The Leukemias

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**OVERVIEW (300 words)**

* Definition
* Origin, lineage, and major groupings
* Highlights of descriptive features: cancer ranking; variation in international incidence; patterns in race/ethnicity, gender, and age, and temporal trends; population-based survival
* Major known causes
* Prevention

**INTRODUCTION**

Worldwide leukemias are ranked 11th among all cancer types, comprising approximately 2.5 percent of all malignancies and an estimated 352,000 incident cases diagnosed in 2012 (<http://www.wcrf.org/int/cancer-fact-figures/worldwide-data>). In the United States, an estimated 60,140 cases will be diagnosed in 2016 (including 19,950 acute myeloid leukemia (AML), 8,220 chronic myeloid leukemia (CML), 6,590 acute lymphocytic leukemia (ALL), 18,960 chronic lymphocytic leukemia (CLL), and 6,420 other leukemias), and the number of deaths from leukemia is estimated as 24,400 (including 10,430 AML, 1,070 CML, 1,430 ALL, 4,660 CLL, and 6,810 other leukemias) [Siegel 2016]. Leukemias are estimated to comprise 4% and 3% of all incident cancers among U.S. males and females, respectively, and 4% of all cancer deaths in both males and females [Siegel 2016]. Most, if not all, acute and chronic leukemias appear to develop from a preleukemic state that progresses to overt leukemia over time [Shlush 2015]. Included among the preleukemic entities are myelodysplastic syndromes (MDS), myeloproliferative neoplasms (MPNs), “overlap” disorders termed myelodysplastic/myeloproliferative neoplasms (MDS/MPN), and monoclonal B-cell lymphocytosis. All of these entities are clonal stem cell disorders that can progress or transform into leukemia. Understanding the epidemiology of the leukemias and the preleukemic states has been complicated by changing classification schemes and by the fact that many preleukemic entities have not always been reportable to cancer registries, thereby often being excluded from population-based cancer statistics. In the United States, all MDS and MPNs became reportable to the National Cancer Institute’s Surveillance, Epidemiology and End Results Program in 2001. In 2012, 3,981 and 3,291 cases of MDS and MPNs, respectively, were diagnosed in 18 cancer registry areas representing 26% of the United States population, including 2,304 and 1,677 cases of MDS and 1,672 and 1,619 cases MPN among males and females, respectively (www.seer.cancer.gov). Because disease complications (e.g., thrombosis, infection, hemorrhage, AML, among others) can contribute to death among patients with MDS and MPNs, death rates are underestimated if only the underlying cause of death is considered. However, if only the underlying cause of death is considered, in 2009 there were 6,007 deaths in the U.S. attributed to MDS [Polednak 2013], and in 2006, 3,303 deaths were attributed to MPNs [Polednak 2011].

The unifying feature of the leukemias is that they arise from an accumulation of multiple, stepwise genetic and epigenetic changes in the hematopoietic stem cell (HSC) and committed progenitors. A preleukemic cell contains only a subset of the genetic and epigenetic changes characterizing leukemic cells [Shlush 2015]. In the normal state, HSCs differentiate into progenitor cells that give rise to myeloid and lymphoid progenitor cells and eventually all mature blood elements (Hoffman, Shizuru). Throughout this highly regulated, hierarchical differentiation and maturation process, lymphoid and myeloid cells acquire distinct phenotypes. Genetic events involving primitive stem cells or early myeloid-committed progenitors result in clonal proliferation and accumulation of immature hematopoietic cells (e.g., blasts) of myeloid lineage (e.g., acute myeloid leukemia (AML)) in the bone marrow, peripheral blood or other tissues (Swerdlow 2008; Kipps). When the affected pluripotent stem cell results in maturation arrest of more mature myeloid cells and ensuing accumulation of these more differentiated phenotypes, chronic leukemias ensue. In chronic myelogenous leukemia (CML) the affected pluripotent stem cell is consistently associated with a *BCR-ABL1* fusion gene located on the Philadelphia chromosome, resulting in the accumulation of more mature myeloid cells of erythroid, granulocytic, monocytic, dendritic, and megakaryocytic lineages (Lichtman). For many of the lymphoid neoplasms, the “cell of origin” represents the stage of differentiation of the tumor cells rather than the cell in which the initial transforming event occurred (Jaffe et al 2002). Genetic mutations involving B-cell progenitors may result in the accumulation of phenotypically immature-appearing lymphoid cells (blasts), as seen in acute lymphocytic leukemia (ALL), or mature-appearing lymphocytes, as in chronic lymphocytic leukemia (CLL). The MDS are a heterogenous group of clonal HSC neoplasms characterized by dysplasia (disordered maturation) in one or more cell lines and ineffective hematopoiesis that may result in peripheral cytopenias of one or more cell lines (Hoffman, Swerdlow). In contrast, the MPNs are clonal HSC neoplasms associated with proliferation of one or more of the myeloid lineages and absence of dysplasia. The MDS/MPNs include both, dysplastic and proliferative features.

