increased have been linked consistently with radiation therapy treatments among adults treated for non-Hodgkin's lymphoma (treated with a range of doses to bone marrow),^{99, 284, 285} breast cancer (estimated marrow doses ranged from less than 5 Gy to more than 9 Gy),⁶¹ uterine cervix cancer (estimated marrow dose = 7 Gy),²⁹ and uterine corpus cancer (estimated marrow dose ranged from 1 to 15 Gy),⁶² and in children treated for Ewing's sarcoma (estimated doses to affected bone ranged from 41 to 60 Gy)^{152, 287} and Wilms' tumor (estimated doses to irradiated fields in the abdomen, and to a lesser extent the thorax, ranged from 6 to 40 Gy, although these patients are treated with radiotherapy less often now than previously).^{36, 124, 157}

The elevated risks of secondary acute nonlymphocytic

leukemia associated with Hodgkin's disease and testicular cancer are most likely due to treatment with alkylating agents, whereas the consistently observed excess of secondary solid tumors in Hodgkin's disease (including breast, lung, thyroid, stomach, bone, connective tissue, and skin cancers) result from radiation therapy treatment.^{135, 277, 286, 292} Results of a randomized clinical trial have shown a higher cumulative incidence of acute leukemia among patients with polycythemia vera treated with the radionuclide ³²P (6%) than among patients treated by phlebotomy alone (1%), but evidence is inconclusive about the potential leukemogenicity of high doses of ¹³¹I for treating thyroid cancer.¹²⁴ Similar to results for the Japanese atomic bomb survivors, the excesses of leukemia subsequent to radiotherapy are generally apparent within the first 5 years following treatment, and most idiogenic leukemia arises within 10 to 15 years. Risk of radiation-induced leukemia appears to be greater when large volumes of bone marrow are treated with lower doses or dose fractions. It has been postulated that the low risk of secondary leukemia associated with high partial-body exposures to radiation is related to the ability of ionizing radiation to sterilize marrow stem cells.¹²⁴

Radiation Therapy: Benign Conditions. Radiation therapy has also been used to treat benign conditions. Close to 14,000 patients treated with radiation therapy (mean total marrow dose = 4.38 Gy) for ankylosing spondylitis during 1935-1954 experienced an elevated mortality risk from leukemia (excluding CLL) that was greatest 1 to 5 years following treatment. In the most recent follow-up through 1991, the relative risk for leukemia in the period 1 to 25 years after exposure to a uniform dose of 1 Gy was estimated to be 7.0.²⁹⁷ Leukemia excesses, ranging from 1.2- to 3.0-fold increases, have been reported in cohorts treated with radiotherapy for other benign conditions, including U.S. women with benign gynecologic disorders,¹²⁶ U.S.¹²⁷ and Scottish women²⁶⁷ with menorrhagia not associated with malignancy, U.S. patients treated for peptic ulcer,¹⁰⁰ and Israeli²³⁰ and U.S. children²⁵⁵ treated for tinea capitis.

Thorotrast. Excess risks of leukemia and other hematologic disorders (as well as liver cancer and other tumors and cirrhosis of the liver) have been found in patients with neurologic disorders who received Thorotrast contrast material during cerebral angiography.^{9, 73, 174, 291} The leukemias observed in patients who received Thorotrast are distinguished by long latency until onset and an increased proportion of erythroleukemias.

Diagnostic X-Ray Procedures. Prenatal exposure of the fetus to diagnostic x-rays has been linked in numerous case-control studies with a subsequent small excess of childhood leukemia (1.4- to 1.5-fold estimated increase),²⁸⁹ but there has been long-standing debate about whether this association is causal.³¹ The relationship of diagnostic x-ray exposure with adult leukemias and breast cancer has long been of interest, particularly for patients undergoing frequent evaluation, females evaluated repeatedly during puberty and early adolescence, those undergoing procedures involving substantial doses, and those evaluated before the 1980s, when radiation doses were higher. Whereas some investigators reported elevated risk of myeloid leukemia and CML,^{104, 221} others found no

relationship or small increases confined to the few years immediately preceding diagnosis,^{32, 78} suggesting that the diagnostic x-rays may have been obtained for early manifestations of leukemia.

