
Graça M. Dores1,2*, Susan S. Devesa2, Rochelle E. Curtis2, Martha S. Linet2, Lindsay M. Morton2

1Department of Veterans Affairs Medical Center, Oklahoma City, OK; 2Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Bethesda, MD

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*Corresponding author:
Graça M. Dores, MD, MPH
Department of Veterans Affairs Medical Center
921 N.E. 13th Street
Oklahoma City, OK 73104
Phone: 405-456-3325
Fax: 405-456-1569
E-mail: doresg@mail.nih.gov
Abstract

Since 2001, the World Health Organization (WHO) classification for hematopoietic and lymphoid neoplasms has provided a framework for defining acute leukemia (AL) subtypes, although few population-based studies have assessed incidence patterns and patient survival accordingly. We assessed AL incidence rates (IRs), IR ratios (IRRs), and relative survival in the United States (2001-2007) in one of the first population-based, comprehensive assessments. Most subtypes of acute myeloid leukemia (AML) and acute lymphoblastic leukemia/lymphoma (ALL/L) predominated among males, from twice higher incidence of T-cell ALL/L among males than among females (IRR=2.20) to nearly equal IRs of acute promyelocytic leukemia (APL) (IRR=1.08). Compared to non-Hispanic whites, Hispanics had significantly higher incidence of B-cell ALL/L (IRR=1.64) and APL (IRR=1.28); blacks had lower IRs of nearly all AL subtypes. All ALL/L but only some AML subtypes were associated with a bimodal age pattern. Among AML subtypes, survival was highest for APL and AML with inv(16). B-cell ALL/L had more favorable survival than T-cell ALL/L among the young; the converse occurred at older ages. Limitations of cancer registry data must be acknowledged, but the distinct AL incidence and survival patterns based on the WHO classification support biologic diversity that should facilitate etiologic discovery, prognostication, and treatment advances.
Introduction

Acute leukemias account for approximately 20,000 cancer diagnoses and 10,000 deaths annually in the United States, but the etiology of most acute leukemias remains unknown. Descriptive epidemiologic studies can provide insight into etiology, identify susceptible populations, and provide information about patient survival in the general population, but to be informative are reliant upon reproducible classification systems that allow for precise diagnoses. The World Health Organization (WHO) developed a consensus-based classification for hematopoietic and lymphoid neoplasms that defines distinct diseases by incorporating information on cell lineage, morphology, immunophenotype, and clinical and genetic features. Since its introduction in 2001 and update in 2008, the WHO classification has provided a framework for reproducibly defining hematopoietic and lymphoid entities worldwide.

Although a few population-based studies recently have analyzed the incidence of acute leukemia utilizing the WHO classification, none have included data beyond 2002 or characterized both incidence and survival by subtypes of acute leukemia. Despite limitations in cancer registry data, such as lack of centralized pathology review and potentially more limited diagnostic evaluation in the general population than in clinical trials, other studies utilizing population-based cancer registries have successfully assessed patterns of hematologic malignancies and related disorders using various disease classification schemes for these neoplasms. Therefore, we sought to substantially extend initial population-based reports and provide the first comprehensive assessment of childhood and adult acute leukemia incidence and patient survival in the United States, guided by the WHO classification. We include acute leukemia cases
diagnosed during 2001-2007, thereby maximizing the proportion likely to have been characterized with immunophenotyping and cytogenetic studies and treated with modern therapies and supportive care. An important clinical and public health objective of our population-based analysis was to identify whether subtype-specific incidence rates suggested biologic and/or etiologic differences and to identify whether opportunities exist for improving diagnostic assessment and therapeutic interventions for particular subpopulations with acute leukemia.

**Material and Methods**

We analyzed cases of acute leukemia diagnosed among residents of 17 population-based cancer registry areas of the Surveillance, Epidemiology and End Results (SEER) Program (SEER-17) during 2001-2007. SEER-17 registries cover approximately 26% of the U.S. population, including eight states (Connecticut, Hawaii, Iowa, Kentucky, Louisiana, New Jersey, New Mexico, and Utah), six metropolitan areas (Atlanta, Georgia; Detroit, Michigan; Los Angeles, San Francisco-Oakland, and San Jose-Monterey, California; Seattle-Puget Sound, Washington), the areas of greater California and rural Georgia, and the Alaska Native Tumor Registry.

**Leukemia classification**

Our analysis is limited to acute leukemias defined in the third edition of the International Classification of Diseases for Oncology (ICD-O-3), which was implemented in the SEER Program for cancer cases diagnosed in 2001 and remains in use in 2011. We classified cases first according to cell lineage, considering separately the incidence
of acute myeloid leukemia (AML), acute (precursor) lymphoblastic leukemia/lymphoma (ALL/L), and acute leukemia of ambiguous lineage.

The broad category of AML included ICD-O-3 morphology codes M-9840, 9861, 9866-9867, 9870-9874, 9891, 9895-9897, 9910, 9920, 9930-9931, and 9987 (Table 1, Figure 1). Guided by the WHO classification, we considered individual AML subtypes (specified in Table 2), including “Group 1” (AML, not otherwise specified (NOS) and related entities, including myeloid sarcoma), “Group 2” (entities with associated cytogenetic abnormalities), and “Group 3” (AML with myelodysplasia-related changes and therapy-related myeloid neoplasms, including therapy-related myelodysplastic syndrome (MDS), NOS since the 2008 WHO classification considers therapy-related AML (t-AML) and therapy-related MDS (t-MDS) as a single biologic entity). All morphology codes for ALL/L (M-9727-9729, 9835-9837) (Table 1, Figure 1) were newly introduced with ICD-O-3. We considered ALL/L subtypes with similar immunophenotypic characteristics (B-cell, T-cell) within the same category, based on the premise that the WHO considers leukemias and lymphomas different manifestations of the same disease. We were able to further classify ALL/L of unknown lineage (M-9727, 9835) into B-cell or T-cell subtype based on available immunophenotyping information (specified in Table 2). We considered acute undifferentiated leukemia (M-9801) and acute biphenotypic leukemia (M-9805) within the category of acute leukemia of ambiguous lineage (specified in Table 2).
Incidence