**EVOLUTION OF HEMATOPIETIC AND LYMPHOID CLASSIFICATION SCHEMES (1500 words)**

Earlier reviews provided a comprehensive summary of the history of leukemia classification (Linet, 1985; Linet and Cartwright, 1988; Linet et al, 2007). The landmark French-American-British (FAB) classification (Bennett et al, 1976(2013), 1989, 1994) achieved international consensus on morphologic criteria. Subsequent efforts to incorporate developmental and functional aspects of hematopoiesis according to lineage as well as key aspects of pathogenesis, and cytogenetic and immunophenotypic characteristics (McKenna, 2000; Bennett, 2000) culminated in the 2001 World Health Organization (WHO) Classification of Tumors of the Hematopoietic and Lymphoid Tissue (Jaffe et al, 2001). This classification included genetic data that were more predictive of disease behavior and outcome than morphology and also added new disease categories. Cytogenetic alterations have long been identified as hallmarks of many cases of hematopoietic and lymphoid tumors, but the advent of and dramatic technical developments in high-resolution profiling led to notable advances in clarifying the genetic basis of these disorders. Certain markers have been identified as clinically meaningful therapeutic targets or as helpful prognostic markers, and some may eventually be associated with etiology (Inaba et al, 2013; Bochtler et al, 2015). With this rapid evolution and emergence of new information, the WHO classification was updated in 2008 (Swerdlow et al, 2008). The 2008 WHO classification considered lineage-specific disease categories (myeloid, lymphoid, and histiocytic/dendritic cell), distinguished precursor neoplasms (e.g., AML, lymphoblastic leukemia/ lymphoma) from more mature neoplasms (e.g., MDS, MPN, MDS/MPN), introduced new disease-defining criteria, and identified new disease entities. Multidisciplinary experts in international working groups (such as the International Working Group for Myelofibrosis Research and Treatment, the European Group for the Immunologic Classification of Leukemia, and the National Cancer Institute-sponsored Working Group on chronic lymphocytic leukemia) continue to meet and provide recommendations to ensure that the classification and updates will be clinically useful.

The 2001 WHO classification of tumors of the hematopoietic and lymphoid tissue categorized the lymphoid neoplasms into 3 broad categories: B-cell neoplasms, T and NK cell neoplasms and Hodgkin lymphoma. Within the former 2 categories, the leukemias were classified with the lymphomas due to several of these entities having solid (tissue) and circulating (blood) phases that represent different manifestations of the same disease (e.g., CLL and small lymphocytic lymphoma, lymphoblastic leukemia and lymphoblastic lymphoma) (Jaffe 2001) . Therefore, with the joint classification of the leukemias and lymphomas, this “leukemia” review will focus on the characteristics, descriptive epidemiology, and known and suspected risk factors of the myeloid neoplasms occurring in adults. However, since earlier descriptions of leukemia incidence and mortality often focused on all forms of leukemia combined (e.g., AML, CML, ALL, CLL; hereafter designated total leukemia) and most epidemiologic studies prior to the last decade or so considered lymphoid leukemias in conjunction with myeloid leukemias, some material on lymphoid leukemias is included in the sections on descriptive and analytical epidemiologic studies. Detailed findings from more recent epidemiologic studies of ALL and CLL will be found in Chapter \_\_\_\_ on non-Hodgkin lymphoma. In addition, this chapter will focus on myeloid neoplasms in adults and the epidemiology of myeloid neoplasms of childhood is covered in Chapter \_\_\_.

The International Classification of Diseases for Oncology (ICD-O) classification, primarily used for coding tumor morphology and topography in cancer registries, has similarly evolved over time and the 2001 WHO classification incorporated codes from the third edition of ICD-O (ICD-O-3) (Fritz et al, 2000). The 2008 WHO classification included ICD-O-3 morphology codes and also proposed provisional codes for the forthcoming edition of ICD-O, ICD-O-4, that remain subject to change. The complex, continuing evolution of the international classification of hematopoietic and lymphoid neoplasms has led population-based cancer registries to develop special measures to improve our understanding and interpretation of information in pathology and clinical records and thereby allow more accurate coding of these neoplasms (Ruhl et al, 2013).