Ionizing radiation induces DNA strand breaks, and most mutations caused by radiation are associated with chromosomal changes such as translocations and deletions.¹⁶⁴ A morphologic review of bone marrow in the mid-1980s affected by acute leukemia and CML among atomic bomb survivors and patients irradiated for cervical cancer revealed that these cases were similar to de novo leukemia cases, although the bone marrows of patients with ankylosing spondylitis more closely resembled occurring the morphologic and cytogenetic patterns seen among secondary leukemias after treatment with alkylating drugs.^{21, 195} More research is needed to determine whether leukemia arising secondary to radiation exposures (from military, occupational, medically related, and environmental sources) is similar to or differs from de novo occurrence, using state-of-the-art morphologic, cytogenetic, and molecular assessment as part of a standardized protocol to evaluate all newly diagnosed secondary leukemia cases.

Nonionizing Radiation

In 1979 a report linked childhood leukemia and other forms of childhood cancer with residential exposure to nonionizing radiation in the form of extremely low frequency (ELF; 50 to 60 Hz) magnetic field exposures induced by nearby power lines.²⁹⁸ Initial small studies appeared to support a 2- to 3-fold increase in risk associated with residential proximity to high-tension power lines.^{82, 166, 247} However, more recent large studies with more extensive and direct measures of children's time-weighted average MF exposures have shown little evidence of elevated risks, except perhaps a very small percentage of children with high MF exposures.^{160, 183, 188, 288} Experimental studies have shown no evidence of carcinogenesis associated with ELF MF exposures.²¹⁹

Since 1982,¹⁸⁹ investigators using job title as a proxy measure of ELF MF exposures reported increased risks of AML, CLL, and brain tumors among adults employed in occupations believed to have high exposure (such as power linemen, utilities workers, electronics workers, and others).²¹⁹ Many of the studies used the dichotomous classification for "electrical jobs" versus "nonelectrical jobs" proposed by Milham.¹⁹⁰ Studies using a range of types of measurements, some in conjunction with job exposure matrices, have shown inconsistent findings.^{83, 85, 134, 165, 175, 192, 240, 246, 283} Meta-analysis suggests nonsignificant small increases in odds ratios for medium (OR = 1.22) and high (OR = 1.15) exposure categories for total leukemia and overall estimated relative risks of 1.4 (95% CI = 1.2-1.7) for AML and 1.6 (95% CI = 1.1-2.2) for CLL.¹⁴⁰ A comprehensive review of data by a working group commissioned by the U.S. National Institute of Environmental Health Sciences concluded that, taken together, the studies suggest an association between exposure to magnetic fields and CLL.²¹⁹ This conclusion was based on small numbers of highly exposed cases from two Swedish studies^{83, 85} and a French-Canadian investigation.²⁸³

Occupational Exposures

Various occupational and environmental chemical exposures have been implicated as causes of leukemia. The oldest and best-known chemical leukemogen is benzene.⁶⁷ Leukemia has been reported to be 1.9- to 10-fold increased in analytic studies of benzene-exposed painters, printers, and workers employed in petroleum refining and in chemical, rubber, Pliofilm, and shoe manufacturing.^{205, 225, 304, 312} In a large study of Chinese benzene-exposed workers, the relative risk of the combined grouping of acute nonlymphocytic leukemia and myelodysplastic syndromes was 4.1 (3.0 for ANLL only) for "ever" versus "never" exposed. The grouping of acute nonlymphocytic leukemia and myelodysplastic syndromes was about threefold and significantly increased among workers with constant benzene exposure levels of less than 10 ppm, and risk rose to 7.1 for those exposed at constant levels of 25 ppm or higher.¹⁰⁹ Although benzene has been most strongly associated with AML and aplastic anemia, limited evidence suggests that CML, myelodysplastic syndromes, and non-Hodgkin's lymphoma may possibly be linked with exposure to this chemical.^{109, 121, 129, 225, 245, 250, 312}

