**Name of Chapter: The Leukemias – Myeloid Neoplasms**  Feb 27, 2016

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**<1> OVERVIEW (word count is 682**

The 2001 World Health Organization (WHO) classification of hematopoietic and lymphoid neoplasms categorized “the leukemias” into two major groupings – myeloid neoplasms and lymphoid neoplasms. **Myeloid neoplasms,** which are the primary focus of this chapter, derive from granulocytic (neutrophil, eosinophil, basophil), monocytic/macrophage, erythroid, megakaryocytic and mast cell lineages, and include acute myeloid leukemia (AML), myelodysplastic syndromes (MDS), myeloproliferative neoplasms (MPNs), and “overlap” disorders termed myelodysplastic/myeloproliferative neoplasms (MDS/MPN). **Lymphoid neoplasms** derive from B-cells, T-cells, and natural killer cellsand include Hodgkin and non-Hodgkin lymphomas, plasma cell neoplasms, and lymphoid leukemias. Because lymphoid leukemias are now understood to represent the circulating (blood-borne) phase of the corresponding solid (tissue) phase of lymphomas[e.g., chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma], their epidemiology is mostly reviewed in Chapter 40, although descriptive patterns and selected etiologic studies are briefly discussed in this chapter because of historical trends and some recent literature that combine data for all types of leukemias.

Worldwide, leukemias are ranked 11th among all cancer types, comprising approximately 2.5 percent of all malignancies, whereas in the U.S. (U.S.) leukemias represent 3-4 percent of all malignancies. For most leukemias, rates are higher in males than females, with the greatest sex-specific difference observed for CLL. Age-adjusted incidence rates during 2003-2007 show more limited international variation than most solid tumors, ranging about 10-fold for AML (highest rates in Manila and lowest in Costa Rica), 4-fold for CML (highest in France and lowest in Bangkok and Osaka), 3-fold for acute lymphocytic leukemia (ALL; highest in regions of Central and South America and among U.S. Hispanics and lowest in parts of Africa and Asia), and 40-fold for CLL (highest in New Zealand and lowest in Osaka). International incidence data are not available for MDS, MPN, or MDS/MPN. In the U.S. temporal trends over the past four decades have shown limited variation in incidence patterns, with stable rates of AML among whites and blacks across four decades, declining rates of CML during the last two decades across all racial/ethnic groups, rising incidence of ALL during the 1970s-80s but stabilizing thereafter, and stable rates of CLL among whites, but slowly declining rates among blacks.

Exposure to ionizing radiation and certain chemical carcinogens (e.g., cytotoxic chemotherapy, benzene, formaldehyde) are the most consistently associated risk factors for AML/MDS. Radiation also has been linked with CML, and cigarette smoking has been associated with AML. Fewer risk factors have been identified for MPNs. Some evidence implicates increased risks of AML in rubber workers (perhaps due to benzene exposure), farmers and other agricultural workers (perhaps due to pesticides), and those with increasing body mass index. Several studies have reported increased risks of multiple types of myeloid neoplasms (including AML, MDS, CML and other MPN) in patients with specific autoimmune diseases, all autoimmune diseases combined, and in recipients of solid organ transplants. These findings suggest that immune perturbation may be a risk factor for myeloid neoplasms. In addition, most myeloid neoplasms, with the possible exception of CML, demonstrate familial aggregation. A small number of rare, highly penetrant mutations have been identified with specific myeloid neoplasm subtypes. Recent technological advances hold great promise for expansion of this area of research, identifying new rare, high-penetrant mutations as well as more common variants that confer low risk.

Since established risk factors do not explain most of the occurrence of myeloid neoplasms, opportunities for prevention are currently limited. Nevertheless, efforts should be made to reduce known medical, occupational, and environmental exposures to radiation and limit occupational and general population exposure to benzene, formaldehyde and other chemicals implicated in myeloid neoplasms. Similarly , treatment of medical conditions with radiation and/or cytotoxic therapies should continue to balance short- and long-term sequelae of these modalities in a continued effort to minimize exposures while ensuring effective treatment is delivered. Important public health initiatives should continue to be directed to cessation and avoidanceof smoking and reduction of the general public’s exposure to toxic chemicals, including benzene in gasoline.

Improvements in classification, ascertainment, diagnosis, and molecular characterization of MDS, MPN, and MDS/MPN worldwide are critical to enable progress in clarifying etiology and developing measures for prevention and effective treatment.

**<1> INTRODUCTION**

Worldwide in 2012, leukemias were ranked 11th among all cancer types, comprising approximately 2.5 percent of all malignancies and an estimated 352,000 incident cases (<http://www.wcrf.org/int/cancer-fact-figures/worldwide-data>). In the U.S., 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 et al, 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 et al, 2016].

Most, if not all, acute and chronic leukemias appear to develop from a preleukemic state that progresses to overt leukemia over time [Shlush and Minden, 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 U.S., 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 U.S. population, including 2,304 and 1,677 cases of MDS and 1,672 and 1,619 cases MPN among males and females, respectively (SEER-18). In 2009 there were 6,007 deaths in the U.S. with an underlying cause of death specified as 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 and Minden, 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 et al, 2013, Shizuru et al, 2005). Throughout this highly regulated, hierarchical differentiation and maturation process, lymphoid and myeloid cells acquire distinct phenotypes. Genetic mutations 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 et al, 2008; Kipps and Huan-You, 2015). 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, 2015). 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 2001). 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 (Swerdlow et al, 2008). 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.

**<1> HEMATOPOIETIC AND LYMPHOID CLASSIFICATION SCHEMES**

**<2> EVOLUTION OF CLASSIFICATION**

Earlier reviews provided a comprehensive summary of the history of leukemia classification (Linet S&F chapter 2006). The landmark French-American-British (FAB) classification (Bennett et al, 1976,1989, 1994,2013) 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 et al, 2000; Bennett, 2000) culminated in the 2001 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 circulating (blood) and solid (tissue) phases that represent different manifestations of the same disease (e.g., CLL (blood phase) and small lymphocytic lymphoma (tissue phase), lymphoblastic leukemia (blood phase) and lymphoblastic lymphoma (tissue phase)) (Jaffe et al, 2001) . Therefore, with the inclusion of of the myeloid and lymphoid leukemias and lymphomas in theWHO classification, 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 40 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 59.

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-4 that remain subject to change. The complex, continuing evolution of the international classification of hematopoietic and lymphoid neoplasms has led some 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, 2015).

**<1> 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 et al, 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 initiation of treatment.

**<2> WORLD HEALTH ORGANIZATION 2001 CLASSIFICATION**

**<3> 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 et al, 2001). Whereas the former (AML with multilineage dysplasia) is often associated with unfavorable cytogenetics, 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 more favorable cytogenetic abnormalities, response to treatment, and prognosis. 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 changes in the 2001 WHO classification 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 (Vardiman et al, 2002; Jaffe et al, 2001).

The 2008 WHO classification added three new AML entities (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 provisional entities (AML with mutated *NPM1* and AML with *CEBPA*) to the category of AML with recurrent genetic abnormalities (Swerdlow et al, 2008, Vardiman et al, 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. The complete list of AML and related myeloid precursors included in the 2008 WHO classification are specified in Table 1.

**<3> Myelodysplastic syndromes**

In 1982 the FAB classification considered 5 entities within the category of MDS (previously also referred to as “pre-leukemia”), with the specified categories based on % of blasts in the peripheral/bone marrow and other morphologic features. The MDS entities included in the FAB classification are specified below, according to bone marrow blast % count.

**Entity Bone marrow blasts**

Refractory anemia <5%

Refractory anemia with ringed sideroblasts <5%

Refractory anemia with excess blasts 5-20%

Refractory anemia with blasts in transformation 21-30%

Chronic myelomonocytic leukemia 5-20%

With the new 20% blast threshold for diagnosis of AML introduced in the 2001 WHO classification, one category, 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 and introduced a new MDS category – refractory cytopenia with multilineage dysplasia – and defined two subtypes of refractory anemia with excess blasts. MDS associated with isolated deletion of 5q was also identified as a new MDS entity. Lastly, resulting from the debate as to whether CMML represents a myelodysplastic or myeloproliferative neoplasm (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. 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. 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 diaagnostic 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.

<3> Therapy-related MDS/AML (t-MDS/AML)

Therapy-related myeloid neoplasms (t-MDS/AML), a new entity included in the 2001 WHO classification that includes t-MDS and t-AML, is a rare but often fatal complication of cytotoxic treatments for malignant and non-malignant diseases. t-MDS/AML occurs as a consequence of acquired genetic alterations in the hematopoietic stem cell and progenitor cell involving multiple pathways (Pedersen-Bjergaard J et al Leukemia 2006). In comparison with *de novo* MDS/AML, t-MDS/AML has a higher rate of clonal abnormalities including -5, -7, 7q-, 13q-, del 17p, and -18. Cytogenetic assessment is important since favorable, intermediate, and unfavorable karyotypes have been related to prognosis, although the frequency of unfavorable karyotype is considerably higher in t-MDL/AML than in *de novo* MDS/AML (Godley LA and Larson RA Semin Oncol 2008). Patients with t-MDS/AML have worse prognosis than those with *de novo* MDS/AML, even when they each have the same chromosomal abnormalities. This suggests that there are biologic differences between t-MDS/AML and *de novo* MDS/AML that are not solely related to the specific chromosomal abnormalities. Some evidence suggests that t-MDS/AML occurring among patients who receive radiotherapy regimens alone differs from t-MDS/AML subsequent to cytotoxic chemotherapy or combined modality therapy, but shares genetic features and clinical behavior with *de novo* MDS/AML (Nardi et al, 2012).

**<3> 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. 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 V617F* mutation substantially facilitated the diagnosis of the myeloproliferative disorders (James et al, 2005; Kralovics et al, 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 and Green, 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 neoplasms, it is found in more than 95% of cases of polycythemia vera and 50-60% of cases of essential thrombocythemia and primary myelofibrosis (Tefferi and Pardanani, 2015). The 2008 WHO classification incorporated information on *JAK2 V617F* 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 essential thrombocythemia 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.

**<3> 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 (Jaffe et al, 2001). Along with CMML, which as noted above was previously included with MDS, this disease category also included atypical CML (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 (Swerdlow et al, 2008). 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, as specified in the table below, 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.

**<1> CLINICAL PRESENTATION**

There is notable variation in severity of disease and patient survival, both within a given myeloid leukemia and preleukemia subtype and between subtypes (Kadia et al, 2015; Ferrara and Schiffer, 2013; Dohner et al, 2015; Dores et al, 2012; Srour et al, 2016; Ades et al, 2014, Tefferri and Pardanani, 2015). Patients with AML often present with complications related to cytopenias involving one or more cell lines (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 neutropenia (which increases risk of infection), although a minority of individuals may have fever related to the leukemia itself. Lymphadenopathy and hepatosplenomegaly are uncommon. Individuals with MDS also typically present with cytopenias involving one or more cell lines, but in contrast to AML, many 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 splenomegaly (with or without hepatomegaly)is common. Individuals may be asymptomatic at presentation, with the diagnosis suspected based on complete blood count abnormalities, hepatosplenomegaly, or thrombosis/bleeding episodes, the latter being common complications of MPN.

**<1> 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 and Levine, 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, 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 (Cancer Genome Atlas Research Network, 2013; Meyer and Levine, 2014; Kadia et al, 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 and Levine, 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 et al, 2015). Chromosomal translocations identified as being frequently mutated included t(15; 17), t(8;21), inv(16), abn11q23, monosomy 5 and monsomy 7 (Meyer and Levine, 2014). The role and prognostic implication of many of these genes remain under study.