**MYELOID NEOPLASMS AND THE WHO CLASSIFICATION**

In the WHO classification the term “myeloid” includes all cells that belong to granulocytic (neutrophil, eosinophil, basophil), monocytic/macrophage, erythroid, megakaryocytic and mast cell lineages (Vardiman 2009). Utilizing the WHO criteria, the diagnoses of myeloid neoplasms utilize morphologic, cytochemical, immunophenotypic, and cytogenetic characteristics to determine the lineage and maturation of the neoplastic cells obtained from peripheral blood and bone marrow upon initial clinical presentation, prior to treatment.

**Acute myeloid leukemia and related precursor neoplasms**

The 2001 WHO classification of AML categorized AML evolving from antecedent MDS or MDS/MPN was categorized separately from AML arising *de novo* to better reflect the postulated distinct underlying leukemogenic mechanisms and prognoses (Jaffe 2001). Whereas the former (AML with multilineage dysplasia) is associated with poor response to treatment, unfavorable prognosis, and genetic insults occurring over a lifetime (reflecting the increasing incidence with age), *de novo* AML typically is not associated with multilineage dysplasia, has a constant incidence throughout life, and is often associated with favorable cytogenetic abnormalities and response to treatment. To better reflect the distinct clinical and biologic features of AML than the preceding morphology-based FAB classification, the 2001 WHO classification considered four major disease subgroups: 1) AML with recurrent genetic abnormalities; 2) AML with multilineage dysplasia; 3) AML and MDS, therapy-related; and 4) AML, not otherwise specified (NOS). Other significant classification changes included a decrease in the blast percentage in the bone marrow or blood required to establish a diagnosis of AML from 30% to 20%. Furthermore, the presence of recurrent genetic abnormalities (t(8;21)(q22;q22), t(15;17)(q22;q12), and inv(16) (p13q22) or t(16;16)(p13;qi22) was deemed diagnostic of AML irrespective of the percentage of blasts (Vardiman2002; Jaffe WHO 2001). The 2008 WHO classification added three new (AML with t(6;9)(p23;q34); AML with inv(3)(q21q26.2) or t(3;3)(q21;q26.2); AML (megakaryoblastic) with t(1;22)(p13;q13)) and two (AML with mutated NPM1 and AML with CEBPA) provisional entities to the category of AML with recurrent genetic abnormalities (Swerdlow 2008, Vardiman 2009), . Additional diagnostic refinements were further specified for acute promyelocytic leukemia with t(15; 17)(q22; q12) and AML with 11q23 (MLL). Other changes included renaming AML with multilineage dysplasia to AML with myelodysplasia-related changes to include AML cases with an antecedent MDS or MPN/MDS, myelodysplasia-related cytogenetic abnormality, or with 50% or more dysplastic changes in two or myeloid cell lines. The AML and MDS, therapy-related category was renamed to therapy-related myeloid neoplasms and eliminated the subcategories of alkylating agent/radiation-related and topoisomerase II inhibitor-related AML. Two additional new AML categories were added: 1) myeloid proliferations related to Down syndrome to include Down syndrome related transient abnormal myelopoiesis, MDS, and AML and 2) blastic plasmacytic dendritic cell neoplasms.