The dose-response pattern and the relevant exposure metric have been much debated.^{59, 60, 211, 290} Peripheral blood lymphocyte counts appear to represent a sensitive marker of benzene exposure levels.^{234, 296} Decreased lymphocyte counts, in conjunction with other forms of hematotoxicity (benzene poisoning), can serve as a biomarker to validate benzene exposure level estimates.⁷² Total leukemia risk was not significantly increased overall or with higher cumulative benzene exposure among petroleum marketing and distribution workers in the United Kingdom or in Canada, although duration of exposure was more closely related to risk in both studies.^{239, 249} Evidence from the U.K. study²³⁹ suggested that the relevant benzene exposure metric (average dose, duration of exposure, etc.) may vary according to leukemia cell type. Data from the Chinese benzene workers study indicated that acute nonlymphocytic leukemia/myelodysplastic syndrome was significantly associated with more recent but not distant exposures, whereas non-Hodgkin's lymphoma was most strongly linked with exposures occurring at least 10 years before diagnosis.¹⁰⁹ If these findings are confirmed, then mechanistic studies should be undertaken to explain the results. A meta-analysis of cohort studies of petroleum workers in the United States and the United Kingdom (including refinery, production, pipeline, and distribution workers) revealed no excess of AML or other leukemia cell types.²²² Thus, the dose-response relationship for benzene requires further clarification, particularly for very low benzene exposure levels.

Other chemicals have been associated with leukemia in some investigations, but the results are not as consistent as the findings for benzene. Exposure to styrene and/or butadiene has been associated with increased risk of lymphomas, lymphatic leukemias, and total leukemia in some studies,^{186, 204} but not in others,³⁰⁵ perhaps due to confounding from other chemicals such as dithiocarbamates.¹³⁰ Recent investigations support the relationship

between styrene-butadiene rubber production (but not exposure to the butadiene monomer alone) and leukemia risk and provide evidence of dose-response relationships with increasing levels of time-weighted average¹⁷⁶ or cumulative butadiene exposure.¹⁶⁸ Ethylene oxide has also been designated as a probable human carcinogen,^{128, 271} based on leukemia and lymphoma excesses, although the findings are not consistent in all studies.^{256, 281, 282, 306}

Data are more limited for other chemical exposures. Leukemia excesses have been observed among rubber workers,^{233, 275} painters,^{51, 179} embalmers,^{108, 163} garage and transport workers,^{120, 122} sawmill, wood, and furniture industry workers,^{177, 193, 209} shoe workers,⁴² hairdressers and cosmetologists,^{167, 191} slaughterhouse and meat-packing industry workers,¹⁸⁷ seamen on tankers,²⁰³ clinical laboratory, radiologic, and science technicians,⁴³ and other occupational and industrial populations.

The role of maternal and paternal occupational exposures in the causation of childhood leukemia has been evaluated for more than 25 years, but the findings have not been consistent. Recent studies have begun to link population-based cancer registry data and other computerized data sources; novel and more precise exposure assessment methods are also being used.^{2, 151, 228} Risks of leukemia in offspring are being evaluated in relation to different exposure times, such as the preconception, prenatal, or postnatal periods.^{133, 261}

Agricultural Exposures

Studies of farmers and farm workers have shown modest excesses of leukemia (risks ranging from 1.1- to 1.4-fold elevated) in some investigations and no increase in risk in others.^{25, 137, 316} There is some variation in risks internationally, perhaps due to differences in agriculture-related exposures.^{6, 13, 66, 150, 199, 302} Almost all leukemia types were increased among farmers in the studies demonstrating statistical associations. In addition to pesticides (particularly animal insecticides, but probably others as well), other suspected exposures include herbicides, fertilizers, diesel fuel and exhaust, infectious agents, and possibly others associated with livestock.²⁶ Although only a few of the earlier studies evaluated specific pesticide exposures in relation to leukemia risk,^{38, 244} later studies have increasingly incorporated newer interview methods and biologic measurement components to evaluate specific pesticide and other agricultural exposures.^{2, 273, 274}

Antineoplastic Treatments

Treatment with certain types of chemotherapeutic agents (primarily alkylating agents and, more recently, epipodophyllotoxins) prescribed for malignant and nonmalignant disorders (the latter including rheumatoid arthritis and other autoimmune diseases) is associated with increased risks of treatment-related myelodysplastic syndromes and/or secondary AML.¹⁵⁵ The myelodysplastic syndromes associated with alkylating agents are frequently characterized by a preleukemic phase, trilineage dysplasia, and frequent cytogenetic abnormalities involving partial dele-

tions of chromosomes 5 and 7. The mean latency period between treatment and occurrence of the treatment-related hematologic disorder is 5 to 7 years. Treatment-related myelodysplastic syndromes and/or AML are more likely to occur following use of certain agents (e.g., melphalan poses higher risk than cyclophosphamide; stem cell priming with VP-16 has also been linked with high risks).¹⁴⁹ Therapy-related myelodysplastic syndromes and AML have been reported subsequent to treatment for Hodgkin's disease; non-Hodgkin's lymphoma; multiple myeloma; polycythemia vera; breast, ovarian, uterine cervix, uterine corpus, and testicular cancers; and other disorders. Risk is quantitatively related to cumulative alkylating drug dose.