**<1> DESCRIPTIVE EPIDEMIOLOGY**

**<2> INTERNATIONAL COMPARISONS**

Internationally, there has been non-uniform implementation of the WHO 2001 classification. Lack of availability of detailed clinicopathologic and molecular characterization in some countries has resulted in use of ICD10 rather than ICD-O-3 even in the most recent volume of Cancer Incidence in Five Continents (Vol X). Comparisons of leukemia data across many countries and populations for the most recent period (2003-2007) are restricted to broad, older categories of the leukemias (AML, CML, ALL, CLL). International comparisons described below are based on registries with fewer than 10% of reported cases of leukemia unspecified as to subtype and restricted to incidence in adults ages 20-79 years at diagnosis.

**<3> International patterns in incidence of broad categories of leukemias by subtype**

Among international cancer registries reporting <10% unspecified leukemia subtypes among adults ages 20-79 years diagnosed during 2003-2007, AML 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.

**<3> International patterns in temporal trends incidence of leukemia by subtype**

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, during the limited timeframe for which racial/ethnic-specific incidence data have been available. In Denmark, incidence of AML, CLL and, to a lesser extent, ALL increased between 1943-2003, whereas CML decreased (Thygesen et al, 2009). Between 1984-1993. AML, MPN (including CML) incidence rates decreased in the United Kingdom, whereas ALL remained stable, and MDS rates increased (McNally et al,1999). Between 1991-2005, AML incidence rates increased in Western Australia (Gangatharan et al, 2013). More recently, several large studies have described incidence rates utilizing the WHO classification scheme (Sant et al, 2010, Smith et al, 2009, Smith 2011, Dores et al, 2012), however, longer follow-up will be needed to assess temporal trends subsequent to 2001.

**<2> DESCRIPTIVE PATTERNS OF MYELOID NEOPLASMS BY WHO SUBTYPE**

Some population-based cancer registries have implemented reporting of myeloid neoplasms using the WHO 2001 classification of hematopoietic and lymphoid neoplasms. U.S. Surveillance Epidemiology and End Results (SEER) population-based registries have trained registry staff to code these neoplasms using ICD-O-3 which has incorporated the WHO 2001 classification. Described below are descriptive patterns for myeloid neoplasms diagnosed in persons ages 20-79 for the period 2001-2012. Consistent with the clinical and molecular heterogeneity described among individuals with AML, incidence rates in the U.S. varied widely across AML subtypes (Table 1). 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.

There have been relatively few published studies of population-based incidence of myeloid neoplasms worldwide. 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 et al, 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 et al, 2010). Similarly, in Burgundy, France, AML cases diagnosed during 1980-2004 and classified according to the WHO 2001 classification 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 et al, 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 (see Table 1). As with other myeloid malignancies (Craig et al, 2012), underreporting of MDS to cancer registries has been described (McQuilten et al, 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 et al, 2010, Cogle, 2015). Considering these caveats, MDS incidence rates in the U.S. (Table 1) were higher among males than females, overall and by race, and across all subtypes, with the exception of MDS with associated 5q deletion. For MDS overall, a similar male predominance was observed in the HAEMACARE (Sant et al, 2010) database and in the Haematological Malignancy Research Network (Smith et al, 2009, Smith et al, 2011).

In the U.S., 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. In the HAEMACARE database where MPNs were grouped somethat diffeentently than in the Table, as a group, MPN crude incidence rates were higher among males (IR=3.5) than females (IR=3.18), with the greatest gender disparity noted for CML, in contrast to other specified MPN subtypes considered as a group (Sant et al, 2010). In the United Kingdom (U.K.), 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 et al, 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.

**<2> 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 20-59 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 et al, 2016 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 et al, 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 (Grimwade, 2001; Grimwade et al, 2010; Wheatley et al, 2009; Rollig et al, 2011, Schlenk et al, 2008, Patel et al, 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 et al, 1997; Greenberg et al, 2012; Voso et al, 2013; Ades et al, 2014). Although several disease-specific prognostic algorithms exist for the MPNs, older age remains a universally poor prognostic feature (Sokal 1984 Barbui et al, 2011, Passamonti et al, 2004, 2008; Tefferi and Pardanani, 2015).

**<1> PHYSICAL AGENTS**

**<2> IONIZING RADIATION**

**<3> Mechanisms of leukemogenesis**

Exposure to ionizing radiation, a clastogen and the most well-studied risk factor for myeloid neoplasms, causes acute and long-term effects in the hematopoietic compartment (Fleenor et al, 2015). Radiation-associated leukemogenesis has been attributed primarily to interaction of radiation with DNA, either directly via ionization or indirectly via free radicals, that results in radiation-induced DNA double-strand breaks. Cells with DNA damage initiate a repair response that differs between cycling and quiescent HSCs. Cycling HSCs preferentially initiate DNA repair by homologous recombination pathway, and quiescent HSCs utilize the more error-prone non-homologous end-joining pathway. Thus, after irradiation, some HSCs may be characterized by radiation-induced genomic aberrations (Fleenor et al, 2015). Although more than 90% of double-strand breaks are repaired within 24 hours, the small fraction of misrepaired breaks can lead to chromosomal translocations and deletions (Tucker, 2010). Radiation-related translocations demonstrate the greatest persistence of all types of chromosomal exchange and damage, and may remain present for decades.

There is no gold-standard radiation signature or biological measure of radiation dose, but quantitative measurement of chromosome translocations in peripheral blood lymphocytes using *fluorescent in situ hybridization* (*FISH*) may reflect radiation dose as well as initiating radiogenic events that lead to radiation-induced leukemia (Tucker, 2010). Translocations may also represent a biomarker of effect because they have been found in most types of neoplasms (Kaye, 2009). Chronic or highly fractionated radiation exposure may result in accumulation of translocations in HSCs unless selective pressure removes these cells via such mechanisms as apoptosis, senescence, or differentiation (Fleenor et al, 2015). It is hypothesized that HSCs with deleterious mutations are removed and cells with advantageous mutations are selected and preferentially expanded. In recent years, mouse models have provided valuable data on genomic changes associated with radiation exposure, including genomic rearrangements, deletions, and changes in methylation (Rivina et al. 2014).

**<3> Individual and combined groupings of myeloid and other hematopoietic disorders and ionizing radiation**

AML is the hematopoietic malignancy most commonly associated with many forms of moderate-to-high ionizing radiation exposure (Boice, 2006). Results from the follow-up study of atomic bomb survivors (Hsu et al, 2013), and, to a lesser extent, epidemiological data from other radiation-exposed populations, also reveal increased risks of CML (Muirhead et al, 2009; Leuraud et al, 2015) and ALL (Hsu et al, 2013) associated with radiation exposure. The epidemiological findings for all leukemias other than CLL (hereafter designated non-CLL leukemias) are described in this section because AML, CML, and ALL are often considered as a combined entity in radiation studies, and radiation-related risks are frequently not quantified for the individual leukemia entities.

**<3> Medical radiation**

***<4> Evolution of medical radiation exposure and changing technologies***

During the past few decades, there have been dramatic changes in medical sources of radiation exposure (NCRP, 2009), mostly due to diagnostic computed tomography (CT) scans, nuclear medicine studies, fluoroscopically-guided interventional procedures, in addition to standard x-ray examinations. The rapidly growing use of these and other diagnostic and treatment modalities has resulted in a 6-fold increase in medical sources of radiation. The clinical indications for and practice of radiotherapy also have undergone notable changes, including advanced imaging to produce more accurate determination of tumor volumes and spatial relationships with surrounding tissues, three-dimensional treatment planning systems and newer modalities of three-dimensional conformal radiation therapy. Implementaton of newer forms of radiotherapy have led to an increase in dose to the tumor target, while reducing/minimizing the volume and dose to surrounding normal tissue structures, although some newer technologies may include a larger volume of normal tissue within the irradiated field that receives low doses (Thariat et al, 2012) (see chapter 13).

***<4> Diagnostic radiologic examinations***

Although most epidemiologic studies evaluating the association of diagnostic x-rays and risk of myeloid leukemia have relied on questionnaire data, a few have assessed the association using radiologic examinations or medical records. In a large case-control study in a health maintenance organization in which over 25,000 x-ray procedures were abstracted from medical records and each procedure was assigned a score based on estimated bone marrow dose, the investigators found a small, non-significant elevation in risk (but no dose-response) using a 2-year lag, but no increase using a 5-year lag (Boice et al, 1991). In an interview and medical record-based study among patients diagnosed with AML during 1987-1994 in Los Angeles that utilized a unique database of estimated doses and dose ranges based on dosimetry literature and consultation with a radiology expert (Preston-Martin and Pogoda, 2003), no association was observed between diagnostic x-rays and risk of adult AML (Pogoda et al, 2011). However, radiographic procedures of the gastrointestinal tract and multiple spinal x-rays were linked with increased risk of CML in a case-control study in Los Angeles (Preston-Martin et al, 1989). Three of four earlier studies of CML and diagnostic radiographic procedures (two based on medical records) reported small increases in risk and one found a dose-response relationship with increasing numbers of x-rays in the 20 years prior to diagnosis. Inconsistent findings in the limited numbers of epidemiologic studies and potential methodologic limitations, along with the relatively small numbers of substantially exposed non-CLL leukemia cases preclude drawing firm conclusions regarding the association between diagnostic x-rays and leukemia risk (Linet et al, 2012).

Risks of myeloid leukemias have been evaluated in relation to diagnostic examinations from radiation sources other than x-rays. Chronic low-dose alpha-particle radiation from injections with the radiographic contrast medium, Thorotrast, which was used in earlier decades for cerebral angiography and for radiologic visualization of other vascular structures, has been consistently associated with increased risk of MDS and AML, considered jointly as (MDS/AML) (IARC, 2001; Travis et al. 2003). During 1928-1954, between 2.5 and 10 million patients worldwide were injected with Thorotrast. The estimated average dose to bone marrow was 100 mGy from an injection of 25 ml. Elevated risk of MDS/AML persisted for 8-50 yearss after exposure (Travis et al, 2003), and cumulative risk ranged from 129-140 MDS/AML cases/104 persons per Gy (IARC, 2001).

***<4> Therapeutic x-rays for benign conditions***

Elevated risks of myeloid neoplasms have been reported in patients with benign conditions who underwent radiation treatment. X-ray radiation treatment for ankylosing spondylitis was associated with a 7-fold increase in non-CLL leukemia during a period of 1-25 years after exposure to a uniform bone marrow dose of 1 Gy; leukemia risk peaked within 10 years of exposure (Weiss et al, 1995). Somewhat lower AML excesses (relative risks ranging from 1.2 to 3.2) have been associated with radiation therapy treatments for benign gynecologic disorders (Sakata et al, 2012), peptic ulcer (Griem et al, 1994), and tinea capitis (Shore et al, 2003). The ongoing use of radiotherapy to treat benign ocular conditions, musculoskeletal diseases, inflammatory and proliferative disorders, and benign vascular proliferations demonstrates the need to follow-up these patients, particularly if treated at younger ages (McKeown et al, 2015). Higher risks and corresponding greater concern is associated with use of radiation therapy for benign tumors and other benign conditions in children and those with tumor predisposing syndromes (Evans et al, 2006). Myeloid leukemia and AML risks were also almost 4-fold increased among ankylosing spondylitis patients treated with radium-224, with a mean estimated dose to the skeleton of 0.67 Gy (Wick et al, 2008).

***<4> Therapeutic x-rays for malignant conditions***

Two-fold increased risks of t-MDS/AML have been described in patients treated with radiotherapy for non-Hodgkin lymphoma, testicular cancer, uterine cervix cancer, uterine corpus cancer, Ewing’ssarcoma and total body irradiation for transplantation treatment (Wright et al, 2010; NCRP, 2011). t-MDS/AML following treatment of testicular cancer has been linked with both radiotherapy and platinum chemotherapy (Howard et al, 2008). Similar to the temporal pattern for occurrence of AML among the Japanese atomic bomb survivors, t-MDS/AML following radiotherapy often appears within five years and most has occurred within 10-15 years (NCRP, 2011). Excess risks of t-MDS/AML following radiotherapy have been associated with estimated bone marrow doses ranging from 1 to 15 Gy for adults (and often higher for children), appear to be greater when large volumes of bone marrow are treated with lower doses or dose fractions, but risks do not continue to increase further at very high doses perhaps due to cell killing (Boice et al, 1987). See chapter 60 for more detail.