We calculated age-adjusted incidence rates (IRs) per 1,000,000 person-years (PY), IR ratios (IRRs), and 95% confidence intervals (CIs) using the Incidence Rate Session in SEER*Stat (version 6.5.2) (www.seer.cancer.gov). All IRs were age-adjusted to the 2000 U.S. standard population. We excluded from analysis 4.8% of cases (n=1,485) that were not specified to be microscopically confirmed, of which 66.3%, 9.8%, and 24.0% were classified as AML, ALL/L, and acute leukemia of ambiguous lineage, respectively. We included in our analysis all cases of acute leukemia, whether diagnosed as a first primary or subsequent malignancy. Of note, however, prior to 2010, the SEER Program did not collect information on acute leukemia that developed subsequent to a diagnosis of another leukemia (e.g., acute leukemia following chronic myelogenous leukemia), MDS, or myeloproliferative neoplasm.

IRs were calculated overall and according to gender (male, female), age (<1, 1-4, 5-9, 10-14, 15-24, 25-34, 35-44, 45-54, 55-64, 65-74, >75 years), race/ethnicity (non-Hispanic whites, Hispanic whites, blacks, Asians/Pacific Islanders (APIs), other/unspecified), calendar year, and leukemia subtype (as specified in Table 2). Age-specific IRs were plotted on a log-linear scale using the midpoint of each specified age group (<1, 1-4, 5-14, 15-24, 25-34, 35-44, 45-54, 55-64, 65-74, 75-84, and >85 years). IRs based on fewer than 10 cases are not shown in the tables and figures, similar to international convention.
Survival

To evaluate patient survival following a diagnosis of acute leukemia, we restricted the cohort to patients diagnosed during 2001-2006 (rather than 2007) and followed them for vital status through 2007 (n=25,428). We excluded cases of acute leukemia diagnosed as a second or later primary cancer (n=3,921) or during July-December 2005 in Louisiana due to population displacement from Hurricane Katrina (n=93), reported only by death certificate or autopsy (n=10), with unknown age (n=1), or with unknown survival time (n=64). Through active tracing, the SEER Program has been successful in attaining >97% follow-up for vital status.

Cause-specific survival is a measure of net survival in the absence of other causes of death; observed survival is the probability of surviving all causes of death for a specified interval; and relative survival (RS) is the ratio of the proportion of observed to expected survivors in a comparable cohort of the general population. We focused our analysis on RS which is not reliant on a potentially inaccurate cause of death, accounts for the underlying disease process or ensuing associated complications, and provides a basis for comparison in the general population. The actuarial method in the SEER*Stat Survival Session was used to estimate 1- and 5-year RS and 95% CIs using monthly intervals. RS was calculated according to leukemia subtype and four age groups (<20, 20-39, 40-59, >60 years). We further divided the younger (<1, 1-4, 5-19 years or <5, 5-19 years) and older (40-49, 50-59, 60-69, 70-79, >80 years) age groups when the number of cases allowed. According to SEER Program convention, RS estimates based on fewer than 25 cases are not shown.
Results

Incidence

Overall acute leukemia patterns by gender, race, and age

During 2001-2007, 29,682 individuals (IR=57.2 per 1,000,000 PY) were diagnosed with acute leukemia in SEER-17. Overall, AML accounted for 65.7% of cases (n=19,497; IR=38.0), ALL/L 31.0% (n=9,188; IR=17.3), and acute leukemia of ambiguous lineage 3.4% (n=997; IR=2.0). AML IRs were remarkably similar among Hispanic whites, blacks, and APIs (IR=32.0-32.3) with rates for each racial/ethnic subgroup approximately 20% lower than among non-Hispanic whites (IR=39.9) (Table 1). AML IRs demonstrated a bimodal age pattern with an initial peak among infants (<1 years, IR=19.9), a decline in childhood, then an exponential rise in IR with advancing age beginning in young adulthood (Table 1, Figure 1). Among blacks and APIs, the initial age peak occurred at 1-4 years; thereafter, IRs nadired at a slightly younger age among blacks and API males than API females. IRs for ALL/L followed different patterns by race/ethnicity and age. Hispanic whites had the highest incidence of ALL/L (IR=24.9), which was 50% higher than the incidence among non-Hispanic whites; blacks had the lowest incidence of ALL/L (IR=10.2), and non-Hispanic whites and APIs had intermediate IRs. ALL/L was also associated with a bimodal age pattern, but unlike AML, the initial age peak occurred among children 1-4 years of age with a decline at ages 20-59 years, followed by a modest rise in IRs at ages >60 years. The ALL/L predominance among Hispanic whites was absent in infants, but noted across virtually all older age groups.
Acute leukemia subtypes and gender

Incidence of AML was 48% higher among males than females, with a male predominance noted for all three AML groups (Table 2). With the exception of therapy-related myeloid neoplasms, which occurred approximately equally among males and females (male-to-female IRR=0.99), all other AML subtypes had higher IRs among males, with male-to-female IRRs ranging from 1.08 for APL with t(15;17) to greater than 2.0 for AML with myelodysplasia-related changes and acute erythroid leukemia. APL with t(15;17) IRs were approximately 20% lower among men than women up through ages 25-34 years, and at older ages IRs were generally higher among males (data not shown); however, only among the 75-84 year age group (male-to-female IRR: 1.66, 95% CI 1.12-2.47) did IRs for APL with t(15;17) differ significantly by gender. Similar to AML, ALL/L also was associated with higher IRs among males than females (IRR=1.33). The male-to-female IRR for T-cell ALL/L was 2.20, significantly greater than that for B-cell ALL/L (IRR=1.20) or ALL/L of unknown lineage (IRR=1.34).