Secondary leukemias related to therapy with topoisomerase II inhibitors (epipodophyllotoxins) have earlier onset than other forms of secondary leukemias and are not preceded by a preleukemic phase. These secondary leukemias frequently show balanced translocations involving 11q23 or, less often, t(8;21), t(3;21), inv(16), t(8;16), t(15;17), or t(9;22).^{7, 79} In a study of 442 children treated with various regimens for germ cell tumors, no treatment-related AML occurred among patients treated with surgery or radiotherapy only, whereas 1% of those treated with chemotherapy and 4.2% of those treated with chemotherapy plus radiotherapy developed treatment-related AML.²⁵¹ In a review of multiple studies of patients treated with topoisomerase II inhibitors, the mean latency period between treatment and occurrence of treatment-related AML was approximately 2 years.⁷⁹

Recent efforts have been directed to identifying factors that may influence risk of developing a secondary treatment-related AML, including polymorphisms of glutathione S-transferase^{242, 307} and of NAD(P)H:quinone oxidoreductase (NQO1),¹⁵⁴ but limited data preclude firm conclusions. A detailed review of secondary leukemia associated with treatment of a wide variety of disorders is provided in Chapters 9 and 11.

Smoking, Alcohol, Diet, and Other Lifestyle Factors

Lifestyle risk factors have either been little studied or been found to play a limited role in the cause of the leukemias, with a few possible exceptions. A few large studies found small increases of adult ALL,^{92, 136, 241} but cohort investigations have reported no excess leukemia associated with cigarette smoking.^{1, 77} Summary assessments have concluded that cigarette smoking is weakly linked (relative risks estimated as 1.3–1.5) with elevated risks of adult myeloid leukemias.^{40, 70} Maternal smoking during pregnancy appears to be unrelated to subsequent risk of childhood leukemia in the offspring,^{37, 243, 252} but some evidence supports an association between paternal preconception smoking and subsequent childhood leukemia.^{133, 269}

A few studies have evaluated the relationship of dietary factors^{123, 153} or alcohol consumption^{23, 39, 46, 114, 132, 248, 303} to the cause of the leukemias in adults, but overall there is little evidence supporting relationships. However, a small U.S. study reported a 10-fold excess risk of infant AML,

but not ALL, linked with increasing consumption during pregnancy of DNA topoisomerase II inhibitor-containing foods.²³² Recent findings from in vivo and in vitro experiments have shown topoisomerase II to be the target of dietary bioflavonoids and suggest a two-stage model for cellular processing of topoisomerase II inhibitors.²⁷⁶ These results support the epidemiologic data and suggest that maternal ingestion of bioflavonoids may induce chromosomal translocations involving the MLL gene in utero, potentially leading to infant leukemia. Longer duration of breast-feeding was linked with reduced risks of childhood AML and ALL in a U.S. study,²⁵⁹ whereas postnatal use of cod liver oil (containing vitamin D) was associated with reduced risk of ALL in Chinese children.²⁵⁸ Two U.S. investigations have reported elevated risks of AML among infants and very young children in relation to maternal alcohol consumption during pregnancy.^{253, 260} Experimental data suggest that calorie restriction may mitigate the leukemogenic effects of exposure to single, high-dose total body radiation.³¹³ These interesting leads deserve further exploration.