**<3> Atomic bomb survivors**

Long-term studies of the Japanese atomic bomb survivors have provided the most important population-based quantitative risk assessment for the risk of leukemia and other cancers associated with ionizing radiation. Studies of this population are the primary basis for international radiation risk protection measures (NRC BEIR VII, 2006) (see chapter13). Atomic bombs detonated over Hiroshima and Nagasaki in August 1945 resulted in many thousands of immediate and short-term deaths. At the end of the 1940s an excess of leukemia was apparent among the Japanese atomic bomb survivors. A long term mortality follow-up of a population-based cohort of survivors, designated the Life Span Study, was launched with ascertainment of deaths since 1950. Follow-up of the Life Span Study cohort for cancer incidence was undertaken beginning in 1958 when population-based cancer registries were established in Hiroshima and Nagasaki (Mabuchi et al, 2011).

Results of dose-response for leukemia mortality through 1982 and leukemia incidence through 1987 have been previously summarized (Boice, 2006; Linet et al, 2006; Mabuchi et al, 2011). Follow-up among 113,011 Life Span Study cohort members through 2001 ascertained 371 incident non-CLL leukemias, including 176 AML, 75 CML, and 43 ALL (Hsu et al, 2013). A nonlinear, upward curving dose-response pattern observed for non-CLL leukemias derived primarily from results for AML. The radiation-associated excess rates for AML according to age at exposure were U-shaped. The high excess rates for those who were children or adolescents at the time of the bombings initially declined over time; However, the excess rates increased with attained age regardless of age at exposure. The temporal patterns for CML and ALL differed from AML. In the period 5-10 years after the bombings, the fraction of ALL and CML attributable to radiation from the bombings among cohort members with >0.0005 Gy was 59% for the entire period (23% for ALL and 36% for CML). However, these two subtypes accounted for 80% (27% for ALL and 53% for CML) of the excess leukemias during 1950-1955, but only 22% (10% for ALL and 12% for CML) during 1991-2001. Hsu et al (2013) speculated that CML and ALL rates may have been even higher than 80% within the first five years after the bombings (1945-1949), prior to availability of systematically ascertained data. In contrast, the fraction of AML attributable to radiation among cohort members with >0.005 Gy was 38% for the entire period studied. AML accounted for only 20% of the excess leukemias during 1950-55, but for 80% of the excess leukemias during 1991-2001. This temporal pattern for AML is markedly from that subsequent to cytotoxic chemotherapy, with most of the excess treatment-related AML occurring within less than 10 years after treatment (see below).

Richardson and colleagues were the first to evaluate leukemia mortality risks in atomic bomb survivors by subtype (Richardson et al, 2009). The investigators followed up mortality among 86,611 survivors during 1950-2000 and identified 310 deaths from all forms of leukemia. For AML mortality, the dose response pattern was best described by a quadratic dose-response function that peaked at approximately 10 years after exposure, while CML and ALL demonstrated a linear dose-response that did not vary with time since exposure. Excess leukemia mortality risk persisted for more than five decades. In the most recent decade evaluated (1991-2000), 34% of leukemia deaths among those with radiation dose >0.005 Gy were estimated to be attributable to radiation from the bombings.

MDS was first linked with radiation exposure in the late 1980s following a detailed histopathological review of myeloid malignancies among atomic bomb survivors after recognition that a substantial proportion of this poopualtion had MDS (Matsuo et al,1988). The first analysis, which was based on only 13 MDS cases, revealed a significant dose-response for MDS mortality; the excess relative risk was several times greater than that seen for all solid cancers combined (Shimizu et al,1999). An assessment of MDS diagnosed during 1984-2004 in two populations of survivors in Nagasaki found a notably increased excess relative risk per Gy of 4.3 (95% confidence interval (CI), 1.6 - 9.5) based on 47 cases in the 22,245 survivors in the Life Span Study and a significant excess based on 151 MDS cases in 64,026 survivors with known distance from the bomb hypocenter (Iwanaga et al, 2011). While the latency period to development of MDS cannot be accurately determined prior to the mid-1980s, a 40-year latency period was observed among survivors after the mid-1980s. This timeframe is similar to that of *de novo* MDS, but differs from the median peak latency of 4-6 years observed for t-MDS/AML (Bhatia, 2013). However, molecular characteristics of MDS in the atomic bomb survivors more closely resemble those of patients treated with alkylating agents, with 6 of 13 atomic bomb survivors with MDS having *AML1* gene mutations compared with 5 of 13 patients treated with alkylating agents developing t-MDS/AML and 2 of 27 patients without these exposures developing *de novo* MDS (Harada et al, 2003). Further study is needed to clarify the molecular features of MDS associated with different exposures.

**<3> Radiation workers**

Historically, the major categories of workers exposed to ionizing radiation include medical radiation workers (radiologists and radiologic technologists), nuclear industry workers, radium dial workers, miners (uranium and tin), flight crew, and military servicemen exposed to above-ground nuclear tests (Wakeford, 2009). Studies quantifying leukemia and other cancer risks in workers are important because the radiation exposures in these populations are protracted over decades and and these populations are monitored. Small radiation exposures are cumulative and, if associated with leukemia, could translate into meaningful numbers of patients with leukemia since there are millions of radiation workers. Furthermore, results from radiation worker studies contribute important information towards defining radiation protection measures (see chapters 13 and 16). These studies are also useful because finidngs could be extrapolated to the general population experiencing low-level protracted exposures to natural background radiation and repeated radiation exposures from diagnostic radiologic examinations. Overall, interpretation of risks for cancer and other serious diseases in long-term studies of medical radiation workers is complicated by the dramatically declining radiation doses to workers over time (Linet et al, 2010). As with most occupational epidemiologic studies of potentially leukemogenic exposures, information on potential confounders (e.g., workers’ personal diagnostic radiological imaging tests, radiotherapy, smoking and genetic characteristics) is lacking, and few of the studies of medical radiation workers include women (see chapter 16).

A large excess mortality risk (approximately 10-fold) of leukemia was initially reported among U.S. radiologists in 1944 (March et al,1950). Eight major cohorts have been actively followed up for leukemia, other cancers, and chronic diseases (reviewed in Yoshinaga et al, 2004; Linet et al, 2010). Collectively, the eight retrospective cohort investigations have studied radiologists or radiologic technologists who first began working over a period spanning more than 80 years, including small numbers who first began working in the earliest years of the professions (e.g., between 1897 and 1926). Radiologists and x-ray technicians employed in the first half of the twentieth century experienced notably elevated leukemia mortality (no subtype information provided), with increased risks ranging from 6- to 8.8-fold among those first joining professional societies (a proxy for first working) before 1940. Significantly elevated risks of incident non-CLL leukemias were seen in U.S. radiologic technologists who worked 5 or more years before 1950. Incidence of total leukemia was significantly elevated in Chinese x-ray workers employed during 1950-1980. Among British radiologists entering the profession after 1921, U.S. radiologists entering the workforce in 1940 or later, or in U.S. radiologic technologists who first worked after 1950, leukemia risks declined notably over time, with no significant excesses observed (Yoshinaga et al, 2004; Linet et al, 2010). Accurate estimation of risk per unit of radiation has been limited due to absence of comprehensive historical dose reconstruction, and particularly absence of recorded individual badge doses in the earliest years when exposures would have been greatest. A recent comprehensive historical reconstruction of individual occupational radiation doses for the U.S. radiologic technologists cohort (Simon et al, 2014) will provide a useful basis for estimating risks per unit dose for hematologic malignancies and other cancers, circulatory diseases, and cataracts.

Results from individual and earlier studies can be found elsewhere (Boice, 2006; Polychronakis et al, 2013). Because radiation exposures of nuclear workers are mostly quite low and myeloid neoplasms are rare, pooled studies including large numbers of workers have been the most informative. A 15-country study examining the relation between estimated cumulative occupational radiation dose and mortality risk of non-CLL leukemia in a population of 407,391 nuclear workers using a 2-year lag found an excess risk per Sievert (Sv) of 1.93 (90% CI = <0-7.14) based on 196 leukemia cases (Cardis et al, 2005). The mean estimated cumulative dose was estimated to be 19.4 mSv. In a subsequent study of 308,297 monitored nuclear workers from three countries employed for at least one year and followed up during the period 1944-2005 and with a 2-year lag, risk of all non-CLL leukemias was significantly elevated (ERR per Gy = 2.96, 90% CI = 1.17-5.21) based on 531 leukemia cases (Leuraud et al, 2015). The mean cumulative occupational radiation dose across the three cohorts was estimated to be 15.9 mGy (range 0.0-1217.5 mGy). The excess risk was primarily due to a significant increase of CML (ERR per Gy = 10.45, 90% CI = 4.48-19.65) based on 100 cases, whereas positive risk estimates for AML (ERR per Gy = 1.29, 90% CI = -0.82-4.28 based on 254 cases) and for ALL (ERR per Gy = 5.80, 90% CI = not evaluable lower bound-31.57, based on 30 cases) did not contribute notably to the overall risk. In contrast to the low-level radiation exposures of most nuclear workers, external radiation exposures were high (mean cumulative dose of 800 mGy) for workers at the Mayak plutonium production facility in the Russian Federation during the early years (1948-1958) of operation. An elevated risk of non-CLL leukemias (ERR per Gy = 0.99, 95% CI = 0.45-2.12) was associated with external radiation exposures using a 2-year lag. Risk from doses received 3-5 years prior to diagnosis of non-CLL leukemia was more than 10 times higher than the risk from doses received more than five years before diagnosis (Shilnikova et al, 2003). There was no evidence of an association of plutonium exposure with non-CLL leukemia in this population. Following the Chernobyl nuclear accident in 1986, clean up operations were carried out for years after the accident. The early clean-up workers (also known as liquidators) experienced higher doses (mean cumulative radiation dose of 92 mGy) than most other nuclear workers (mean cumulative dose of 20 mGy). In a nested case-control study of leukemia in a cohort of 110,645 Chernobyl clean-up workers from Ukraine, a significant linear dose-response was observed for all leukemias based on 117 cases (ERR per Gy = 2.38, 95% CI = 0.49-5.87) (Zablotska et al, 2013). Unexpectedly, in this study risks were significantly elevated for CLL (ERR per Gy = 2.58, 95% CI = 0.02-8.43) as well as for non-CLL leukemias (ERR per Gy = 2.21, 95% CI = 0.05-7.61); 16% of the leukemias diagnosed in this population (18% of CLL and 15% of non-CLL leukemias) were attributed to radiation exposure. MDS cases have been described in Chernobyl clean-up workers, but radiation-related risks have not been reported (Gluzman et al, 2015).

Epidemiologic studies of uranium miners (Tomasek et al, 1993; Darby et al, 1995; McLaughlin, 2012; Zablotska et al, 2014) have shown no overall association of cumulative radiation dose with leukemia mortality, although leukemia mortality risk was increased within 10 years of first exposure (Darby et al, 1995). Studies of radium dial workers (painters?) who experienced excess risks of osteosarcomas and cancers of the nasal sinuses, have found no clear evidence of excess risk of myeloid neoplasms (Boice, 2006), although in males occupationally exposed to radium, there is some evidence of an excess of leukemia, particularly of the same morphology as seen in patients who received Thorotrast (Stebbings, 1998).

Excess risks of AML were described in Canadian airline pilots (Band et al, 1996) and in Danish cockpit crew flying more than 5,000 hours (Gundestrup and Storm, 1999), but pooled analysis of airline crew cohorts from 10 countries found no evidence of elevated myeloid leukemia risk (Hammer et al, 2014).