Acute leukemia subtypes and race

Compared to non-Hispanic whites, IRs of most AML and ALL/L subtypes were lower among Hispanic whites, blacks, and APIs (Table 3). Notable exceptions included significantly higher IRs for APL with t(15;17), B-cell ALL, and ALL/L of unknown lineage among Hispanic whites compared to non-Hispanic whites (Hispanic white-to-non-Hispanic white IRR of 1.28, 1.64, and 1.49, respectively). Although differences were not significant, AML with inv(16) and acute biphenotypic leukemia IRs were >10% higher among Hispanic whites than non-Hispanic whites; acute megakaryoblastic leukemia
and acute undifferentiated leukemia IRs were >10% higher among blacks than non-Hispanic whites; and acute megakaryoblastic leukemia, AML with t(8;21), and AML with 11q23 abnormalities IRs were >10% higher among APIs than non-Hispanic whites.

**Acute leukemia subtypes and age**

Age-specific incidence of subtypes of AML, ALL/L, and acute leukemia of ambiguous lineage are depicted in Figure 2 for all races and genders combined. A bimodal IR pattern with an initial peak in infancy (<1 year) was apparent for AML, NOS; acute myelomonocytic leukemia; acute monoblastic and monocytic leukemia; and acute megakaryoblastic leukemia. A slightly older initial age peak (1-4 years) occurred for B-cell ALL/L, ALL/L of unknown lineage, acute undifferentiated leukemia, and acute biphenotypic leukemia; an older (5-14 years), less prominent age peak was noted for T-cell ALL/L. In contrast, several AML subtypes occurred rarely in infancy and childhood, including AML with 11q23 abnormalities, AML with myelodysplasia-related changes, therapy-related myeloid neoplasms, acute erythroid leukemia, acute panmyelosis with myelofibrosis, and myeloid sarcoma. In adulthood, most AML subtypes increased sharply with advancing age, although a more attenuated rise in incidence with age was suggested for AML with inv(16) or t(16;16) and APL with t(15;17). Although only a subtle rise in incidence at older ages was suggested for B- and T-cell ALL/L, the incidence of ALL/L of unknown lineage rose prominently beginning in mid-life.

*Unspecified acute leukemia subtypes by calendar year*
Incidence of AML, NOS declined significantly from 2001 (IR=19.3; 45.9% of AML cases) to 2002 (IR=16.4, 42% of AML cases) but then remained relatively stable through 2007 (IRs ranging from 15.8-16.7). In contrast, incidence of ALL/L of unknown lineage decreased progressively from 2001 (IR=4.6) to 2007 (IR=2.0), accounting for 27.6% and 10.8% of ALL/L cases, respectively. A continuous rise in incidence of B-cell ALL/L was observed from 2001 (IR=9.6) to 2007 (IR=13.4) with B-cell ALL/L accounting for 57.6% of ALL/L in 2001 and 74.8% in 2007. No temporal pattern was apparent for T-cell ALL/L.

**Relative survival**

**AML: subtypes and age**

Infants (<1 year) with AML had less favorable 1- and 5-year RS than older children and adolescents (1-4 and 5-19 years). This exception aside, beginning at 1-4 years, RS decreased progressively with increasing age at AML diagnosis (Supplementary Table). Based on broader age groups, a similar pattern of progressive decrease in patient survival with increasing age at diagnosis was observed for most AML subtypes (Figure 3 and Supplementary Table). Compared to all other subtypes of AML, for each age group studied, 5-year RS was most favorable for APL with t(15;17) and AML with inv(16). Survival also was favorable for AML with t(8;21) among individuals <20 years, but intermediate among older age groups. Most AML Group 1 subtypes had intermediate 5-year survival for age groups <60 years; prognosis was uniformly poor (RS <10%) for patients diagnosed at ages >60 years, with the exception of acute panmyelosis with myelofibrosis and myeloid sarcoma. Among each affected
age group, patients with acute erythroid leukemia tended to have the least favorable survival. In contrast to most other AML subtypes, survival for APL with t(15;17) decreased precipitously within the first two months of diagnosis, most prominently among the oldest age group, but thereafter remained generally stable over the ensuing 5-year period.

ALL/L: subtypes and age

Similar to the pattern observed for AML, infants (<1 year) with ALL/L had worse survival than older children and adolescents (1-4 and 5-19 years). Among ALL/L subtypes, children 1-4 years of age had the highest survival for all subtypes; thereafter, survival decreased with increasing age at diagnosis, with a relatively notable decline in survival beginning at ages 20-39 years for all ALL/L entities. Infants with B-cell ALL/L and ALL/L of unknown lineage had intermediate survival as compared with the 5-19 year and 20-39 year age groups. Notably, children and young adults 1-4 and 5-19 years of age with B-cell ALL/L had more favorable survival than those with T-cell ALL/L. In contrast, survival for T-cell ALL/L was substantially higher than B-cell ALL among adults 20-39, 40-59, and >60 years. Survival for patients with ALL/L of unknown lineage was generally similar to that of B-cell ALL/L.

Acute leukemia of ambiguous lineage: subtypes and age

Similar to AML and ALL/L subtypes, survival of patients with acute leukemia of ambiguous lineage decreased markedly with advancing age. Most notably, individuals
>60 years with acute undifferentiated leukemia, the most commonly affected age group, was particularly poor, with a 5-year survival rate of 3%.

**Discussion**

In the first comprehensive, population-based analysis of incidence patterns of acute leukemia subtypes and patient survival in the United States guided by the 2001 WHO classification scheme, we observed substantial differences in incidence among acute leukemia subtypes by age, gender, and race/ethnicity. Infants and children demonstrated increased susceptibility to ALL/L and some, but not all, AML subtypes, with variation in the age at occurrence of the initial incidence peak. Age patterns in adults also varied among acute leukemia subtypes with respect to the rate of rise in incidence with advancing age. Most, but not all, acute leukemia subtypes predominated among males and non-Hispanic whites. Despite the 43.9% of AML, NOS and 17.2% of ALL/L of unknown lineage, these frequencies have decreased compared to prior SEER-based studies. The decline in the IR for AML, NOS from 2001-2002 and then relative stability through 2007 suggests that a further decrease is unlikely with the current ICD-O-3 classification and will require additional disease entities, such as those proposed in the 2008 WHO classification for the next ICD-O revision (ICD-O-4). In contrast, the progressive decrease in incidence of ALL/L of unspecified lineage during 2001-2007 is consistent with increased utilization of immunophenotyping and/or reporting of immunophenotype to cancer registries. We found that acute leukemia survival was highly dependent on age at diagnosis and notably less favorable across all subtypes among individuals diagnosed at >60 years of age. Among AML subtypes, survival was
highest for Group 2 entities, particularly for APL with t(15;17) and AML with inv(16) for most age groups. B-cell ALL/L had more favorable survival than T-cell ALL/L among the young, whereas the converse occurred at older ages. We conclude that acute leukemia subtypes defined by the WHO classification have distinct incidence and survival patterns pointing to biologic diversity and etiologic heterogeneity.