Infectious Agents

Retroviruses

Certain retroviruses have been associated with one or more forms of leukemia. Because many aspects, including the epidemiology, of these viruses are examined in greater detail in Chapter 10, they are only briefly mentioned here. HTLV-I is endemic in southwestern Japan, Jamaica, Trinidad, many regions in Africa, native ethnic groups in the Andes highlands, population subgroups in Brazil, and among Caribbean immigrants in Brooklyn, a borough of New York City.^{12, 89, 156, 170, 173, 218, 311} Infection with HTLV-I is estimated to affect 10 to 20 million persons worldwide.⁷⁶ Most carriers remain asymptomatic, but some develop adult T-cell leukemia/lymphoma, whereas others experience HTLV-I-associated myelopathy/tropical spastic paraparesis.¹⁷³ In the endemic area of Nagasaki, Japan, a serosurvey of 18,485 persons for HTLV-I revealed an overall seroprevalence of 16.2%.¹² The age-standardized annual incidence rate of ATLL in persons age 30 years or older was 10.5 per 100,000 persons for men and 6.0 for women. Cumulative lifetime risk of developing ATLL was estimated as 6.6% for men and 2.1% for women. Between 1985 and 1995, 989 cases of ATLL, compared with 1745 cases of other non-Hodgkin's lymphoma, were registered at the Nagasaki Prefecture Cancer Registry. Molecular study has shown that isolates of HTLV-I from Brazilians of various ethnic origins (whites, blacks, mulattos, Japanese immigrants) resembled those of seropositive persons from other South American countries but differed from HTLV-I isolates from Africa and Japan.³¹¹ The virus is spread vertically (from mother to child) during breastfeeding and horizontally (between adults) by sexual intercourse, intravenous drug use, and blood transfusions prior to routine screening of donor blood.²⁷

Other Infectious Agents

Kinlen¹⁴¹ described excesses of common ALL associated with population mixing, in which a higher incidence

occurred among children born into relatively isolated populations subsequent to contact of adults from those communities with migrants from nonisolated communities. He hypothesized that childhood leukemia may be a rare response to an unidentified mild or subclinical infection (occurring in utero or postnatally). Transmission is facilitated by newly occurring proximity of infected persons to previously nonexposed persons residing in an isolated, nonendemic region following the population mixing. To date, Kinlen and colleagues have described a variety of examples of population mixing, all demonstrating elevated occurrence of childhood leukemia in the formerly isolated populations.^{141, 142, 144-148} Although these studies are intriguing, no specific candidate organism has yet been identified.

Greaves and Alexander^{95, 96} developed a hypothesis, based on several lines of evidence (including historical trend data, international rate comparisons, geographic variation, socioeconomic factors, and community characteristics), suggesting that the common form of ALL arises in affluent societies as a rare response to a common infection. A key element of the hypothesis is the role of the pattern and timing of infections in infancy and early childhood in relation to immune system development. Several aspects of lifestyle in developed countries (such as child rearing and social, breast-feeding, and hygiene practices) may affect the developing immune system. Specifically, the hypothesis proposes that the childhood common ALL peak is temporally related to a relative paucity of infections in infancy and early childhood, absence of or very limited breast-feeding, social isolation, and/or delayed exposure of the infant or young child to other children. Clinical leukemia arises as a result of an initial, spontaneous mutation in lymphoid tissue during fetal development that remains silent until delayed exposure to an infectious agent or other promoter causes an abnormal immune response, which is followed after a relatively brief interval by the onset of common ALL. Some epidemiologic data support the hypothesis.^{215, 259, 265} but other studies provide only limited or little support.^{101, 201}

Alexander and colleagues^{3, 4} evaluated the hypothesis that population density may be linked with an increased risk of childhood leukemia using data for 13,551 incident cases of childhood leukemia in 17 European countries and population data for small census units. These investigators found modest but statistically significant evidence of clustering, with incidence showing a curvilinear association with population density. Incidence was highest in areas that were somewhat more densely populated (500 to 750 persons/km²). Statistically significant evidence of clustering was evident in areas of intermediate density (250 to 499 persons/km²). Among children 2 to 4 years old, risks were slightly increased for all population densities except the lowest density areas, but there was no evidence of any trends. As the authors¹ and others²³¹ conclude, such ecologic data cannot provide strong support for any specific hypothesis but may present some leads that should be explored in additional descriptive, ecologic, and analytic studies. Nevertheless, ecologic data are characterized by important limitations that must be acknowledged.