A critical question that is difficult to address in a single epidemiological study is risk of non-CLL leukemia following low-dose, protracted radiation exposure. In a meta-analysis addressing this question, Daniels and Schubauer-Berigan modeled results from 10 studies that were cohort or nested case-control in design, reported quantitative estimates of exposure, were screened to reduce information overlap, and analyzed data using relative or excess relative risk per unit of radiation exposure (Daniels and Schubauer-Berigan, 2011). These investigators estimated an excess relative risk at 100 mGy of 0.19 (95% CI = 0.07-0.32) after adjusting for publication bias. They found no evidence of between-study variance. The excess relative risk estimate was in agreement with the non-CLL leukemia risk from the Life Span Study of the atomic bomb survivors.

**<3> Military workers exposed to nuclear weapons tests and to depleted uranium**

Military participating in maneuvers during nuclear weapons testing have been evaluated in a series of epidemiologic studies (reviewed in Boice, 2006). An excess of leukemia mortality (based on 10 cases), but not total cancer mortality, was reported among approximately 3,000 military participants during a 1957 nuclear test in the U.S. (Caldwell et al,1980). Among approximately 70,000 U.S. military personnel who participated in one of five nuclear tests during the 1950s, a non-significant increase in risk for leukemia mortality was observed (IOM, 2000). A study of 21,357 UK military participants reported an increased relative risk of non-CLL leukemia mortality but noted that this may have reflected a reduced risk in controls (Muirhead et al, 2003). None of these studies, or others, included estimated radiation doses. Using recently available digital records, Till and colleagues have been undertaking dose reconstruction for a planned case-cohort study of leukemia and male breast cancer in a cohort of 115,000 U.S. military participating in eight nuclear test series. Further work is underway, but the investigators have reported estimated median radiation doses ranging from 9.5 to 24 mGy (Till et al, 2014).

Based on concerns raised about a possible association of leukemia among military exposed to ammunition reinforced by depleted uranium, Storm and colleagues studied 13,552 men and 460 women deployed to the Balkans during 1992-2001 and followed up through 2002. These investigators found no excess of leukemia (Storm et al, 2006).

**<3> Environmental radiation**

Although an ecological study suggested a correlation between indoor radon and myeloid leukemia (Henshaw et al, 1990), a subsequent comprehensive and critical review concluded that there was little evidence of a link (Laurier et al, 2001). Few studies have examined natural background radiation and leukemia. An intriguing investigation that evaluated approximately 80,000 stable residents residing in underground dwellings in China who experienced about three-fold higher cumulative radiation levels (6.4 mSv) than the average population worldwide, found no evidence of an increase in leukemia (Wei and Sugahara, 2000). Among the limited numbers of studies of radon or of natural background radiation and leukemia, most have examined pediatric leukemia . Most of the studies of adult leukemias have been ecologic in design, few have included individual measurements, and those with measurements have been underpowered given the low radiation exposure levels (Boice, 2006).

A population of approximately 30,000 persons residing in villages next to the Techa River were exposed to chronic external and internal radiation during 1950-1960 from releases from the Mayak nuclear weapons plutonium production plant in the Russian Federation. The median cumulative red bone marrow dose was 0.2 Gy, but doses ranged up to 2 Gy. In a follow-up during 1953-2005, a significant dose-response relationship was seen with an estimated excess relative risk of 4.9 (95% CI = 1.6-14.3) based on 70 non-CLL leukemia cases. No dose-response relationship was observed for CLL (Krestinina et al, 2010).

Spurred by a report from the United Kingdom of increased risk of leukemia and lymphoma occurring among young persons residing in proximity to nuclear plants, many ecologic studies and a few analytic epidemiologic studies have been conducted. Most of the studies have focused on childhood leukemia (Laurier et al, 2008). A large ecologic investigation examined total and specific forms of adult cancers, including leukemia, but found no association (Jablon et al, 1991). Limitations acknowledged by the authors included lack of radiation dose measurements, absence of information about potential confounders, and the likely underpowered nature of the study despite including a large population base of more than 900,000 cancer deaths from 1950 through 1984 (Jablon et al, 1991). A borderline significant increase in risk of non-CLL leukemia and of ALL was observed in a case-control study of more than 1,000 leukemia deaths among persons living in southwest Utah in proximity to the Nevada Test Site (Stevens et al, 1990). Risks were significantly elevated for those exposed to fallout under 20 years fo age.

**<2> NON-IONIZING RADIATION – EXTREMELY LOW-FREQUENCY MAGNETIC FIELDS AND RADIOFREQUENCY**

**<3> Exposures and biological effects from extremely low-frequency magnetic fields**

Electromagnetic fields are produced by a growing number of sources that are ubiquitous worldwide. These include extremely low-frequency magnetic fields from the generation, transmission, and use of electricity, and microwaves generated by radio and television applilcations, microwave ovens, mobile telephones and base stations, wireless local area networks, and smart meters (<http://ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_o_041.pdf>; (also see chapter 15 for more details). The primary known biological effect of electromagnetic fields is tissue heating. Electromagnetic fields generate energy that is proportional to the frequencies emitted(measured in hertz), and the energy they produce is too weak to break chemical bonds or to cause translocations in DNA.. To date, laboratory studies have failed to demonstrate consistent, reproducible evidence of carcinogenicity, with the possible exception of a co-carcinogenic effect of radiofrequency fields and a chemotherapy agent (see chapter 15). Exposures largely have been studied in residential settings, in which most studies have assessed risks of pediatric leukemia and brain tumors (see chapters 15 and 59), or in occupational settings.

**<3> Residential exposures to extremely low-frequency magnetic fields**

Residential investigations of extremely low-frequency magnetic field exposures in Nordic countries based on calculated historic exposures have shown no evidence of a significant increase in risk of leukemia in adults in Finland (Verkasalo et al, 1996) or Norway (Tynes and Haldorsen, 2003), but a borderline increase in risk of AML and CML among persons residing in homes exposed to the highest estimated fields in Sweden (Feychting and Ahlbom, 1994). Risk of AML was not increased in adults residing in homes with measured exposures to extremely low-frequency magnetic field levels in western Washington state (Severson et al, 1988) nor was risk of total leukemia elevated in persons living in close proximity to high power lines in the U.K. (Elliott et al, 2013).

**<3> Occupational exposures to extremely low-frequency magnetic fields**

Most epidemiologic studies of myeloid leukemia (or brain tumors) in workers considered to have high exposure to extremely low-frequency magnetic fields (*e.g*., power linemen, utilities workers, and electronics workers) haveused job titles and/or a job exposure matrix as proxy measures of exposure (see chapter 16). A few studies that incorporated measurements as reviewed earlier reported inconsistent findings for AML (Linet et al, 2006). A meta-analysis published in 1997, that described an overall 40% increase in risk of AML among workers in jobs with high extremely low-frequency magnetic field exposures (Kheifets et al, 1997), was updated a decade later and reported a lower pooled estimate for AML (pooled RR = 1.09, 95% CI = 0.98-1.21) in this population (Kheifets et al, 2008). Risk for CML was also lower in the more recent meta-analysis (RR=1.11, 95% CI = 0.94-1.31) compared with the earlier one (RR = 1.24, 95% CI = 0.98-1.57). Based on these results, Kheifets and colleagues concluded that the lack of a clear pattern of extremely low-frequency magnetic field exposures and risks for AML, CML, and other leukemia subtypes did not support the hypothesis that these exposures were responsible for the observed excess risks.Subsequent to the 2008 meta-analysis, an update of a cohort study of Danish utility workers found no evidence of increased risk of total leukemia(Johansen et al, 2007), while a population-based cohort study in the Netherlands that utilized a job exposure matrix found a dose-response relationship with estimated low and high exposure to extremely low-frequency magnetic fields and AML (Koeman, 2014).

**<3> Radiofrequency exposures**

There is little evidence that myeloid neoplasms are increased among people using mobile telephones or living in proximity to base stations (IARC, 2013). There are few epidemiologic studies of workers exposed to radiofrequency fields, and some of the results are difficult to interpret. In general risks of leukemia overall and myeloid leukemia were not increased (IARC, 2013). An exception was an elevated risk of AML mortality among aviation electronics technicians (RR = 2.60, 95% CI = 1.53-4.43, based on 23 deaths) (Groves et al, 2002). In this same cohort, a non-significant increase in AML (RR = 1.87, 95% CI = 0.98-3.58) was observed among 20,109 U.S. Navy personnel who served on ships during the Korean War and were characterized as having high radiofrequency exposure based on expert assessment.

**<1> CHEMICAL EXPOSURES: MANUFACTURING, FARMING, MEDICATIONS**

**<2> MANUFACTURING**

**<3> Benzene**

Benzene has been used for more than a century as a key component in the manufacturing of shoes, leather, rubber goods, paints, dyes, inks, lubricants, detergents, pesticides, and pharmaceuticals, and more recently in the production of styrene, polymers, latexes, hydroquinone, benzene hexachloride, plastics, resins, and insecticides (IARC, 2012). Jobs in crude oil refining and in sea and land transport of crude oil and gasoline also involve exposure to benzene as do jobs in auto repair and bus garages. Surveys have led to estimates of more than 2.1 million benzene-exposed manufacturing workers worldwide. Exposure sources to the general population include motor vehicle exhaust, tobacco smoke, contaminated water and foods, gasoline at pumping stations and leaking underground gasoline storage tanks.

In 1982, the International Agency for Research on Cancer (IARC) concluded that there was sufficient evidence linking benzene with leukemia, particularly AML. The updated assessment by IARC noted that cohort studies in multiple industries and different countries demonstrated a dose-response pattern for AML (IARC, 2012). Myeloid and lymphoid neoplasms as well as many other types of cancer have been described following benzene exposure to mice and rats (IARC, 2012). A systematic review and meta-analysis of four studies focusing on cumulative exposure to benzene found evidence of a dose-response pattern, with 3.2-fold relative risk of AML for benzene exposure levels > 100 ppm-years, although the trend was not statistically significant (Khalade et al, 2010). Data on AML risk at low levels of benzene exposure have been relatively limited due to small numbers of cases available for study. Among Chinese benzene-exposed workers with cumulative exposures less than 40 ppm-years, risks of AML (RR = 1.9, 95% CI = 0.5-7.0, based on 5 cases) and the combined category of MDS/AML (RR = 2.7, 95% CI = 0.8-9.5, based on 7 cases) were non-significantly increased (Hayes et al, 1997). In a pooled and updated analysis of three nested case-control studies carried out among cohorts of petroleum distribution workers with low levels of benzene exposure from Australia, Canada and the United Kingdom, AML risks rose modestly but not significantly with increasing cumulative level of benzene exposure (<0.348 ppm-years: OR = 1.00 [referent], based on 20 cases; 0.348-2.93 ppm-years: OR = 1.04, 95% CI = 0.50-2.19, based on 19 cases; >2.93 ppm-years: OR = 1.39, 95% CI = 0.68-2.85, based on 21 cases). A similar relationship was observed for duration of exposure and peak exposure, but there was no clear pattern for average or maximum intensity of exposure. Risks were highest in the top quartiles of average and maximum exposure and increased in those with peak exposure <3 ppm. Significantly elevated risks of AML were seen among those who had ever been tanker drivers or those who had been tanker workers at terminals (Schnatter et al, 2012; Rushton et al, 2013). MDS/AML was associated with recent, but not distant benzene exposure among Chinese benzene-exposed workers (Hayes et al, 1997). Data from the long-term follow-up of a cohort of U.S. pliofilm workers suggest that the excess risk of leukemia diminished with time since exposure (Rinsky et al, 2002). In addition to AML, benzene also causes hematotoxicity at very low levels in benzene-exposed workers (Lan et al, 2004). Some (Talbott et al, 2011; Raaschou-Nielsen et al, 2016), but not all (Wilkinson et al, 1999) studies have reported increased risks of AML among community members exposed to gasoline vapors or traffic-related air pollution and among those who reside in proximity to oil refineries. Efforts are underway to understand the mechanisms underlying benzene-associated leukemogenesis by identifying the critical genes and pathways that are involved in inducing genetic, chromosomal and epigenetic abnormalities and genomic instability in HSCs; altered proliferation and differentiation of the HSCs; and dysregulation of stromal cells (McHale et al, 2012). These effects are likely modulated by benzene-induced oxidative stress, reduced immunosurveillance, and aryl hydrocarbon dysregulation.