The striking differences in incidence patterns among acute leukemia subtypes by age are strongly supportive of etiologic heterogeneity. Certain subtypes demonstrated a bimodal incidence pattern by age, with variation of the initial peak from infancy (<1 year) to early or later childhood (1-4 or 5-14 years, respectively). In contrast, some AML subtypes occurred rarely in infancy and childhood and increased exponentially with advancing age. Acute megakaryoblastic leukemia, acute panmyelosis with myelofibrosis, and AML with 11q23 abnormalities were largely limited to the adult population, although the early-onset age peak of acute megakaryoblastic leukemia we observed at ages <1 and 1-4 years is consistent with the median age of 23 months (range 6.7-208.9 months) reported at a pediatric institution. Similar to our findings, other series have reported a median age of 42.5 years for adult acute megakaryoblastic leukemia and 67 years for acute panmyelosis with myelofibrosis.

The age-dependent incidence patterns we observed are consistent with the age-specific patterns of recurrent chromosomal and genetic abnormalities that are a hallmark of acute leukemia. For example, the Philadelphia chromosome t(9;22) is the most common rearrangement in adult ALL/L, whereas high hyperdiploidy (51–65 chromosomes) and the t(12;21) translocation are the most common cytogenetic abnormalities in childhood ALL/L. In both infant ALL/L and AML, the t(4;11)
translocation involving the MLL gene is the most common abnormality. However, 11q23 abnormalities involving MLL and various translocation partners are found across all ages. The multiple breakpoint positions within MLL have an age-dependent distribution, potentially accounting for the distinct biologic behavior of acute leukemia in infants compared to children and adults, despite phenotypically and cytogenetically similar disease. 11q23 abnormalities have been described in AML evolving from MDS, therapy related AML, and in several subtypes included in the French-American-British classification. The prominent adult-onset age pattern we observed in AML with 11q23 abnormalities, as was similarly seen with therapy-related myeloid neoplasms, may reflect the higher incidence of therapy-related neoplasms and MDS among adults than children. Together, these observations suggest that for selected acute leukemia subtypes, information on age may merit inclusion in future WHO classification revisions, as has been suggested for lymphoid neoplasms where age has been closely associated with disease biology or etiology (e.g., pediatric marginal zone lymphoma, Epstein Barr virus-positive diffuse large B-cell lymphoma of the elderly).

The age-dependent incidence patterns further support the findings of Moorman and colleagues who assessed age-specific patterns of acute leukemia according to cytogenetic classification and suggested that these patterns might provide insight into the number of required molecular abnormalities for leukemogenesis. Based on the observation of constant incidence of APL (n=149) across all ages, Vickers et al hypothesized that a single, rate-limiting genetic event might be sufficient to initiate the disease, assuming a constant mutation rate with advancing age. Other population-based studies, and the findings we report, also suggest a slowly progressive rise in
incidence of APL with advancing age, which in our study was less prominent than for most Group 1 and Group 3 AML subtypes. Together these reports underscore the need to consider the cytogenetic classification of acute leukemia subtypes in future etiologic research.

The male predominance of acute leukemias\textsuperscript{5-7, 23} showed substantial variation among AML subtypes, ranging from similar IRs for males and females for therapy-related myeloid neoplasms (IRR=0.99) and APL (IRR=1.08) to >2.0-fold higher incidence among males than females for AML with myelodysplasia-related changes, acute erythroid leukemia, and T-cell ALL/L. Similar to findings in a recent study from Sweden based on 105 cases,\textsuperscript{22} APL predominated among women at younger ages and among males at older ages, although gender differences in our study were nonsignificant across most age groups. It is notable that the male predominance in the incidence of AML with myelodysplasia-related changes parallels the estimated 70% higher incidence of MDS occurring among males than females.\textsuperscript{24} Acute erythroid leukemia may arise \textit{de novo}, but may similarly evolve from preceding MDS, thereby possibly accounting for the male predominance we observed, as also reported in clinical series.\textsuperscript{25} We noted the most prominent gender disparity for T-cell ALL/L, with incidence among males more than twice that among females. Notably, an inactivating mutation and deletions in an X-linked tumor suppressor gene, \textit{PHF6}, have been identified in T-cell ALL,\textsuperscript{26} possibly contributing to the male predominance for this subtype. Future studies of genetic and hormonal characteristics, environmental exposures (e.g., pesticides, fertilizers, benzene, formaldehyde, tobacco products) and exposure levels...
are likely to provide insight into the gender differences observed by acute leukemia subtype.

Distinct racial/ethnic patterns by disease subtype support differences in host susceptibility among the acute leukemias. Although non-Hispanic whites had the highest rates of most subtypes, we also observed significantly elevated rates among Hispanic whites for APL with t(15;17), B-cell ALL/L, and ALL/L of unspecified unknown lineage, consistent with most previous reports.6, 27-29 An earlier study in the SEER Program found the incidence rates of APL among Hispanics exceeded that among whites among those under age 45 years but not among older ages.30 Investigations of three breakpoint sites (bcr1, bcr2, bcr3) of the *PML* gene involved in APL with t(15;17), have described significantly higher prevalence of bcr1 among individuals from Latin America compared to published reports of non-Latino populations in U.S. and Europe.31, 32 In addition, several recent genome-wide association studies of childhood ALL/L have identified risk loci with varying effects by racial/ethnic group for B- and T-cell ALL/L,33, 34 further highlighting the importance of considering disease subtypes according to race/ethnicity and age in etiologic investigations.