**Myelodysplastic syndromes**

In 1982 the FAB classification considered 5 entities within the category of MDS (previously also referred to as “pre-leukemia”): 1) refractory anemia, 2) refractory anemia ringed sideroblasts, 3) refractory anemia with excess blasts, 4) refractory anemia with blasts in transformation, and 5) chronic myelomonocytic leukemia (CMML). The refractory anemia categories were largely based on % blasts in the bone marrow: <5% (refractory anemia and refractory anemia ringed sideroblasts) , 5-20% (refractory anemia with excess blasts), and 21-30% (refractory anemia with blasts in transformation). With the new 20% blast threshold for diagnosis of AML introduced in the 2001 WHO classification, refractory anemia with blasts in transformation became an obsolete entity. The 2001 WHO classification refined the diagnostic criteria for refractory anemia and refractory anemia ringed sideroblasts to include dysplasia limited to the erythroid series, to reflect the improved prognosis among this patient population. To this end, a new MDS category was introduced in 2001 – refractory cytopenia with multilineage dysplasia – to include cases with uni- or multi-lineage dysplasia affecting granulocytic and megakaryocytic cell lines with worse prognosis than those cases with isolated and limited erythroid dysplasia. In addition two subtypes of refractory anemia with excess blasts were defined based on blast percentage and the less favorable prognosis associated with higher blast counts: refractory anemia with excess blasts-1 (5-9% bone marrow blasts) and refractory anemia with excess blasts-2 (10-19% bone marrow blasts). MDS associated with isolated deletion of 5q was also identified as a new MDS entity given the consistent associated clinical findings (refractory macrocytic anemia, normal or increased platelet count, and increased bone marrow megakaryocytes) and long survival among individuals with this syndrome and <5% blasts in the bone marrow or blood. Lastly, resulting from the debate as to whether CMML represents a myelodysplastic or myeloproliferative disease (it has clinical and pathologic features of both), it was moved to a new disease group – MDS/MPN. The 2008 WHO classification introduced additional changes to the diagnosis and classification of MDS, including a new broad category of refractory cytopenia with unilineage dysplasia to include individuals with refractory anemia (RA), refractory neutropenia, or refractory thrombocytopenia with <1% blasts in the blood and <5% blasts in the bone marrow. A new provisional category of refractory cytopenia of childhood was proposed due to differences in clinical and pathologic features of MDS occurring among children and adults, although children not meeting criteria for this entity are categorized using the same diagnostic criteria as adult MDS. In sum, the 2008 WHO classification scheme includes seven broad disease categories of MDS:

**Myelodysplastic syndromes ICD-O code\***

Refractory cytopenia with unilineage dysplasia

Refractory anemia 9980/3

Refractory neutropenia 9991/3 (proposed)

Refractory thrombocytopenia 9992/3 (proposed)

Refractory anemia with ring sideroblasts 9982/3

Refractory cytopenia with multilineage dysplasia 9985/3

Refractory anemia with excess blasts 9983/3

Myelodysplastic syndrome associated with isolated del(5q) 9986/3

Myelodysplastic syndrome, unclassifiable 9989/3

Childhood myelodysplastic syndrome

Refractory cytopenia of childhood (provisional) 9985/3

\* All are ICD-O-3 codes, unless specified as “proposed”.

With the WHO classifications outpacing the update of the ICD-O, some MDS entities are currently associated with a proposed ICD-O code. From an epidemiologic standpoint, it is important to recognize the evolution of diagnostic criteria that has ensued since the FAB classification, both within and between entities, and that the diagnostic criteria for an entity with an assigned ICD-O-3 code today may not reflect the same diagnostic criteria for that entity with an ICD-O-3 code assigned in the past. The same caveat should be considered when ICD-O-4 codes are introduced and applied to cases diagnosed in the past.

**Myeloproliferative neoplasms**

The term “myeloproliferative disorders” was initially introduced in 1951 (Dameshek 1951) and encompassed four disease entities that shared clinical and pathologic features: CML, polycythemia vera, essential thrombocythemia, and primary myelofibrosis. These chronic myeloproliferative disorders were further defined according to clinical and morphologic criteria by the Polycythemia Vera Study Group (PVSG) (PVSG 1995). One major change associated with the 2001 WHO classification was that the diagnosis of CML could be “unequivocally” confirmed based on the presence of an associated genetic abnormality – the Philadelphia chromosome or BCR/ABL fusion gene. There were no other genetic abnormalities that had been identified for the other myeloproliferative disorders. Two additional disease entities were incorporated into the category of myeloproliferative disorders: chronic neutrophilic leukemia and chronic eosinophilic leukemia, including hypereosinophilic syndrome). In 2005, the discovery of the *JAK2 V617* mutation substantially facilitated the diagnosis of the myeloproliferative disorders (James 2005; Kralovics 2005). Janus kinase 2 (JAK2) is a cytoplasmic tyrosine kinase that is integral for signaling by the receptors for erythropoietin, thrombopoietin, granulocyte colony-stimulating factor, granulocyte-macrophage colony-stimulating factor, and interleukin-3 (Campbell 2006). An acquired point mutation in JAK2 leads to pathologic proliferation of myeloid precursors, and while it can be found in several MPNs, MDS/MPNs, and other myeloid disorders, it is found in more than 95% of cases of polycythemia vera and 50-60% of cases of essential thrombocythemia and primary myelofibrosis (Tefferi 2015). The 2008 WHO classification incorporated information on *JAK2 V617* mutations, as well as other activating mutations (e.g., *CALR*, *MPL*) into the diagnostic criteria for polycythemia vera, essential thrombocythemia, and primary myelofibrosis. Additional changes in the 2008 WHO classification included lowering the diagnostic platelet count threshold for ET from >600 x 109/L to >450 x 109/L. Furthermore, the term “chronic myeloproliferative disorders” was changed to “MPN” to reflect the malignant nature of these clonal diseases, and systemic mastocytosis, which was considered as a separate disease category in the 2001 WHO classification, was incorporated into the MPN category. The specific MPN entities and their respective ICD-O-3 codes are included in the Table.