Data assessing an association between benzene and MDS are limited. Risks of mortality from MDS were significantly increased among benzene-exposed (7 cases) compared with unexposed workers (0 cases) among Chinese benzene-exposed workers followed up during 1972-1999 (Linet et al, 2015). Cumulative benzene exposure demonstrated a monotonic dose-response relationship and significant trend with increasing benzene dose and MDS in the pooled 3-country study of petroleum distribution workers (OR = 4.33, 95% CI = 1.31-14.3 at a cumulative exposure >2.93 ppm-years, based on a total of 29 cases with all levels of cumulative exposure) (Schnatter et al, 2012). Higher risks for MDS were observed among workers employed at terminal facilities and among tanker drivers. Similar, albeit non-significant or borderline significant, dose-response patterns were observed for average exposure, maximum exposure, and peak exposures (>3 ppm) to benzene and MDS.

Although based on relatively few studies, CML has not been consistently linked with benzene exposure (IARC, 2012; Khalade et al, 2010), although a meta-analysis found a moderate increase in risk of CML in studies of benzene workers that commenced follow-up after 1970 (Vlaanderen et al, 2012). MPN has only been studied in the 3-country investigation (Glass et al, 2014). Dose-response trends for CML (based on 28 cases) and MPN (excluding CML) (based on 30 cases) were not statistically significant for cumulative, average, or maximum benzene exposure, but risks rose notably with increasing cumulative dose experienced 2-20 years before diagnosis of CML or MPN (excluding CML) (Glass et al, 2014).

**<3> Formaldehyde**

Concerns have arisen about health effects, including leukemia, associated with workplace (health care, embalming, and manufacturing workers) and general population exposures, the latter from formaldehyde levels in new homes. In follow-up during 1966-2004 of 25,619 manufacturing workers in 10 plants, risk of myeloid leukemia was associated with peak formaldehyde exposures (Hauptmann et al, 2003; Beane Freeman et al, 2009). Myeloid leukemia risk was highest before 1980, but only achieved statistical significance in the mid-1990s when sufficient deaths had occurred. Risks were highest in the first 25 years following exposure, and declined with continued follow-up. The pattern was consistent with the wave-like exposures observed for myeloid leukemia seen for other chemical exposures (Linet et al , 2006).

Based on a follow-up during 1960-1986 of a cohort of embalmers identified from funeral directors’ associations and licensing boards, a nested case-control study of leukemia and selected other categories of cancer deaths was carried out. Risk of myeloid leukemia rose significantly with increasing number of years of embalming, increasing number of embalmings performed, increasing estimated lifetime formaldehyde exposure in ppm-years, and increasing peak formaldehyde levels (Hauptmann et al, 2009). A study of 43 formaldehyde exposed versus 51 unexposed workers in China demonstrated numerical chromosomal aberrations in myeloid progenitor cells (including chromosome 7 monosomy and chromosome 8 trisomy) consistent with MDS/AML, as well as other changes in peripheral blood reflecting bone marrow effects (Zhang et al, 2010). Meta-analyses have provided evidence in favor of (Schwilk et al, 2010) and against (Bachand et al, 2010) an association of formaldehyde and leukemia. The IARC working group cited results from recent studies and evidence of a biologically plausible mechanism to conclude that evidence was sufficient to designate formaldehyde as causal for leukemia, particularly myeloid leukemia (IARC, 2012).

**<3> Styrene and butadiene rubber manufacturing**

Workers in the styrene and butadiene rubber manufacturing industry have been repeatedly found to have excess mortality of total leukemia, more recently determined to be mostly due to CML, CLL, and, to a lesser extent myeloid neoplasms (IARC, 2008). Although the most recent follow-up data show only moderate excess risk of total leukemia, notable leukemia excesses were apparent in workers hired in the 1950s, those who were 20-29 hears since hire, and had worked >10 years . Risks were increased in areas of the plants with higher exposures and in hourly workers, especially those hired in the 1950s when exposures were higher. There were no measurements available before the 1970s. Average levels of butadiene from the 1970s through much of the 1980s ranged from 8-20 mg/m3 while those from the 1990s to the present have generally been <2 mg/ m3. Dose response relationships have been observed for butadiene with CML and with myeloid neoplasms, but estimates are imprecise due to small numbers of workesr with specific leukemia subtypes. Evidence of carcinogenicity was considered to be sufficient for leukemia in workers in the styrene and butadiene rubber manufacturing and for butadiene (IARC, 2008). An IARC Working Group reaffirmed this conclusion as part of the comprehensive re-evaluation published in IARC monograph 100f (2012).

**<3> Farming, agricultural and related exposures**

As described previously, some studies of farmers and farm workers have shown modest excess risks of AML and virtually all other subtypes of leukemia (risks ranging from 1.1-to-1.4-fold), while others have shown no increase in risk of AML (Linet et al, 2006). International variation in risks may reflect differences in agriculture-related exposures such as pesticides (particularly animal insecticides and herbicides), fertilizers, diesel fuel and exhaust, or infectious agents (Blair and Zahm, 1995). Few earlier studies that reported increased risk of AML among those living on a farm (Sinner et al, 2005; Wong et al, 2009) evaluated specific pesticide exposures in relation to AML. In the Agricultural Health Workers cohort, excess risk of leukemia was associated with use of chlordane and heptachlor (Purdue et al, 2007), alachlor (Lee et al 2004), and the organophosphates fonofos (Mahajan et al, 2006) and diazinon (Beane Freeman et al, 2005). Myeloid leukemia was increased among 20,000 persons residing in Seveso and ages 0-19 years within 10 years after an industrial accident caused contamination of the region with 2,3,7,8-*tetrachlorobibenzo-p-dioxin* (Pesatori et al, 1993). Recent review of the evidence for dioxin does not support a strong association with myeloid leukemia (IARC, 2012). Biomarkers are needed that provide information about long-term exposure to pesticides and that assess their chronic effects. Few studies have evaluated farming or agricultural work and risk of MDS or MPN and findings, to date, are inconsistent (Anderson et al, 2012).

**<2> MEDICATIONS**

**<3> Cytotoxic chemotherapy**

***<4> Overview***

Relative risks of developing t-MDS/AML following cytotoxic treatments are substantial (*e.g.*, ≥ 3-fold increased) and lifetime cumulative risks of t-MDS/AML range from <1 to 10% (Leone et al, 2010; Candelaria and Duanes-Gonzalez, 2015). Although data are limited on the changing occurrence of t-MDS/AML over calendar time, a 34-year assessment (1975-2008) of 426,068 adults treated with chemotherapy for first primary cancers in the population-based SEER Program demonstrated that there have been substantial changes in t-AML risks over time that are consistent with known changes in treatment practices (Morton et al, 2013). That study identified 801 cases of t-MDS/AML, a rate 4.7-fold higher than expected in the general population, with nearly half occurring after breast cancer or non-Hodgkin lymphoma. Over the study period (1975-2008), t-MDS/AML risks following treatment of NHL rose steadily, but declined over the calendar year period following treatment of ovarian cancer and multiple myeloma. t-MDS/AML rates were highest during 1975-78 after treatment of primary breast cancer and Hodgkin lymphoma, then declined during the 1980s, followed by modest increases in the 1990s. Risks for t-MDS/AML were highest among those treated with chemotherapy for primary cancers at younger ages, although elevated risks were apparent regardless of age at treatment. Excess absolute risks of t-MDS/AML were highest following treatment of Hodgkin lymphoma and of multiple myeloma; intermediate following treatment of lung and ovarian cancers and non-Hodgkin lymphoma; and lowest after treatment of breast cancer. Combination chemotherapy with radiotherapy non-significantly increased risks of t-MDS/AML after treatment of cancers of the lung, breast, and ovary, but not any of the lymphoproliferative malignancies. The 2008 WHO classification removed the distinction between alkylating agent-related and topoisomerase II inhibitor-related t-MDS/AML, but for etiologic purposes the literature on t-MDS/AML risks associated with these two categories of chemotherapy is discussed separately below.

***<4> Alkylating agents***

t-AML associated with alkylating agents generally occurs as a result of damage to DNA by methylation of DNA inter-strand crosslink formation. The main methylating forms of alkylating agents include procarbazine, dacarbazine, and temozolomide (Leone et al, 2009). Nitrosoureas and procarbazine are associated with a high risks of t-MDS/AML. For example, patients with Hodgkin lymphoma treated with MOPP (nitrogen mustard, vincristine, procarbazine and prednisone) had an absolute risk of developing t-MDS/AML of 3.4% compared with 1.3% for Hodgkin lymphoma patients treated with ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine), a regimen not including procarbazine. Busulfan and melphalan are linked with higher risk of t-AML than cyclophosphamide. As a result, cyclophosphamide has replaced busulfan and melphalan in several treatment regimens. Pathogenesis is frequently characterized by a preleukemic phase, tri-lineage dysplasia, and cytogenetic abnormalities involving monosomy of chromosome 5 or deletion of 5q and/or monosomy of chromosome 7 or deletion of 7q. t-MDS or t-AML cases with monosomy of chromosome 17 or deletion of 17p, dicentric chromosomes, duplication or amplification of chromosome band 11q23 and other karyotypic abnormalities, but without abnormalities of chromosome 5 often have methylation of the *CDKN4B* gene promoter and somatic mutations of *RUNX1* (Leone et al, 2009). t-MDS and t-AML have been reported subsequent to treatment of Hodgkin lymphoma, non-Hodgkin lymphoma, multiple myeloma, polycythemia vera, and breast, ovarian, and testicular cancers with alkylating agents. Typically, t-AML occurs 5-7 years following treatment, and risk is related to cumulative alkylating drug dose.

***<4> Topoisomerase inhibitors***

Topoisomerase II inhibitors that bind to the enzyme/DNA complex at the strand cleavage stage of the topoisomerase reaction have been linked with elevated risk of t-AML (Nitiss, 2009). As a result of blockage of the enzyme reaction, topoisomerase II inhibitors may leave DNA with a permanent DNA strand break. Both the anti-neoplastic effect and the leukemogenic effect of topoisomerase II inhibitors are due to chromosome translocation. Drugs that interact with topoisomerase II include epipodophyllotoxins that intercalate (such as doxorubicin) and those that don’t intercalate (such as etoposide and teniposide). With the more recent widespread introduction of topoisomerase II inhibitors, including anthracyclines, anthracenedione, and bisdioxopiperazine derivatitives, elevated risks of t-AML have been observed. The resultant t-AML is generally not preceded by MDS, develops after a shorter latency period (median latency typically 2-3 years), and has different cytogenetic abnormalities, in particular balanced translocations involving the *MLL* gene on chromosome band 11q23 (Cowell et al, 2012). Most *MLL* rearrangements are reciprocal translocations with many different partner genes including t(9;11) or t(4:11); others include internal duplications, deletions or inversions. Questions about the relationship between cumulative dose and frequency of treatment with epipodophyllotoxins with risk of t-AML remain, as some previous studies were limited by the use of chemotherapeutic regimens that include both topoisomerase II inhibitors and alkylating agents. Risks appear to be higher among those treated at younger ages. The resulting treatment-related leukemias may be myeloid (with the partner gene of *MLL* being chromosome 9) or lymphoid (with the partner gene being chromosome 4) in lineage; studies of gene expression profiles suggest that the leukemia originates within an undifferentiated hematopoietic stem cell.

***<4> Other chemotherapy agents used to treat cancer***

Platinum agents (e.g., cisplatin, carboplatin, oxaliplatin) are similar to alkylating agents in their mechanisms of action and resistance with the exception that they do not alkylate DNA but rather form covalent metal adducts with DNA (Chabner et al, 2011). Increasing doses of platinum-based chemotherapy for ovarian (Travis et al, 1999) and testicular cancers (Howard et al, 2008) have been quantitatively associated with increasing risks for t-AML. A 10-fold higher risk of t-MDS/AML has been observed in breast cancer patients treated with mitoxantrone and methotrexate or methotrexate and mitomycin C (Saso et al, 2000).