Survival information and identification of prognostic features that influenced the WHO classification system of AML have been derived largely from clinical series. Our investigation, the first population-based study to comprehensively describe patient survival by acute leukemia subtype, revealed advancing age to be an important determinant for survival among nearly all acute leukemia subtypes. This overall age pattern is similar to the results for all AML subtypes combined, reported in other population-based studies.8, 35-37 The 5-year RS of AML we report in SEER-17 (2001-
2006) was generally comparable to the 5-year RS reported in Sweden (1997-2005),\(^8\) and notably improved among infants (<1 year) compared to that previously reported in nine SEER areas during 1995-1999 (RS=39.0; 95% CI=18.7-59.3).\(^{36}\) Individuals diagnosed with AML between 41-60 years of age in Sweden, had a 1-year RS of 61%,\(^8\) which compares with 1-year RS of 63% and 53% of AML in the SEER Program among individuals 40-49 and 50-59 years of age, respectively.

We found substantial variation in survival among patients with different AML subtypes. Individuals with Group 2 AML subtypes (5-year RS=60.8%) had more favorable survival as compared with Group 1 or Group 3 AML subtypes (5-year RS=21.1% and 13.3%, respectively), which is consistent with the prognostic significance of cytogenetics reported in clinical trials, where (15;17), t(8;21), and inv(16) emerge as favorable features among individuals of all ages.\(^{38, 39}\) Notable variation in survival was seen for APL according to age at diagnosis in our study, with 76-77% RS for ages <40, 68% for ages 40-59, and 43% for ages >60. We confirmed recent population-based reports, including a SEER-based study, of a high early death rate following a diagnosis of APL, particularly among older patients.\(^{21, 22}\) Possible reasons to account for the early death rate in APL, including disease sequelae (e.g., hemorrhage, hyperleukocytosis), treatment complications, lack of timely initiation of treatment, and other factors, have recently been reviewed.\(^{21}\) Improving upon the substantial heterogeneity that exists in the definition of treatment-related mortality across studies,\(^{40}\) should help elucidate reasons for early death rates in APL reported internationally. Also, of particular interest was the apparent worse relative survival in all age groups for AML t(8;21) compared to APL with t(15;17) and AML with inv(16). In contrast to our
findings, clinical series have reported similar overall (observed) 5-year survival among younger individuals (median age 35 years; n=377) with AML with t(15;17), t(8;21), and inv(16) (63%, 69% and 61%, respectively), although survival differences by AML subtype have been reported among older patients (38%, 35%, and 17%, respectively, median age 66 years; n=78).\textsuperscript{38, 39} Theoretically, a varying prevalence of KIT mutations in the general adult population with AML with t(8;21) compared with individuals participating in clinical trials could account, at least in part, for these findings. Notably, the adverse impact of KIT mutations on survival in AML with t(8;21) or inv(16) appears to be limited to adults.\textsuperscript{41, 42}

The overall survival patterns for Group 1 AML subtypes were less diverse than the incidence patterns, perhaps related to the widespread use of cytarabine- and anthracycline-based therapy for all of these subtypes.\textsuperscript{43} The 2008 WHO classification includes provisional entities that incorporate information on new cytogenetic abnormalities that may facilitate development of targeted therapies and predict survival. Although information on presumed prognostic markers (e.g., NPM1, CEBPA) is not considered within distinct entities in the current WHO classification, as additional clinical data accumulate, newly defined AML subtypes that incorporate this information may be included in future revisions of the classification.

Our population-based data support previous clinical series showing that infants and older adults have a less favorable prognosis than children and young adults with ALL/L.\textsuperscript{44} Overall 5-year survival rates of approximately 40% have been reported among adults with ALL/L, with individuals >60 years having 5-year overall survival rates of less than 10%.\textsuperscript{45} New in our study was the ability to compare RS patterns for B- versus T-
cell ALL/L. Among patients in the general population diagnosed with ALL/L at ages 1-19 years, we demonstrated significantly higher survival for those with B-ALL/L compared with T-cell ALL/L. These findings contrast with previous results from clinical trials showing that cellular phenotype is of less prognostic importance in childhood ALL/L. However, for each age group 20 years or older, we found that T cell ALL/L was associated with a more favorable prognosis than B-ALL/L, in agreement with clinical series that found significantly better 5-year overall survival (48%) than B-cell phenotype (41%) among individuals 15-59 years of age. The age-specific survival differences in B-cell ALL/L we observed may, in part, be due to the increasing prevalence of t(9;22) with advancing age, a well-described, poor prognostic feature.

Notably, tyrosine kinase inhibitors have favorably affected survival of Philadelphia chromosome-positive ALL across all ages. The 2008 WHO classification proposed a new category for B-cell ALL/L with t(9;22)(q34;q11.2), which will allow greater insight into future studies of etiology and survival of this disease entity.

Strengths of our study include the large numbers of cases available in a population-based setting, thus avoiding biases related to referral patterns or population differences in clinical series. Further, the large number of cases categorized using ICD-O-3 codes allowed us to evaluate incidence and patient survival guided by the WHO classification. With improved classification over time, we report more than 80% of ALL/L cases with known B- versus T-cell lineage, far higher than previous large studies.

Limitations of our analysis include the absence of a centralized expert hematopathology review. Although the proportion of AML, NOS was higher in an earlier
report describing SEER data, a sizeable number of AML cases in our study were classified as AML, NOS (44% of our AML group), particularly at older ages. It is plausible that elderly individuals, untreated patients, and those diagnosed outside major academic centers may have undergone less intensive diagnostic testing, and thus the AML, NOS category likely includes cases that should be classified to more specific WHO AML subtypes in Groups 1, 2, and 3. In addition, the AML, NOS group likely also contains cases with cytogenetic abnormalities that do not have a corresponding ICD-O-3 histology code. Although, we are unable to differentiate AML cases that did not undergo complete diagnostic evaluation from those with abnormal karyotype but for which no ICD-O-3 code exists and those associated with normal karyotype, the frequency of AML with normal karyotype is reported to comprise 41-48% of cases of AML in other series.