Genetics

Twin Studies

Several lines of epidemiologic evidence support an important role for genetic factors in the origins of the leukemias. A high degree of concordance has been observed for childhood leukemia among monozygotic twins,^{125, 169, 194} although data from one twin study led to the conclusion that a strong constitutional genetic component for childhood leukemia and other cancers was lacking, except for retinoblastoma.⁴¹ Molecular data also suggest that the leukemia concordance in twins is likely due to shared placental circulation rather than to an inherited genetic mutation.^{86, 300}

Familial Aggregation

Epidemiologic studies have repeatedly confirmed familial occurrence of the leukemias, although only a small percentage of cases have affected close family members.¹¹⁸ Familial leukemia is generally characterized by concordance of the leukemia cell types among the affected family members, particularly CLL. Among all types of familial cancer, familial CLL is one of the most common.⁹³ Recent studies of familial occurrence of CLL in parent and offspring have shown a substantially younger age at onset in the offspring compared with the affected parent (a genetic feature designated as "anticipation").^{94, 119, 315} Only a small proportion of familial leukemia is characterized by discordance of the leukemia types.¹⁰⁵ More commonly, relatives of leukemia cases also appear to be at higher risk of developing other hematopoietic and lymphoproliferative neoplasms,^{63, 161, 184} results postulated as consistent with a defect in the pluripotent hematopoietic stem cell.²⁵⁷ The mode of inheritance of familial leukemia and/or other hematopoietic or lymphoproliferative neoplasms is unknown, although it has been hypothesized that an autosomal-dominant gene is responsible in pedigrees with multiple affected members. Postulated mechanisms for familial leukemia include inherited cytogenetic abnormalities, genetic mutations, or primary immunologic alterations; sharing of common haplotypes; and/or consanguinity, possibly in conjunction with leukemogenic environmental influences.

Germline Mutations and Genetic Syndromes

Childhood leukemia is part of the highly penetrant Li-Fraumeni cancer family syndrome, which also features sarcomas, breast cancer, brain tumors, and adrenal carcinoma as well as multiple primary cancers.¹¹⁵ Some Li-Fraumeni families have inherited germline mutations in the *TP53* gene. A report implicates mutations in the tumor suppressor *bCHK2* gene, whose activation prevents cellular entry into mitosis.¹⁵

Approximately 5% of ALL and AML cases have been associated with inherited genetic syndromes, often involving genes functionally linked to DNA repair or other aspects of genomic stability.²⁷⁹ Children with Down's syndrome (trisomy 21) are at increased risk of developing acute leukemia, particularly the M7 (megakaryoblastic)

variant of AML,^{107, 172, 318} perhaps due to a functional role of mutant p53 in the evolution from a transient form of leukemia to acute megakaryoblastic leukemia. It is also noteworthy that acquired trisomy 21 may occur in children and adults without Down's syndrome who develop certain forms of ALL or AML.²³⁷ Another chromosomal syndrome that increases risk of leukemia is ataxia-telangiectasia, associated with ALL and non-Hodgkin's lymphoma.¹¹⁰ Fanconi's anemia, linked with AML, is a congenital disorder in which morphologic myelodysplasia is frequent and associated with poor survival but is independent of the occurrence of cytogenetic clonal variation (including disappearance of clones, clonal evolution, and appearance of new clones).⁵ Bloom's syndrome, associated with both ALL and AML, is a disorder in which the specific chromosome bands nonrandomly affected by spontaneous chromosomal aberrations are also significantly correlated with the fragile sites, breakpoints, and rearrangements characteristic of AML.^{28, 90, 210} Other genetic bone marrow failure syndromes that appear to be linked with leukemia include Diamond-Blackfan and amegakaryocytic thrombocytopenia, and perhaps Klinefelter's syndrome and D trisomy.^{88, 314, 320}

Cytogenetic Abnormalities and Oncogenes

The Philadelphia (Ph) chromosome was the first cytogenetic abnormality linked to a majority of cases with a disease entity, namely CML.²³⁶ The Ph chromosome results from the transposition of part of the oncogene *abl* from chromosome 9 to an abbreviated gene within the breakpoint cluster region (*bcr*) at band q11 on chromosome 22, leading to the creation of a new gene with abnormal messenger RNA and a resultant abnormal protein product. Other oncogenes frequently implicated in the leukemias include *b-ras* and *c-myc*. A specific susceptibility to breakage at the centromere after exposure to alkylating agents is suggested as the explanation for the frequent loss of whole chromosomes (in particular, chromosomes 5 and 7) in therapy-related myelodysplastic syndromes and AML.⁸ A few case-control studies of AML have reported associations of various other exposures (paints, cigarette smoking, alcohol use) with karyotypic abnormalities observed in myelodysplastic syndromes and AML such as 5/5q, 7/7q, +8, and t(8;21).^{58, 65}