***<4> Antimetabolites for treatment of malignant and non-malignant conditions***

Antimetabolites, including methotrexate, azathioprine, 6-thioguanine, and fludarabine, are used for some cancer treatments, as immunosuppressants in autoimmune diseases, or in recipients of organ transplants, the latter often including combination treatment with cyclosporine A and steroids.The antimetabolites share structural similarities with nucleotides and can be incorporated into DNA or RNA, thus causing inhibition of cell proliferation. Risks may be higher in patients with low thiopurine S-methyltransferase activity and mechanisms may include aberrant mismatch repair and microsatellite instability (Karran, 2006). Increased risks of AML have been reported in patients treated with azathioprine after organ transplantation or for autoimmune disease (Yenson et al, 2008).

***<4> Other agents and uses***

t-MDS/AML is increased among patients treated with nucleoside analogs (such as fludarabine, which is used in treatment of patients with Waldenstrom’s macroglobulinemia) or nucleoside analogs in combination with alkylating agents (such as the combination of chlorambucil and fluderabine, which are used to treat patients with chronic lymphocytic leukemia (Leone et al, 2009). t-MDS/AML has also been associated with the intensity of pretransplantation chemotherapy (*e.g*., mechlorethamine) (Metayer et al, 2003) and/or conditioning treatments (*e.g*., total body irradiation) (Pedersen-Bjergaard et al, 2000), particularly at doses >12 Gy, or VP-16 in preparation for autologous stem cell transplantation for lymphoma and other malignant diseases (Metayer et al, 2003). Intensive efforts are underway to identifying host-related genetic variables that influence risk of developing t-AML .

***<4> Transformation of MPN to t-AML: role of single vs multiple treatments or other factors is unclear***

AML develops in patients with MPN including polycythemia vera, essential thrombocytopenia, and primary myelofibrosis (Abdulkarim et al, 2009). There is variability in the risks of developing AML after different forms of MPN (Barbui, 2004; Mesa et al, 2005; Passamonti et al, 2008). Mechanisms involved in transformation are not well understood, particularly because of the rarity of the event, the difficulty of disentangling the role of one or more treatments, and the likelihood that that the causes of transformation are multi-factorial. For example, in a nationwide Swedish cohort of 11,039 MPN patients diagnosed during 1958-2005, 292 patients developed AML (271) and MDS (21) (Bjorkholm et al, 2011) and a significantly increased risk of developing MDS/AML was observed among MPN patients who received ≥1,000 MBq 32P, but it was unclear whether the patients receiving this high dose of 32P had also received alkylating agents and/or hydroxyurea.

**<3> Other medications**

***<4> Chloramphenicol***

Use of chloramphenicol has long been linked with bone marrow depression and risk of aplastic anemia (Fraumeni, 1967). Some patients with this hematological disorder have developed AML (Cohen and Creger, 1967), but risk of AML following use of chloramphenicol is unclear because rigorous epidemiological data are lacking (Fraumeni , 1967). A dose-response relationship was observed between use of chloramphenicol and risk of for childhood AML and ALL in Shanghai (Shu et al, 1987), but studies in adults using medical or pharmacy records have shown no association (Doody et al, 1996) or a non-significant excess risk of acute leukemia (Traversa et al, 1998). Use of topical chloramphenicol was not significantly associated with risk of acute leukemia or AML based on data abstracted from general practitioner medical records in a large case-control study in the United Kingdom. In the U.K. study, risk was non-significantly increased if topical chloramphenicol was used 3 or more times, but there was no significant dose-response relationship (Smith et al, 2000).

***<4> Non-steroidal anti-inflammatory drugs***

Clinical reports described leukemia following treatment with phenylbutazone, but high-quality epidemiologic studies are limited. In a prospective study of hematopoietic neoplasms in a health maintenance organization for which pharmacy records were the basis of information, there was no evidence of a significant association or a relationship with duration or cumulative amount of use of phenylbutazone and myelocytic leukemia(Friedman, 1982).

Limited data have linked use of non-steroidal anti-inflammatory drugs (NSAIDs) with risk of AML, but findings generally show a modestly reduced risk. A case-control study in Los Angeles reported that use of NSAIDs was associated with a decreased risk of AML (Pogoda et al, 2005). Based on pharmacy records from the National Health System in the population-based case-control study in the Province of Rome, use of very high doses of NSAIDS was linked with a modest, non-significant reduction in risk of acute leukemia (Traversa et al, 1998 ). In case-control, interview-based studies in Buffalo (Weiss et al, 2006) and Minnesota (Ross et al, 2011), aspirin was associated with a decreased risk of AML and acetaminophen was linked with an increased risk. NSAIDS are characterized by anti-inflammatory, anti-pyretic and analgesic properties and target the COX enzymes, thus inhibiting prostaglandin synthesis, oxidative cell damage, angiogenesis, and potentially signal transduction pathways which are believed to influence risk of malignancy, although the specific mechanism that may be responsible in hematopoietic malignancies is unknown (Bernard et al, 2008).

**<1> LIFESTYLE FACTORS**

**<2> SMOKING**

Since the early 1990s, a substantial number of studies have reported associations of cigarette smoking with AML. A recent meta-analysis of 23 studies that included 7,746 AML cases reported significantly elevated risks for current smokers (RR = 1.40, 95% CI = 1.22-160) and ever smokers (RR = 1.25, 95% CI = 1.15-1.36) (Fircanis et al, 2014). Risks were notably higher for those who had smoked for ≥20 versus <20 years, and rose significantly with increasing number of cigarettes smoked per day and increasing number of pack-years smoked. A growing number of studies have evaluated cigarette smoking and risk of MDS. A meta-analysis of 14 studies that assessed 2,588 MDS cases found significantly elevated risks among current (RR = 1.81, 95% CI = 1.24-2.66) and ever (RR = 1.45, 95% CI = 1.25-1.68) smokers, along with higher risks among those who smoked for ≥20 versus <20 years, those who smoked ≥20 versus <20 cigarettes per day, and those with higher number of pack years of smoking (Tong et al, 2013). Combining AML and MDS in a meta-analysis of 25 studies with 8,074 cases of myeloid neoplasmss that overlapped with the above described meta-analyses, investigators found similar results as for AML alone (Wang et al, 2015). Risks for MDS/AML were significantly increased for current smokers (RR = 1.45, 95% CI = 1.30-1.62) and for ever smokers (RR = 1.23, 95% CI = 1.15-1.32), and were higher for those who smoked ≥20 versus < 20 years, ≥20 versus <20 cigarettes per day, and a greater number of pack years. Cigarette smokers are exposed to more than 70 chemicals that have been linked with cancer including known leukemogens including benzene, formaldehyde, and polonium-210 (CDC Surgeon General’s Report 2010). Smoking has been shown to decrease circulating CD34 progenitor cells in healthy persons (Ludwig et al, 2010) as well as decreasing the number of erythrocyte and granulocyte colony-forming units, upregulating toll-like receptor expression, increasing NF-kB, AKT, and ERK expression, and inducing IL-8 and TGF-b1 production (Zhou et al, 2011).

There have been fewer studies of cigarette smoking and risk of CML, with some (Kinlen and Rogot, 1988; Kabat et al, 2013; Musselman et al, 2013), but not others (Bjork et al, 2001; Fernberg et al, 2007; Strom et al, 2009; Richardson et al, 2008) finding an association. More recently, investigators examining the relationship of smoking with subtypes of MPN found polycythemia vera, but not essential thrombocythemia, associated with smoking (Leal et al, 2014). Leal and colleagues postulated etiologic differences, with smoking-related carcinogenic pathways linked with polycythemia vera, whereas obesity-related inflammatory pathways appeared to be more important for essential thrombocythemia. In a population-based case control study of myeloid leukemia, the elevated risk of AML associated with cigarette smoking declined with increasing number of years since quitting, while the risk reduction was more gradual for CML (Musselman et al, 2013).

**<2> DIET**

Overall, there have been a few exploratory studies assessing the possible role of diet in AML and even fewer in MDS and MPN. Two case-control (Li et al, 2006; Yamamura et al, 2013) and one cohort study (Ma et al, 2010) found that consumption of beef or meat in general increased risk of AML (Li et al, 2006; Ma et al, 2010; Yamamura et al, 2013), but no evidence of an association with level of doneness or meat mutagens (Ma et al, 2010). Findings are inconsistent, however, as to whether those who consume high levels of vegetables or fruits experience reduced risks of AML (Ma et al, 2010; Yamamura et al, 2013). Higher dietary intake of isoflavones was associated with reduced risk of MDS in a hospital-based case contol study in China (Liu, 2015).

**<2> ALCOHOL**

Some types of alcoholic drinks contain substances that have anti-carcinogenic properties, particularly polyphenols (Arranz et al, 2012). Evaluation of the relationship of alcohol consumption and acute myeloid leukemia has generally not found a relationship (Williams and Horm, 1977; Blackwelder et al, 1980; Hinds et al, 1980; Carstensen et al, 1990), demonstrated a modest inverse association Brown et al, 1992) or showed divergent results with reduced risks for light or moderate beer intake and increased risks for moderate to heavy red wine consumption (Rauscher et al, 2004).

Hospital-based, case-control studies assessing alcohol consumption and MDS have shown conflicting results (Ido et al, 1996; Liu et al, 2016), while a large cohort study found no association (Ma et al, 2010). A meta-analysis including 745 cases of MDS from five studies found a non-significant increase in MDS (RR = 1.31, 95% CI = 0.79-2.18) with higher alcohol consumption (Du et al, 2009). No association was observed between alcohol consumption and MPN in two cohort studies of women (Kroll et al, 2012; Leal et al, 2014).

**<2> BODY MASS INDEX (BMI)**

A meta-analysis including seven studies found an association of increasing BMI with increased risk of AML, which was estimated as a 3.1% increase in risk of AML per kg/m2. There were five studies in a meta-analysis of CML that revealed an increase in relative risk among obese, but not overweight persons, but there was no evidence of a linear trend (Castillo et al, 2012). A large cohort study found increasing risk of MDS with increasing level of BMI (Ma et al, 2009). A case-control study revealed that obesity in early life is as strongly associated with risk of AML as is obesity later in life (Poynter et al, 2016) The Iowa Women’s cohort study found that increased BMI was associated with increased risk of ET, but not PV (Leal et al, 2014). Although the biological mechanism(s) that may be responsible has not been clearly identified, possibilities include insulin-like growth factor-1 (which is increased in response to the insulin resistance associated with obesity and demonstrates mitogenic activity in myeloid and lymphoid leukemia cell lines), higher leptin levels (which is increased in obesity and affects proliferation and differentiation of myeloid leukemia cell lines), other hormonal alterations (such as adiponectin, insulin or sex steroids), or changes in the bone marrow environment (Karmali et al, 2015; Poynter et al, 2016).

**<2> HAIR DYE USE**

Hair dyes, particularly in past decades, contained some carcinogenic chemicals, but the chemical constituents have changed over time (IARC, 2010). Hair dye use, particularly dark hair dyes for longer duration, has been weakly linked with adult AML in a large case-control study(Rauscher et al, 2004), but not in a large cohort study (Altekruse et al, 1999). Most studies have found no relationship for total or specific types of leukemias (Correa et al, 2000; IARC, 2010; Zhang et al, 2012). Weak associations have been reported in some case-control studies of MDS (Ido et al, 1996), CML (Cantor et al, 1988) and essential thrombocythemia (Mele et al, 1996) based on small numbers of exposed cases and limited exposure data.