The occurrence of Group 3 AML (AML with myelodysplasia-related changes and therapy-related myeloid neoplasms) is likely under-ascertained in these population-based data because the ICD-O codes for these entities were newly introduced in 2000, and history of previous cytotoxic therapy may not be reliably reported. As previously noted, our study does not include cases of acute leukemia occurring among individuals with MDS, myeloproliferative neoplasms, or other leukemias. A study of adults with non-APL AML in Sweden (1997-2005) reported 24% of cases were secondary to prior hematologic disease. Although we included in our incidence analysis patients with acute leukemia following non-hematologic malignancies (some of whom were treated with cytotoxic therapy for a first primary malignancy), these patients accounted for a small proportion (2-5%) of the total number of cases and thus were unlikely to
substantially bias the reported incidence data. Our survival analyses did not account for
treatment which may, at least in part, account for the age-specific survival differences
observed. Treatment with chemotherapy has been shown to be associated with
improved survival, and that use of chemotherapy is less frequent among older than
younger patients.50

In summary, in the first comprehensive, population-based assessment of acute
leukemia incidence and patient survival according to the 2001 WHO classification, the
heterogeneous incidence patterns by gender, racial/ethnic group, and most strikingly by
age suggest that the WHO classification can discriminate between etiologically and/or
biologically distinct acute leukemia subtypes. Our survival data by acute leukemia
subtypes serves as a contemporary clinical resource for patients with acute leukemia in
the general population. The notable influence of older age on survival across all
leukemia subtypes highlights the need to develop nontoxic therapies and to include
these higher risk individuals in clinical trials. The distinct acute leukemia incidence and
survival patterns by subtype suggest that the WHO classification will facilitate future
etiologic discovery, prognostication, and treatment advances.
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This work was supported by the Department of Veterans Affairs Medical Center in Oklahoma City, OK and the Intramural Research Program of the National Cancer Institute, National Institutes of Health, Department of Health and Human Services in Bethesda, MD. The authors thank William F. Kern, MD, Department of Pathology, University of Oklahoma Health Sciences Center, Oklahoma City, OK for valuable input on earlier versions of the manuscript and David Check, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD for expert assistance with the figures.

Authorship Contributions and Disclosure of Conflicts of Interest

Conceived and designed research: GMD, SSD, REC, MSL, LMM

Performed statistical analysis: GMD

Analyzed and interpreted data: GMD, SSD, REC, MSL, LMM

Wrote the manuscript: GMD and LMM

Critically reviewed and edited the manuscript for important intellectual content: GMD, SSD, REC, MSL, LMM

The authors have no conflicts of interest to declare.
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Table 1. Age-adjusted incidence rates and incidence rate ratios of acute myeloid leukemia and acute (precursor) lymphoblastic leukemia/lymphoma according to race/ethnicity and age, SEER-17, 2001-2007*

<table>
<thead>
<tr>
<th></th>
<th>Acute myeloid leukemia (AML)</th>
<th></th>
<th>Acute (precursor) lymphoblastic leukemia/lymphoma (ALL/L)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (%) IR IRR (95% CI)</td>
<td></td>
<td>No. (%) IR IRR (95% CI)</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>19,497 (100) 38.0 NA</td>
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<td>9,188 (100) 17.3 NA</td>
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</tr>
<tr>
<td><strong>Race/ethnicity</strong></td>
<td></td>
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<tr>
<td>Non-Hispanic whites</td>
<td>14,177 (72.7) 39.9 1.00</td>
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<td>4,761 (51.8) 16.6 1.00</td>
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</tr>
<tr>
<td>Hispanic whites</td>
<td>2,216 (11.4) 32.3 0.81 (0.77-0.85)</td>
<td></td>
<td>2,907 (31.6) 24.9 1.50 (1.43-1.58)</td>
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</tr>
<tr>
<td>Blacks</td>
<td>1,492 (7.7) 32.0 0.80 (0.76-0.85)</td>
<td></td>
<td>644 (7.0) 10.2 0.61 (0.56-0.67)</td>
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<tr>
<td>Asians/Pacific Islanders</td>
<td>1,439 (7.4) 32.3 0.81 (0.76-0.85)</td>
<td></td>
<td>715 (7.8) 14.8 0.89 (0.82-0.96)</td>
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</tr>
<tr>
<td>Other/unspecified</td>
<td>173 (0.9) ~ ~</td>
<td></td>
<td>161 (1.8) ~ ~</td>
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<tr>
<td><strong>Age (years)</strong></td>
<td></td>
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<tr>
<td>&lt;1</td>
<td>154 (0.8) 19.9 1.00</td>
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<td>163 (1.8) 21.1 1.00</td>
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<tr>
<td>1-4</td>
<td>297 (1.5) 9.9 0.50 (0.41-0.61)</td>
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<td>2,357 (25.7) 78.7 3.74 (3.19-4.41)</td>
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<tr>
<td>5-19</td>
<td>840 (4.3) 7.3 0.37 (0.31-0.44)</td>
<td></td>
<td>3,004 (32.7) 26.3 1.25 (1.07-1.47)</td>
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<tr>
<td>20-39</td>
<td>1,869 (9.6) 12.3 0.62 (0.53-0.74)</td>
<td></td>
<td>1,329 (14.5) 8.6 0.41 (0.35-0.49)</td>
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<tr>
<td>40-59</td>
<td>4,505 (23.1) 30.4 1.53 (1.30-1.81)</td>
<td></td>
<td>1,189 (12.9) 8.1 0.39 (0.33-0.46)</td>
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<tr>
<td>60-74</td>
<td>5,588 (28.7) 109.2 5.49 (4.68-6.48)</td>
<td></td>
<td>711 (7.7) 13.7 0.65 (0.55-0.78)</td>
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<tr>
<td>&gt;75</td>
<td>6,244 (32.0) 208.9 10.50 (8.95-12.41)</td>
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<td>435 (4.7) 14.7 0.70 (0.58-0.84)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: SEER-17, 17 cancer registry areas of the Surveillance, Epidemiology and End Results Program; No., number; IR, incidence rate; IRR, incidence rate ratio; CI, confidence interval; NA, not applicable; ~, IRRs and IRRs not calculated for other/unspecified race.