**Myelodysplastic/myeloproliferative neoplasms**

The category of myelodysplastic/myeloproliferative diseases was newly introduced with the 2001 WHO classification to include entities associated with both dysplastic and proliferative features, although either may predominate to different degrees. Along with CMML, which as noted above was previously included with MDS, this disease category also included atypical chronic myeloid leukemia (lacks the Philadelphia chromosome); juvenile myelomonocytic leukemia (lacks the Philadelphia chromosome); and myelodysplastic/myeloproliferative disease, unclassifiable. In the 2008 WHO classification, atypical CML was renamed *BCR-ABL*-negative CML to emphasize that it is a distinct entity from *BCR-ABL*-positive CML. Some cases of CMML with eosinophilia were reclassified to the new disease category of “myeloid and lymphoid neoplasms with eosinophilia and abnormalities of *PDGFRA*, *PDGFRB*, or *FGFR1*”, and refractory anemia with ringed sideroblasts associated with marked thrombocytosis was introduced as a provisional entity. While each of these entities is associated with an ICD-O-3 morphology code, some codes are shared with other disease entities, an important consideration in epidemiologic studies.

**Myelodysplastic/myeloproliferative neoplasms ICD-O-3 code**

Chronic myelomonocytic leukemia 9945/3

Atypical chronic myeloid leukemia, *BCR-ABL1*-negative 9876/3

Juvenile myelomonocytic leukemia 9946/3

Myelodysplastic/myeloproliferative neoplasm, unclassifiable 9975/3\*

Refractory anemia with ringed sideroblasts associated with

marked thrombocytosis (provisional) 9982/3†

\* This ICD-O-3 code also defines myeloproliferative neoplasm, unclassifiable in the MPN category.

† This ICD-O-3 code also defines Refractory anemia with ringed sideroblasts in the MDS category.

**CLINICAL PRESENTATION**

There is notable variation in severity of disease and patient survival, both within a given leukemia and preleukemia subtype and between subtypes (Kadia 2015; Ferrara 2013; Dohner 2015; Dores2012; Srour 2016; Ades 2014, Tefferri 2015). Patients with AML often present with complications related to cytopenias related to one or all cell lineages (anemia, leukopenia, thrombocytopenia), with a smaller proportion of patients presenting with complications of extreme leukocytosis. Generalized fatigue and weakness are common and often attributed to anemia. Bleeding, bruising, and petechiae are manifestations of thrombocytopenia and/or disseminated intravascular coagulation. Fever is most often related to underlying infection related to underlying neutropenia which increases risk of infection, although a minority of individuals have fever related to the leukemia itself. Lymphadenopathy and hepatosplenomegaly are uncommon. While individuals with MDS may have a similar presentation as individuals with AML due to cytopenias of one or all cell lineages, many patients are asymptomatic at presentation. Similar to AML, lymphadenopathy and hepatosplenomegaly are uncommon. In contrast, individuals with MPNs generally present with elevations in one or more cell lines (erythrocytosis, leukocytosis, thrombocytosis), and hepatomegaly and splenomegaly, in particular, are common. Individuals may be asymptomatic at presentation, with diagnosis suspected based on complete blood count abnormalities, or they come to medical attention due to thrombosis or bleeding episodes, common complications of MPN.