**<1> INFECTIOUS AGENTS**

Few studies have assessed the potential role of infectious agents in the etiology of myeloid neoplasms, and findings have not been consistent (Doody et al, 1992; Zheng et al, 1993). An intriguing finding was a positive association between early age at onset of childhood viral infections and risk of AML (Cooper et al, 1996). Excess risk of myeloid leukemia has also been reported in patients with AIDS (Shiels and Engels, 2012), but the reasons are unknown. In a large study in Sweden that linked hospital discharge data with population-based cancer registry data, the investigators found modest 30 percent statistically significant excess risks of adult AML and of MDS associated with a history of any prior infectious disease. These findings were based on elevated risks of AML in relation to prior pneumonia, tuberculosis, intestinal infections, septicemia, hepatitis C, pyelonephritis, sinusitis, nasopharyngitis, upper respiratory infections, meningitis, cytomegalovirus and cellulitis, with individual risk estimates ranging from 1.2-5.6, but the majority <2-fold elevated (Kristinsson et al, 2011). The elevated risks were still apparent when infections occurring less than 3 years before diagnosis were excluded. Increased risk of MDS was associated with prior history of pneumonia and cellulitis; again the elevated risks were apparent when a latency of 3 or more years was considered. The Swedish linked registry analysis was based on infections treated on an inpatient basis, without specific validation of the diagnoses of infection, and without available treatment data and other potentially confounding information. These associations need to be confirmed in other populations. Given the indolent nature of many MDS cases and the often lengthy period between onset and clinical diagnosis, future studies should consider long latency periods. Identification and validation of relevant infectious agents would be helpful if sufficient numbers of MDS cases could be evaluated in a large cohort pooling project as would animal studies to determine the likelihood that the associations are etiological in nature.

**<1> REPRODUCTIVE FACTORS**

Data are limited and inconsistent on the relationship between exogenous hormone use and myeloid neoplasms. A small population-based case-control study of acute leukemia in the Province of Rome described an increased risk of AML among women who took oral contraceptives based on drugs received through the National Health Service in Italy at least 12 months before diagnosis, while a small case-control study in Minnesota reported a protective effect between longer duration of oral contraceptive use and adult acute leukemia (Poynter et al , 2013). The Minnesota study found little evidence for an association between other reproductive factors or use of hormone replacement therapy and risk of myeloid leukemia overall or AML or CML specifically.

**<1> MEDICAL CONDITONS**

**<2> AUTOIMMUNE DISORDERS**

Using linkage of medical record or medical insurance information with population-based cancer registry incidence data has been used to to assess the relationship between autoimmune disorders and myeloid neoplasms. Kristinsson and colleagues considered 25 autoimmune disorders combined and found 1.7-fold increased risk of AML based on 359 AML patients with any autoimmune disease among 9,468 AML cases. The excess risk was somewhat lower (1.4-fold increased), albeit still significantly increased if autoimmune disorders diagnosed within 3 years of diagnosis of AML. Combining the same 25 autoimmune disorders, Kristinsson and colleagues reported that risk of MDS was increased 2.1-fold based on 133 patients with any autoimmune disorder among 1,662 MDS cases; excluding patients whose autoimmune disorders were diagnosed within 3 years of MDS diagnosis, a lower 1.7-fold excess risk was apparent (Kristinsson et al, 2011). Using a subset of the same Swedish linked registry data, Hemminki and colleagues reported a similar significantly elevated risk of AML associated with a combined grouping of 33 autoimmune diseases (standardized incidence ratio [SIR] = 1.85), and risks of similar magnitude for CML (SIR = 1.68), other myeloid leukemia (SIR = 2.20), but somewhat lower risk for myelofibrosis (SIR = 1.36) (Hemminki et al, 2013). Based on an evaluation of 27 autoimmune diseases and risk of myeloid neoplasms among patients ages 66-99 years old, results from a linkage of the U.S. population-based Surveillance, Epidemiology and End Results cancer registries with Medicare data revealed increased risks of AML (odds ratios [OR] = 1.29) based on 973 cases with any autoimmune disorder among of 7,824 with AML and MDS (OR = 1.50) based on 574 cases with any autoimmune disorders among 2,471 with MDS (Anderson et al, 2009). AML was associated with rheumatoid arthritis, systemic lupus erythematosus, polymyalgia rheumatic, autoimmune hemolytic anemia, systemic vasculitis, ulcertative colitis and pernicious anemia, while MDS was associated with ulcerative colitis and pernicious anemia, although many of these associations were based on small numbers. Risks were not increased for CML or MPN. Anderson and colleagues suggested that the associations could be due to medications used to treat the autoimmune disorders (including alkylating agents and azathiaprine), shared genetic predispositions between autoimmune disorders and myeloid neoplasms, or involvement of the bone marrow by the autoimmune disorders. Several case-control studies have found inconsistent associations of rheumatoid arthritis and myeloid neoplasms (Severson et al, 1989; Cartwright et al, 1988; Zheng et al, 1993; Cooper et al, 1996).

**<2> ORGAN TRANSPLANT PATIENTS**

Solid organ transplant recipients were found to have significantly elevated risk of all myeloid neoplasms (SIR = 4.6), AML (SIR = 2.7), MDS (SIR = 2.7), CML (SIR = 2.3) and polycythemia vera (SIR = 7.2) (Morton et al, 2015). Risks were highest among the patients who were youngest at the time of transplantation, and declined notably with increasing age at transplantation for all disease subtypes. There was some variability in risk by time since transplantation, although the patterns were not generally consistent except for a high rate in the first year for polycythemia vera that the investigators considered to potentially be spurious. Risks varied somewhat by type of organ transplant, with particularly high risk for lung recipients, which was consistent with increased AML and MDS risk associated with use of azathioprine and other antimetabolites as described above (Yenson et al, 2008). However, the relatively small numbers of any given type of transplant and subsequent myeloid neoplasm made it difficult to estimate risks precisely. The finding of increased risks of myeloid neoplasms following organ transplantation, which were similar to the elevated risk of myeloid neoplasms among patients with HIV/AIDS and those with autoimmune diseases, suggest that immune dysfunction may be important in the etiology of myeloid neoplasms. Since use of azathioprine in solid organ recipients has declined over time due to availability of alternate agents, it is possible that risks of myeloid neoplasms may decrease with follow-up of more recent organ recipients.

**<2> ALLERGIC DISORDERS**

Overall, the evidence is weak for a relationship of allergic disorders and myeloid neoplasms. Some (Severson et al, 1989), but not all (Cartwright et al, 1988; Doody et al, 1992; Zheng et al, 1993; Cooper et al, 1996), case-control studies reported a reduced risk of all or specific allergic conditions and AML. A U.S. cohort study found little evidence of a protective effect, but included small numbers of all types of leukemia cases combined (Mills et al, 1992). Another U.S. cohort study described no association of all or specific allergic conditions with myeloid neoplasms (Shadman et al, 2013). A Swedish cohort investigation reported that those with asthma and those with hives had an increased incidence of non-CLL leukemia based on small numbers of exposed cases. (Soderberg et al, 2004).

**<1> GENETIC RISK FACTORS**

Diverse lines of evidence provide strong support for a heritable component in the development of leukemia in general, and myeloid neoplasms in particular, but relatively few specific genes have been identified. Although individuals with a family history of leukemia have an elevated risk of developing leukemia themselves, familial aggregation of leukemia is rare. Stronger evidence for the genetic basis of leukemia derives from studies of patients with rare genetic syndromes, but these cases account for only a small proportion of leukemias. Substantial advances in molecular techniques in the last decade have enabled increasingly broad investigations of the potential role of common genetic variation in leukemogenesis. Such studies hold great promise for further advancing our understanding of genetic susceptibility to leukemia, particularly as they consider specific leukemia subtypes and account for potential interactions of genetic susceptibility with other leukemia risk factors.

**<2> FAMILIAL AGGREGATION AND RARE GENETIC SYNDROMES**

The few studies of familial AML pedigrees, which generally include individuals diagnosed across a broad age range and with different types of MDS/AML, have identified several predisposing rare germline mutations with varying penetrance. The most established of these are in *RUNX1*, *CEBPA*, and *GATA2*, transcription factors that are thought to regulate myeloid differentiation (Owen et al, 2008; Pan et al, 2015; Song et al, 1999; Hahn et al, 2011; Smith et al, 2004; Nickels et al, 2013; Churpek et al, 2013; Babushok et al, 2015). Familial platelet disorder with propensity to develop AML occur(s) due to mutations in *RUNX1* (Mangan and Speck, 2011). Key observations among individuals with this disorder include variable rates of hematologic abnormalities such as thrombocytopenia, bleeding, and abnormal platelet aggregation, and occurrence of a range of MDS/AML subtypes. Families with *GATA2* mutations also frequently demonstrate hematologic abnormalities, including MonoMac syndrome, which reduces monocytes, natural killer cells, and B cells and is associated with increased risk of infections; and Emberger syndrome, which is characterized by lymphedema. Risk of MDS/AML is strongly elevated, but penetrance is incomplete. In contrast, nearly all individuals in families with mutations in *CEBPA* eventually develop AML, most commonly acute myeloid leukemia with minimal maturation or actue myeloid leukemia with maturation, without preceding hematologic abnormalities.

Because of the rare nature of pure familial MDS/AML pedigrees, insight into the genetic basis of myeloid neoplasms is more likely to derive from studies of individuals with inherited genetic syndromes with diverse associated phenotypes or from investigation of common genetic variants for specific myeloid neoplasms, as discussed further below. However, several new susceptibility genes have been proposed recently based on familial aggregation. *TGM6* was identified as one such AML susceptibility gene based on linkage analysis and next-generation sequencing of a multi-generational family with 11 AML cases inherited in an autosomal dominant fashion, without a clear pattern of preceding hematologic abnormalities {Pan, 2015 #40}. In another study based on four families, germline duplication of *ATG2B* and *GSKIP* on 14q32.2 was recently reported in association with megakaryopoiesis, with frequent progression to AML but also the occurrence of CMML and CML {Saliba, 2015 #58}.  That study represents one of the few familial studies of myeloid neoplasms other than AML/MDS. Such studies are needed, based on data from large-scale, multi-generational cancer registries that show strong familial aggregation for MPNs {Landgren, 2008 #60} but not for CML {Bjorkholm, 2013 #59}.

A number of rare, inherited genetic syndromes are characterized by elevated risk for developing leukemia, although they have a diverse set of presenting features. The best studied of these are the bone marrow failure syndromes, including Fanconi anemia, dyskeratosis congenita, congenital neutropenia, and Shwachman-Diamond syndrome, which increase risk for both AML and MDS {Rommens, 2008 #3;Alter, 2010 #4;Alter, 2010 #4;Babushok, 2015 #55}. The magnitude of the risks can be difficult to quantify precisely because most studies include small numbers of patients. However, it is clear that risks of AML/MDS are striking in these patients. For example, in a cohort of patients with dyskeratosis congenita, risk for AML was approximately 200-fold increased, and risk for MDS was over 2000-fold increased {Alter, 2009 #51}. The mechanisms underlying these elevated risks are incompletely understood but are thought to relate to abnormal telomere maintenance, defective DNA repair, and abnormal hematopoietic differentiation and proliferation. Recent progress in understanding the genetic basis of these disorders in general holds promise for elucidating the mechanisms that confer such striking (extreme?) leukemia risks {Khincha, 2013 #56}. For example, the number of known susceptibility genes for dyskeratosis congenita has moved substantially beyond *TERT* and *TERC* to include a range of other genes {Federman, #5;Savage, 2008 #57}.

Other hereditary conditions associated with increased risk of AML/MDS include Li-Fraumeni syndrome, ataxia-telangiectasia, and Bloom syndrome {Varley, 1997 #6;Olsen, 2001 #8;Arora, 2014 #69;Ballinger, 2015 #71}. Although the precise mechanism of leukemogenesis is not known, it is likely related to underlying defects in genomic instability and DNA repair.