* All incidence rates are age-adjusted to the 2000 U.S. standard population and expressed per 1,000,000 person-years. IRRs are based on unrounded rates.
Table 2. Age-adjusted incidence rates and incidence rate ratios of acute myeloid leukemia, acute (precursor) lymphoblastic leukemia/lymphoma, and acute leukemia of ambiguous lineage according to subtype and gender, SEER-17, 2001-2007*

<table>
<thead>
<tr>
<th>Subtype</th>
<th>No. (%)</th>
<th>IR</th>
<th>Median age (yrs)</th>
<th>Total</th>
<th>Male</th>
<th>Female</th>
<th>Male-to-female</th>
<th>IRR (95% CI)</th>
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</thead>
<tbody>
<tr>
<td><strong>Acute myeloid leukemia (AML)</strong> †</td>
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<tr>
<td>AML, NOS; [M-9861]</td>
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<tr>
<td>AML with minimal differentiation; (FAB M0) [M-9872]</td>
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<tr>
<td>AML without maturation; (FAB M1) [M-9873]</td>
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<tr>
<td>AML with maturation; (FAB M2) [M-9874]</td>
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<tr>
<td>Acute myelomonocytic leukemia; (FAB M4) [M-9867]</td>
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<tr>
<td>Acute megakaryoblastic leukemia; (FAB M5) [M-9891]</td>
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<tr>
<td>Acute erythroid leukemia; (FAB M6) [M-9840]</td>
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<td>Acute basophilic leukemia; [M-9870]</td>
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<tr>
<td>Acute panmyelosis with myelofibrosis; [M-9931]</td>
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<td>Myeloid sarcoma; [M-9930]</td>
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<td>Group 2</td>
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<td>AML with t(8;21); (FAB M2, t(8;21)) [M-9896]</td>
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<td>AML with inv(16) or t(16;16); (FAB M4Eo) [M-9871]</td>
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<tr>
<td>APL with t(15;17); (FAB M3) [M-9866]</td>
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<td>AML, 11q23 abnormalities; [M-9897]</td>
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<td>Group 3</td>
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<td>AML with myelodysplasia-related changes; [M-9895]</td>
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<tr>
<td>Therapy-related myeloid neoplasms; [M-9920, 9987]</td>
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<tr>
<td><strong>Precursor lymphoblastic leukemia/lymphoma (ALL/L)</strong> †</td>
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<td>Subtype</td>
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<tr>
<td>B-cell lymphoblastic leukemia/lymphoma; [M-9727(B), 9728, 9835(B), 9836]</td>
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<tr>
<td>T-cell lymphoblastic leukemia/lymphoma; [M-9727(T), 9729, 9835(T), 9837]</td>
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<tr>
<td>Lymphoblastic leukemia/lymphoma, unknown lineage; [M-9727(U), 9835(U)]</td>
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<tr>
<td><strong>Acute leukemia of ambiguous lineage</strong> †</td>
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<td>Subtype</td>
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<tr>
<td>Acute undifferentiated leukemia; [M-9801]</td>
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<tr>
<td>Acute biphenotypic leukemia; [M-9805]</td>
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</tbody>
</table>

Abbreviations: SEER-17, 17 cancer registry areas of the Surveillance, Epidemiology and End Results Program; No., number; IR, incidence rate; yrs, years; IRR, incidence rate ratio; CI, confidence interval; ~ IRs not calculated for fewer than 10 cases; NOS, not otherwise specified; FAB, French-American-British classification; APL, acute promyelocytic leukemia; (B), B-cell immunophenotype; (T), T-cell immunophenotype; (U), immunophenotype not specified.

* All incidence rates are age-adjusted to the 2000 U.S. standard population and expressed per 1,000,000 person-years. Incidence rate ratios are based on unrounded rates.

† Includes all International Classification of Diseases for Oncology, third edition (ICD-0-3) morphology codes specified within the respective subtype categories. ICD-0-3 codes are specified within brackets.
Table 3. Age-adjusted incidence rates and incidence rate ratios of acute myeloid leukemia, acute (precursor) lymphoblastic leukemia/lymphoma, and acute leukemia of ambiguous lineage according to subtype and race/ethnicity, SEER-17, 2001-2007*