**TUMOR PROGRESSION MODELS (AML)**

Genomic and molecular data support that AML is a heterogeneous disease comprised of multiple distinct entities. Genetic changes resulting in distinct functional effects on hematopoietic precursors has led to the concept of leukemogenesis as a multi-step process that eventually leads to malignant transformation (Meyer 2014). Whole genome sequencing in a study of 200 cases of de novo AML in the Cancer Genome Atlas Project found that among adult cancers, AML had the fewest number of mutations (CA Genome Atlas Research **Network** NEJM 2013). On average 13 coding mutations were identified per case and of these, an average of 5 genes were recurrently mutated, suggesting a role for driver mutations resulting in leukemic transformation (CA Genome Atlas Research Network NEJM 2013; Meyer 2014; Kadia 2015). At least one potential driver mutation was identified in each case of AML, confirming the recurrent nature of other passenger mutations that accumulate during leukemogenesis but do not have transforming capability (Meyer 2014). The most common mutated genes mutated at >5% frequency (e.g., NPM1, FLT3, DNMT3a, IDH1, IDH2, TET2, RUNX1, TP53, CEBPA, NRAS, WT1) were organized into functionally related categories hypothesized to be of biologic importance: 1) myeloid transcription-factor fusions/mutations, 2) NPM1 mutations 3) tumor suppressor gene mutations, 4) epigenome-modifying gene mutations, 5) activated signaling pathway gene mutations, 6)cohesion-complex gene mutations, and 7) sliceosome-complex gene mutations (Kadia 2015). Chromosomal translocations identified as being frequently mutated included t(15; 17), t(8;21), inv(16), abn11q23, monosomy 5 and monsomy 7 (Meyer 2014). The role and prognostic implication of many of these genes remain under study.

**DESCRIPTIVE EPIDEMIOLOGY**

**International comparisons: All leukemias**

Among international cancer registries reporting <10% unspecified leukemia subtypes among adults ages 20-79 years diagnosed during 2003-2007AML rates ranged from highs of 4.7 among males and 5.0 among females in Manila to lows of 1.9 and 1.5 in Costa Rica (high/low rate ratios of 2.5 and 3.3 among males and females, respectively) (Figure 1). AML incidence rates were highest and generally similar across North, Central, and South America; Europe; Oceania; and parts of Asia, while lowest in Africa and parts of eastern Europe and east Asia. With rare exception (Mumbai, India and Manila, Philippines), incidence of AML was higher among males than females, with 40% or higher rates among males in Murcia, Spain; Hong Kong, China; Osaka, Japan; and New South Wales, Australia. CML rates varied about four-fold from 2.9 in France to 0.7 in Bangkok among males and from 1.5 in Cali and Belgium to 0.4 in Osaka and Bangkok among females, with slightly higher rates in Oceania, North America, and western Europe. The male-to-female incidence rate ratio for CML was <1.00 only in Quito, Ecuador and Gharbiah, Egypt, and exceeded 2.00 in Loire Atlantique, France; Hong Kong, China; and Osaka Prefecture, Japan. ALL generally was the least frequent adult leukemia type, and rates were notably highest in Central and South America and among U.S. Hispanic Whites in the Surveillance, Epidemiology and End Results (SEER) program and otherwise similar across other geographic areas. While there was a tendency for male predominance in ALL, the rate ratio was <1.00 in seven registries. CLL incidence rates varied the most, with the highest rates in New Zealand of 8.1 (males) and 4.2 (females) 40 times the lowest rates in Osaka of 0.2 (males) and 0.1 (females);rates were also high in Canada and U.S. whites in North America; western, northern, and eastern Europe; and New South Wales, and low in east Asia. Worldwide, CLL incidence rates were higher among males than females everywhere except in Manila.

**Temporal Trends: All leukemias**

Comparison of temporal trends between studies is limited by calendar years included, given the potential influence of changing classification schemes over time. In the U.S. incidence of AML has remained stable among whites and blacks across four decades, 1973-2012 (Figure 2). In contrast, CML rates have been declining during the last two decades across all racial/ethnic groups, including Hispanic whites and Asians/Pacific Islanders. ALL incidence rose during the 1970s-80s, but rates generally stabilized thereafter among whites and blacks. CLL rates have remained stable among whites, but rates have slowly decreased since the 1970s among blacks. The CLL rates among Hispanic whites and Asians/Pacific Islanders have not changed greatly. In Denmark, incidence of AML, CLL and, to a lesser extent, ALL increased between 1943-2003, whereas CML decreased (Thygesen 2009). Between 1984-1993. AML, MPN (including CML) incidence rates decreased in the United Kingdom, whereas ALL remained stable, and MDS rates increased (McNally1999). Between 1991-2005, AML incidence rates increased in Western Australia (Gangatharan 2013). More recently, several large studies have described incidence rates utilizing the WHO classification scheme (Sant 2010, Smith2009, Smith 2011, Dores 2012), however, longer follow-up will be needed to assess temporal trends subsequent to 2001.