Studies of workers with high levels of benzene exposure (a known leukemogen) but no evidence of leukemia have shown similar types of cytogenetic abnormalities as have been observed in myelodysplastic syndromes (pre-leukemia) or AML. These include increased aneusomy and long-arm deletions of chromosomes 5 and 7 in lymphocytes³¹⁷ and translocations in chromosomes 8 and 21.²⁶⁶

Gale et al⁹¹ demonstrated that unique or clonotypic *MLL-AF4* genomic fusion sequences were present in neonatal blood spots of children diagnosed with ALL at ages 5 months to 2 years and thus must have arisen during fetal hematopoiesis in utero.⁹¹ These data confirm the prenatal initiation of acute leukemia in very young children. In addition, Wiemels et al²⁹⁹ identified *TEL-AML1* gene fusion in neonatal blood spots of children newly diagnosed at ages 2 to 5 years with the common form

of acute lymphoblastic leukemia characterized by this chromosomal translocation, thus demonstrating that the event initiating the chromosomal translocation must have occurred in utero. Yet, the delay in onset of common childhood ALL until years after the translocation also suggested that a postnatal promotional event was required.

Genetic Polymorphisms

For an unknown proportion of leukemia patients, certain polymorphisms of genes that encode metabolizing enzymes, detoxification of carcinogens, immune-related mechanisms, and other physiologic functions may modify (by increasing or reducing) leukemia risk associated with specific exposures. Individuals with specific polymorphisms in the methylenetetrahydrofolate reductase gene have been found to be at reduced risk of adult ALL.²⁶⁵ Adult AML was weakly associated with both *GST T1* null and *GST M1* null polymorphisms, whereas adult ALL was linked with *GST T1* null, even though no associations were found between smoking and disease risk in relation to *GST T1* and *GST M1* polymorphisms.²²⁷ Benzene poisoning (hematotoxicity), a strong predictor for adult myelodysplastic syndromes and AML, was found to be associated with polymorphisms in genotypes of enzymes that activate (i.e., *CYP2E1*) and detoxify (i.e., *NQO1*) benzene and its metabolites among Chinese benzene-exposed workers.²³⁵ Infants developing leukemia characterized by *MLL* gene rearrangements were more than twice as likely to have genotypes with low *NQO1* function (a polymorphism in an enzyme that detoxifies quinones, which are a structural feature shared by many topoisomerase II-inhibiting drugs as well as other chemicals) than healthy children or childhood leukemia patients with *TEL-AML1* gene fusions or with hyperdiploidy.³⁰¹ The subset of infants whose *MLL* gene rearrangement resulted in an *MLL-AF4* gene fusion had an eightfold increased risk of low *NQO1* function.³⁰¹ Chen and colleagues⁵⁰ reported a higher frequency of the double null genotype (lacking both glutathione S-transferase M1 (*GSTM1*) and *GSTT1* genotypes) in African-American children with ALL, but this double-null genotype was not associated with prognosis. The relationship of this finding, if any, to the lower incidence of ALL in African-American rather than white children is unclear.

PROSPECTS FOR PREVENTION

In the absence of more substantial knowledge about major risk factors for leukemia, it does not appear that leukemia incidence can be substantially reduced in the near future. It is important to avoid unnecessary exposures to ionizing radiation, and the benefits of diagnostic and therapeutic medical radiation exposures must continue to be weighed against their risks. The ubiquitous exposure to benzene from environmental sources (cigarette smoking, automobile fuel and exhaust, and chemical contaminants) or industrial sources (occupational exposures in chemical manufacturing, petroleum refining, and other industrial plants) is now increasingly regulated

throughout the industrialized world. However, the present state of knowledge is insufficient to recommend curtailing or modifying use of agricultural chemicals to prevent leukemia. Increasingly stringent measures are being used to prohibit smoking in public or work places, to prevent children from initiating smoking, and to limit smoking by a variety of public health and economic measures. The spread of HTLV-I can be disrupted by screening blood products, educating infected mothers not to breast feed, and discouraging needle sharing by parenteral drug users.

The principal risk factors for most forms of leukemia are as yet undiscovered. Thus, the prevention of leukemia awaits further advances in our knowledge of etiology. Variations in leukemia occurrence by subtype suggest that risk factors may not be identical for the different forms of leukemia. Future analytic studies should evaluate postulated host and environmental risk factors for homogeneous, biologically defined leukemia subtypes; improve the accuracy of exposure assessment; and incorporate detailed evaluation of a broad range of genetic factors that may affect the risk of developing leukemia.

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