<table>
<thead>
<tr>
<th>Subtype</th>
<th>NHW</th>
<th>HW</th>
<th>Blacks</th>
<th>API</th>
<th>IR</th>
<th>HW:NHW</th>
<th>Blacks:NHW</th>
<th>API:NHW</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute myeloid leukemia (AML)*</td>
<td>14,177</td>
<td>39.9</td>
<td>2,216</td>
<td>32.3</td>
<td>1,492</td>
<td>32.0</td>
<td>1,439</td>
<td>32.3</td>
</tr>
<tr>
<td>AML, NOS; [M-9861]</td>
<td>6,355</td>
<td>17.6</td>
<td>821</td>
<td>13.6</td>
<td>719</td>
<td>16.1</td>
<td>583</td>
<td>13.5</td>
</tr>
<tr>
<td>AML with minimal differentiation; (FAB M0) [M-9872]</td>
<td>552</td>
<td>1.6</td>
<td>85</td>
<td>1.2</td>
<td>67</td>
<td>1.5</td>
<td>59</td>
<td>1.3</td>
</tr>
<tr>
<td>AML without maturation; (FAB M1) [M-9873]</td>
<td>764</td>
<td>2.2</td>
<td>145</td>
<td>2.1</td>
<td>62</td>
<td>1.3</td>
<td>102</td>
<td>2.2</td>
</tr>
<tr>
<td>AML with maturation; (FAB M2) [M-9874]</td>
<td>910</td>
<td>2.6</td>
<td>142</td>
<td>2.1</td>
<td>80</td>
<td>1.8</td>
<td>113</td>
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<tr>
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<td>1,282</td>
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<td>223</td>
<td>3.2</td>
<td>128</td>
<td>2.8</td>
<td>122</td>
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<tr>
<td>Acute monocytic leukemia; (FAB M5) [M-9891]</td>
<td>1,106</td>
<td>3.2</td>
<td>167</td>
<td>2.3</td>
<td>84</td>
<td>1.6</td>
<td>99</td>
<td>2.2</td>
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<td>Acute erythroid leukemia; (FAB M6) [M-9840]</td>
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<td>28</td>
<td>0.4</td>
<td>17</td>
<td>0.4</td>
<td>29</td>
<td>0.7</td>
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<tr>
<td>Acute megakaryoblastic leukemia; (FAB M7) [M-9910]</td>
<td>117</td>
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<td>40</td>
<td>0.4</td>
<td>25</td>
<td>0.4</td>
<td>22</td>
<td>0.5</td>
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<tr>
<td>Acute basophilic leukemia; [M-9870]</td>
<td>4</td>
<td>~</td>
<td>0</td>
<td>~</td>
<td>0</td>
<td>~</td>
<td>~</td>
<td>~</td>
</tr>
<tr>
<td>Acute panmyelosis with myelofibrosis; [M-9931]</td>
<td>104</td>
<td>0.3</td>
<td>8</td>
<td>~</td>
<td>11</td>
<td>0.3</td>
<td>10</td>
<td>0.2</td>
</tr>
<tr>
<td>Myeloid sarcoma; [M-9930]</td>
<td>120</td>
<td>0.3</td>
<td>24</td>
<td>0.3</td>
<td>17</td>
<td>0.4</td>
<td>10</td>
<td>0.2</td>
</tr>
<tr>
<td>AML with t(8;21); (FAB M2, t(8;21)) [M-9896]</td>
<td>215</td>
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<td>38</td>
<td>0.4</td>
<td>24</td>
<td>0.4</td>
<td>34</td>
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<tr>
<td>AML with inv(16) or t(16;16); (FAB M4eo) [M-9871]</td>
<td>136</td>
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<td>41</td>
<td>0.5</td>
<td>8</td>
<td>~</td>
<td>15</td>
<td>0.3</td>
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<tr>
<td>APL with t(15;17); (FAB M3) [M-9866]</td>
<td>871</td>
<td>2.6</td>
<td>316</td>
<td>3.3</td>
<td>140</td>
<td>2.5</td>
<td>101</td>
<td>2.0</td>
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<tr>
<td>AML, 1q23 abnormalities; [M-9897]</td>
<td>97</td>
<td>0.3</td>
<td>15</td>
<td>0.2</td>
<td>6</td>
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<td>15</td>
<td>0.4</td>
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<tr>
<td>AML with myelodysplasia-related changes; [M-9895]</td>
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<td>84</td>
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<td>62</td>
<td>1.5</td>
<td>96</td>
<td>2.3</td>
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<tr>
<td>Therapy-related myeloid neoplasms; [M-9920, 9987]</td>
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<td>1.0</td>
<td>39</td>
<td>0.6</td>
<td>42</td>
<td>0.8</td>
<td>28</td>
<td>0.6</td>
</tr>
<tr>
<td>Precursor lymphoblastic leukemia/lymphoma (ALL)***</td>
<td>4,761</td>
<td>16.8</td>
<td>2,907</td>
<td>24.9</td>
<td>644</td>
<td>10.2</td>
<td>715</td>
<td>14.8</td>
</tr>
<tr>
<td>Therapy-related myeloid neoplasms; [M-9920, 9987]</td>
<td>337</td>
<td>1.0</td>
<td>39</td>
<td>0.6</td>
<td>42</td>
<td>0.8</td>
<td>28</td>
<td>0.6</td>
</tr>
<tr>
<td>Therapy-related myeloid neoplasms; [M-9920, 9987]</td>
<td>337</td>
<td>1.0</td>
<td>39</td>
<td>0.6</td>
<td>42</td>
<td>0.8</td>
<td>28</td>
<td>0.6</td>
</tr>
</tbody>
</table>

Abbreviations: SEER-17, 17 cancer registry areas of the Surveillance, Epidemiology and End Results Program; NHW, non-Hispanic whites; HW, Hispanic whites; API, Asians/Pacific Islanders; IR, incidence rate; IRR, incidence rate ratio; CI, confidence interval; ~ IRs not calculated for fewer than 10 cases; NOS, not otherwise specified; FAB, French-American-British classification; APL, acute promyelocytic leukemia; (B), B-cell immunophenotype; (T) T-cell immunophenotype; (U), immunophenotype not specified.

* All incidence rates are age-adjusted to the 2000 U.S. standard population and expressed per 1,000,000 person-years. IRRs are based on unrounded rates.

** Includes all International Classification of Diseases for Oncology, third edition (ICD-O-3) morphology codes specified within the respective subtype categories. ICD-0-3 codes are specified within brackets.
Figure legends

Figure 1. Age-specific incidence rates of acute myeloid leukemia (AML) and acute (precursor) lymphocytic leukemia/lymphoma (ALL/L) according to gender and race/ethnicity, SEER-17, 2001-2007.

Figure 2. Age-specific incidence rates of acute myeloid leukemia (AML), acute (precursor) lymphocytic leukemia/lymphoma (ALL/L), and acute leukemia (AL) of ambiguous lineage according to subtype, SEER-17, 2001-2007. Abbreviations: NOS, not otherwise specified; APL, acute promyelocytic leukemia.

Figure 3. Relative survival of acute myeloid leukemia (AML), acute (precursor) lymphocytic leukemia/lymphoma (ALL/L), and acute leukemia (AL) of ambiguous lineage according to subtype and age among individuals diagnosed in SEER-17 during 2001-2006 and followed through 2007. Abbreviations: NOS, not otherwise specified; APL, acute promyelocytic leukemia.

Graça M. Dores, Susan S. Devesa, Rochelle E. Curtis, Martha S. Linet and Lindsay M. Morton