Familial monosomy 7, with inherited partial or complete monosomy 7 (a common cytogenetic abnormality in AML/MDS), is associated with increased risk of developing AML/MDS and is also associated with neurologic abnormalities, such as cerebellar ataxia or atrophy. {Gaitonde, 2010 #45}. As described further in Chapter 59, children with Down syndrome (trisomy 21) also have very high risk of developing AML {Bjørge, 2008 #12;Xavier, 2010 #13}. Whereas the genetic syndromes described previously generally increase risk for AML/MDS, neurofibromatosis 1 is associated with elevated risks for juvenile myelomonocytic leukemia (JMML), AML, and CML {Rosenbaum, 2014 #61;Seminog, 2013 #68}, and Noonan syndrome is associated with JMML {Strullu, 2014 #70}. Both of these associations may be related to *RAS* activation.

Twin studies have provided insight into the genetic basis and natural history of leukemia, most notably demonstrating that concordant occurrences of leukemia in monozygotic twin pairs have a common clonal origin {Greaves, 2003 #35;Greaves, 2003 #37}. Twins with concordant leukemia most frequently develop ALL {Alpar, 2015 #34;Couto, 2005 #2}, though some cases of AML have been reported {Udayakumar, 2014 #36;Ng, 1999 #38;Debeljak, 2013 #39}. However, these studies predominantly reflect childhood rather than adult leukemias.

**<2> COMMON GENETIC VARIATION**

Early studies of common genetic variation in germline DNA and leukemia risk yielded modest insights into leukemogenesis. Most studies focused on genes related to DNA repair, carcinogen metabolism, and folate metabolism because of the importance of ionizing radiation and chemical exposures in the etiology of leukemia {Bolufer, 2006 #14;Vijayakrishnan, 2010 #15}. However, results from these studies were often inconsistent, possibly due to limited statistical power, broad case definitions, and investigation of relatively few genetic variants.

With the advent of microarray technology for identifying large numbers of common genetic variants, agnostic interrogation of susceptibility variants across the entire genome is now possible. Although a number of genome-wide association studies (GWAS) have been performed for ALL, as described in Chapter 59, only four GWAS have investigated susceptibility loci for any type of myeloid neoplasm. A study of 671 CML cases of Korean and European descent identified CML susceptibility loci at 6q25.1 and 17p11.1 {Kim, 2011 #74}. Two GWAS of myeloproliferative neoplasms, with over 3500 cases, identified a number of susceptibility loci, including 3q26.2, 3p24.2, 5p15.33, 6q23.3, and 9p24.1 {Kilpivaara, 2009 #76;Tapper, 2015 #77}. The associations for some loci differed by *JAK2* mutation status, supporting the importance of uniform case definitions in such studies. Finally, a study of 150 cases of t-AML of European descent identified a locus at 17q12, albeit not at genome-wide significance, that appeared to have a greater effect when the case population was restricted to t-AML cases with abnormalities in chromosomes 5 and/or 7, which is highly correlated with antecedent alkylating agent exposure {Knight, 2009 #75}. That study supports the intriguing possibility that certain susceptibility variants may only confer risk in the presence of a particular leukemogenic exposure. To maximize the discovery potential for identifying germline susceptibility to myeloid neoplasms, future investigations should account for heterogeneity in both exposures and disease subtypes.

Attention is increasingly turning to the potential role of common genetic variation in relation to therapeutic response and disease prognosis. Results of initial studies that have focused on candidate genes that may confer drug resistance (e.g., drug metabolizing enzymes) have been conflicting and expanded pharmacogenetic studies and GWAS are underway {Drenberg, 2015 #49;Choi, 2013 #73}. For myeloid neoplasms, the investigation of germline variants related to therapeutic response and disease prognosis is in its infancy, in stark contrast to the extensive understanding of the prognostic as well as diagnostic importance of certain somatic changes.

Additional research is needed to understand the mechanisms by which putative loci may contribute to leukemia development or prognosis, and to identify other associated genetic loci. Important directions for future research will be to compare risks for different myeloid neoplasms, and to consider whether underlying susceptibility variants may interact with other leukemia risk factors {Knight, 2009 #20}.

**<1> OPPORTUNITIES FOR PREVENTION**

Advances in molecular biology, genetics, and mechanistic aspects of pathogenesis of myeloid neoplasms have been notable, but progress has been slower in identifying etiologic factors, which limits opportunities for prevention. Nevertheless, efforts should be made to reduce medical, occupational, and environmental exposures to radiation, and balance risks versus benefits of cytotoxic and other medications and chemicals implicated in myeloid neoplasms.

Radiologists, radiologic technologists, medical physicists, and manufacturers of x-ray equipment should continuously seek to optimize diagnostic radiologic procedures to provide clinically important information at the lowest possible doses achievable and to provide estimates of radiation exposure from such procedures to physicians and patients. Reducing radiation exposure from diagnostic procedures is a shared responsibility of the referring medical practitioner and the radiologist, with increasing input from professional societies in the form of evidence- and/or consensus-based guidelines about the most appropriate examinations or modalities produced by a panel of experts (<http://www.acr.org/quality-safety/standards-guidelines/practice-guidelines-by-modality/ct>; <http://www.acr.org/quality-safety/radiology-safety/radiation-safety>; Einstein et al, 2014). Unnecessary medical diagnostic radiologic procedures should be avoided. Radiation and medical oncologists should continue to weigh risks from leukemia, second cancers and other serious adverse effects (sequelae) from therapeutic radiation and from cytotoxic therapy against the clinical benefits. Newer radiation therapy techniques and modalities have been designed to limit radiation scatter to normal tissue from therapeutic radiation. Research is needed to ascertain whether t-AML and other second cancer risks are lower with newer radiotherapy techniques or modalities than with conventional radiotherapy. Similarly, research is needed to better understand the risks associated with newer cytotoxic agents and other systemic therapies (e.g., taxanes, immunotherapy).

Radiation workers should employ all radiation protective safety measures feasible. Medical radiation workers should actively seek maximal use of all personal protective measures (including full coverage lead aprons, thyroid shields, and lead goggles), other protective measures (room shields), maintenance of the longest distance feasible from radiation sources that is still consistent with good patient care, and use of all badge monitoring devices as recommended by radiation safety officers. Radiation safety officers, radiologists, and hospital administration should select x-ray equipment that provides the best visualization for the lowest possible exposures to patients and radiation workers, the greatest flexibility to incorporate adjustments for body size, and meaningful estimates of radiation exposure associated with radiological examinations. Nuclear workers should similarly use all recommended badge monitoring devices, and radiation safety officers should seek to reduce all unnecessary exposures.

Workers in industries that utilize benzene and formaldehyde in manufacturing, transport, or storage and those in the rubber manufacturing industry should regularly employ all personal protective (respirators, clothing and use of equipment to limit dermal exposures) and workplace safety measures (improve ventilation, reduce levels of these chemicals to the lowest achievable), wear monitoring devices, participate in formal safety training, and undergo regular evaluation to minimize their exposures to these chemicals. Manufacturers should reduce the percent of benzene in gasoline, paints, solvents and other sources. Formaldehyde levels should be reduced and alternative less toxic agents should be sought. Although further clarification is needed of the relation between specific pesticides and myeloid neoplasms, protective measures should be utilized in jobs and industries using such agents to limit exposures.

For the general population, the most important personal measure to reduce risk of myeloid neoplasms is to avoid use of tobacco, while gasoline service stations should continue to upgrade devices to minimize exposure to benzene by those who pump gasoline. While the association of myeloid neoplasm risk with body mass index remains to be elucidated, reducing overweight or obesity to normal weight has numerous other health benefits, including cancer prevention.

**<1> FUTURE DIRECTIONS**

AML has long been reported to population-based cancer registries, but other major categories and subtypes of myeloid neoplasms have not been included until recently in some countries or at all in others. With the rapid evolution of molecular markers, it is importantfor clinicians to incorporate the most recent guidelines into diagnostic evaluations, both for precision in disease classification anad selection of appropriate treatment. Incomplete disease registriaton or inadequate diagnostic evaluation of myeloid neoplasms in the general population is a major obstacle for characterizing patterns and trends. . Efforts are needed worldwide to completely ascertain, correctly diagnose and employ state-of-the-art molecular characterization of subtypes of AML, MDS, MPN, and MDS/MPN to facilitate progress in identifying etiologic factors, preventive measures, and appropriate therapies.

Epidemiologic studies have focused on acute myeloid leukemia and to a lesser extent on MDS, t-MDS/AML, and CML, but there has been little evaluation of risk factors for other subtypes of AML or of MPN or MDS/MPN. Gaps in understanding of pathogenesis of myeloid neoplasms remain, even for well-established risk factors. Epidemiologic studies of radiation and myeloid neoplasms have generally not evaluated subtypes of AML, MDS, MPN, or MDS/MPN.. The intriguing association of radiation dose and risk of MDS in the atomic bomb survivors requires further follow-up in that population and comprehensive dose-response assessment in other radiation-exposed populations.. The association of low-level benzene exposure with MDS and absence of associations with AML and MPN in the pooled Canadian, United Kingdom and Australian study should be examined in other populations with varying levels of benzene exposure and in relation to time since first exposure and other temporal characteristics. Incidence of myeloid neoplasms by major category and subtypes should be evaluated in exposed occupational populations in relation to dose response and temporal characteristics. Epidemiologic studies of cytotoxic agents have often focused on a single drug and have not adequately considered joint effects of multiple medications or confounding exposures. Most studies of well-established risk factors have not assessed genetic or familial factors in these associations.

Promising leads for further study include clarification of the association with body mass index, and the intriguing associations with infectious and inflammatory conditions from the linked registry study in Sweden. Although the statistical associations of selected autoimmune conditions and specific myeloid neoplasms have been reproduced in Swedish and U.S. populations, it will be clinically important to clarify whether these associations are related to medications used to treat these conditions, the conditions themselves, and/or genetic characteristics Further large-scale studies are needed to identify genetic predisposition to myeloid neoplasms, considering both rare, high-penetrant and more common low-risk variants. Such studies should consider both commonalities and differences in genetic susceptibility among the myeloid neoplasms..

Few epidemiologic studies to date have been designed specifically to assess risk factors for MPN. Most of the reports on MPN have derived from studies designed to focus on other outcomes or exposures not specifically implicated in occurrence of MPN. Data are limited on identification of determinants of transformation of MDS or MPN to AML. Clinically, it would be valuable to clarify what ‘exposures’ or genetic characteristics facilitate or protect against such transformation. Linked registry studies of transformation of MPN to AML have limited information on confounders and have not disentangled main effects under study from known or suspected confounding exposures.

The ultimate goal of epidemiologic research on myeloid neoplasms would be preventing occurrence of pre-leukemic and leukemic entities. The uncommon incidence of the major categories of myeloid neoplasms, changing classification schemes, and the rarity of subtypes within these major categories complicate efforts to undertake epidemiologic studies. Standard, single center case-control studies have limited power to identify statistical associations that are modest to moderate in level, even if such risk factors (*e.g.*, cigarette smoking, body mass index, or diagnostic radiological procedures) involve millions of persons and are of public health importance. Lack of reproducibility of findings and delays between reports from the few existing case-control studies have hampered progress. A multi-center, inter-disciplinary approach (e.g., epidemiologists working together with expert hematopathologists, clinical hematologists/oncologists, and experienced cancer registry staff) is needed. Strategies might include (1) establishment of large cohorts of newly diagnosed patients with specific pre-leukemic disorders for long-term follow-up to identify risk factors that increase risk of transformation and identify determinants that prevent transformation through cohort and nested case-cohort studies; (2) identification of cohorts of families with multi-generation occurrence of specific or mixtures of myeloid neoplasms for detailed genetic studies and investigations to assess gene-environment interaction; and, if feasible, (3) large population-based case-control studies of groups of patients with specific pre-leukemic disorders and of myeloid leukemias to evaluate and compare risk factors more generally.

The WHO 2001 and 2008 update of the classification of hematopoietic and lymphoid malignancies has transformed understanding of pathogenesis, clinical, and prognostic aspects of these disorders and offered new opportunities for epidemiologic research. Epidemiologic studies of myeloid neoplasms require a shift in standard methods as well as international, multi-disciplinary efforts to clarify risk factor differences and similarities across subtypes and to identify preventive measures.

**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.** U.S. 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 U.S. 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 U.S. 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.)