**Incidence: Myeloid neoplasms**

Consistent with the clinical and molecular heterogeneity described among individuals with AML, during 2001-2012, incidence rates in the U.S. are noted to vary widely across AML subtypes (Table). The highest incidence rates were for the least specific AML subtype - AML, NOS (IR for all races combined=2.74/100,000 person-years), and IRs were intermediate for AML with myelodysplasia-related changes (IR=0.45), acute myelomonocytic leukemia (IR=0.43), AML with t(15;17) (IR=0.39), and acute monblastic and monocytic leukemia (IR=0.33). AML incidence rates were higher among males than females for nearly all subtypes, with gender disparities least evident for AML with t(15;17), particularly among Hispanic whites, blacks, and Asians/Pacific Islanders; AML with t(9;11), and therapy-related myeloid neoplasms. Among cases in the Haematological Malignancy Research Network diagnosed during 2004-2008 in the United Kingdom, the overall male-to-female rate ratio of AML was 1.1, ranging from 1.9 for AML with core binding factor (e.g., AML with t(8;21) and AML with inv(16)) <1.0 for AML with MLL (11q23), therapy-related AML, and AML with t(15;17) (Smith 2009). In the European HAEMACARE project, a male predominance was most notable in the nonspecific AML group (not otherwise specified) and only slight for AML with multilineage dysplasia and evolving from MDS, whereas incidence of AML with recurrent genetic abnormalities predominated slightly among females compared to males (Sant 2010). Similarly, in Burgundy, France, AML cases diagnosed during 1980-2004 and classified according to the WHO 2001classification a male predominance was noted for most subtypes of AML, not otherwise specified, whereas AML with cytogenetic abnormalities predominated among females (male-to-female incidence rate ratio 0.95), largely attributed to AML with t(8;21) and AML with t(15;17) (Maynadie 2011).

Incidence patterns for MDS by subtype should be interpreted with caution given changing classification schemes noted above, and due to the majority of cases being categorized as MDS, unclassifiable or NOS (n=25,277; IR=3.71). As with other myeloid malignancies (Craig 2012), underreporting of MDS to cancer registries has been described (McQuilten 2014), but in addition underdiagnosis is suspected based on many cases of nonspecific anemia that may not undergo evaluation or may not receive a definitive diagnosis (Goldberg 2010, Cogle 2015). Considering these caveats, in the U.S. incidence rates were higher among males than females, overall and by race, across all subtypes except MDS with associated 5q deletion. For MDS overall, a similar male predominance was observed in the HAEMACARE (Sant 2010) database and in the Haematological Malignancy Research Network (Smith 2009, Smith 2011).

MPN incidence rates were highest for total CML (IR=1.69), polycythemia vera (IR=1.51), and essential thrombocythemia (IR=1.33). Across all races, MPN and MDS/MPN subtypes, incidence was higher among males than females with the notable exception of essential thrombocythemia which was associated with significantly lower incidence among males than females of all races. As a group, MPN crude incidence rates were higher among males (IR=3.5) than females (IR=3.18) in the HAEMACARE database, with the greatest gender disparity noted for CML, in contrast to other specified MPN subtypes considered as a group (Sant 2010). CML and PMF were both associated with nearly 2-fold higher incidence rates among males than females in the Haematological Malignancy Research Network in contrast to chronic myeloproliferative neoplasm (ICD-O-3 code 9960) which was associated with a significantly lower incidence rate among males than females (Smith 2009).

Age-specific incidence patterns differ between myeloid entities and within disease subtypes (Figure 3). Reflecting distinct postulated underlying leukemogenic mechanisms described above, AML associated with recurrent genetic abnormalities had a constant incidence throughout life, whereas incidence of AML, NOS increased with advancing age, likely reflecting an accumulation of genetic mutations over a lifetime. Incidence of MDS increased exponentially with age, a pattern that supports accumulated genetic insults over a lifetime. In contrast, CML, the majority of cases likely to be associated with BCR-ABL1 or t(9;22), has a pattern similar to that of AML with recurrent cytogenetic abnormalities, with less pronounced rise in incidence with increasing age. Polycythemia vera and essential thrombocythemia rates rose progressively with age, beginning in the young adult through older ages. In contrast, primary myelofibrosis occurs infrequently at young adult ages and incidence rises more steeply with age than polycythemia vera and essential thrombocythemia. Despite differences in incidence rates, all myeloid entities demonstrate similar age-specific incidence patterns by sex and race.

**Survival: Myeloid neoplasms**

Five-year relative survival differs markedly across myeloid neoplasms (Figure 4). All AML NOS is associated with the least favorable survival; CML among patients <60 years of age, polycythemia vera and essential thrombocythemia have the most favorable survival; and AML with recurrent genetic abnormalities, MDS, CML among those >60 years of age, and primary myelofibrosis have intermediate survival. Younger (<60 years) individuals fare better than older (>60 years) individuals irrespective of myeloid entity considered, with the narrowest disparities noted for polycythemia vera and essential thrombocythemia (Srour in press). Worldwide, the CONCORD-2 study reported age-standardized 5-year net survival for adult leukemia of 50-60% in 21 countries in North America, west Asia, Europe, and Oceania, with lower survival in east Asia (19-23%) (Allemani 2015). In Europe, cases reported to the HAEMACARE and EUROCARE databases, from 1997-2008, had significant improvement in 5-year relative survival for AML (without AML with t(15;17)), AML with t(15;17), CML, and MPN between 1997-1999 and 2006-2008. In 2006-2008, MPN (without CML) (74.9%) and APL (61.9%) were associated with the most favorable survival, CML (54.4%) and MDS (48.8%) with intermediate survival, and AML (without AML with t(15;17)) (14.8%) with the least favorable survival (Sant 2014). Notably, while AML with t(15;17) has a long term favorable survival, it continues to have an early death rate (within 1 month of diagnosis) related to hemorrhagic complications from disseminated intravascular coagulation classically associated with this subtype of AML (Park 2011, Lehmann 2011, Dores 2012). Age (older age worse prognosis) and cytogenetics are among the most important prognostic factors for AML (Grimwade2001, Grimwade 2010, Wheatley 2009, Rollig 2011, Schlenk 2008, Patel 2012). Prognostic features in MDS are often defined according to the original and revised International Prognostic Scoring Systems (IPSS, IPSS-R) which include bone marrow blast percentage, karyotype, and peripheral blood cytopenias (anemia, thrombocytopenia, neutropenia) (Greenberg 1997, Greenberg 2012, Voso 2013, Ades 2014). Although several disease-specific prognostic algorithms exist for the MPNs, older age remains a universally poor prognostic feature (Sokal 1984, Barbui 2011, Passamonti 2004 and 2008, Tefferi 2015).

**FIGURE LEGENDS**

**Figure 1.** International variation in adult (ages 20-79 years) leukemia incidence rates per 100,000 person-years (age-adjusted, 1960 world standard) by continent, registry, and sex. Four specific cell types, circa 2003-2007. (*Source*: Forman D et al. Cancer Incidence in Five Continents, vol. 10. Lyon, France: IARC Scientific Publication Number 164, 2014.)

**Figure 2.** United States trends in adult (>20 years) leukemia incidence (age-adjusted, 2000 U.S. standard population) by race for total leukemia and by leukemia subtype in nine cancer registry areas of the Surveillance, Epidemiology and End Results (SEER) program (SEER-9), 1973-2012, and thirteen cancer registry areas of the SEER program (SEER-13), 1993-2012.

(*Source*: 1) Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER\*Stat Database: Incidence - SEER 9 Regs Research Data, Nov 2014 Sub (1973-2012) <Katrina/Rita Population Adjustment> - Linked To County Attributes - Total U.S., 1969-2013 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released April 2015, based on the November 2014 submission. 2) Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER\*Stat Database: Incidence - SEER 13 Regs Research Data, Nov 2014 Sub (1992-2012) <Katrina/Rita Population Adjustment> - Linked To County Attributes - Total U.S., 1969-2013 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released April 2015, based on the November 2014 submission.)

**Figure 3.** Age-specific incidence rates of acute myeloid leukemia, myelodysplastic syndromes, and myeloproliferative neoplasms diagnosed among adults (>20 years) in 18 cancer registry areas of the Surveillance, Epidemiology and End Results program in the United States according to subtype and sex, 2001-2012.

(*Source*: Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER\*Stat Database: Incidence - SEER 18 Regs Research Data + Hurricane Katrina Impacted Louisiana Cases, Nov 2014 Sub (2000-2012) <Katrina/Rita Population Adjustment> - Linked To County Attributes - Total U.S., 1969-2013 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released April 2015, based on the November 2014 submission.)

**Figure 4.** Five-year relative survival rates for adult (>20 years) patients diagnosed with acute myeloid leukemia, myelodysplastic syndromes, and myeloproliferative neoplasms diagnosed in 18 cancer registry areas of the Surveillance, Epidemiology and End Results program in the United States according to subtype, age and sex, 2001-2011 and followed through 2012.

(*Source*: Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER\*Stat Database: Incidence - SEER 18 Regs Research Data + Hurricane Katrina Impacted Louisiana Cases, Nov 2014 Sub (1973-2012 varying) - Linked To County Attributes - Total U.S., 1969-2013 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released April 2015, based on the November 2014 submission.)