**PHYSICAL AGENTS**

**IONIZING RADIATION**

**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 CJ et al Radiat Res 2015). Radiation-associated leukemogenesis has been attributed primarily to interaction of radiation with DNA, either directly via ionization or indirectly via free radicals, that result in radiation-induced DNA double-strand breaks. 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 JD Environ Molec Mutagen2010). Radiation-related translocations demonstrate the greatest persistence of all types of chromosomal exchange and damage, and may be 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 be a correlate for the initiating radiogenic lesions leading to radiation-induced leukemia (Tucker JD Environ Molec Mutagen2010). Translocations may also represent a biomarker of effect because they have been found in most types of neoplasms (Kaye FJ Mol Cancer Ther 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 CJ et al Radiat Res et al 2015). It is hypothesized that HSCs with deleterious mutations would be removed and cells with advantageous mutations would be selected and preferentially expanded. Cells with damaged DNA initiate a response with the type of response differing between cycling HSCs, that preferentially initiate repair by homologous recombination repair, and quiescent HSCs that utilize the more error-prone non-homologous end-joining pathway. Thus, after irradiation, some HSCs may be characterized by radiation-induced genomic aberrations (Fleenor CJ et al Radiat Res 2015). In recent years, mouse models have provided valuable data on radiation-induced leukemogenesis, including clarification of genomic changes such as rearrangements, deletions, and changes in methylation (Rivina L et al Hum Genomics 2014).

**Individual and combined groupings of myeloid and other disorders and ionizing radiation**

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

**Medical radiation**

During the past few decades, there have been dramatic changes in medical sources of radiation exposure (NCRP 2009). The contribution from medical sources has increased 6-fold mostly due to the notable increase in diagnostic computed tomography (CT) scans and nuclear medicine cardiac examinations as well as the rapidly growing use of fluoroscopically-guided interventional procedures in an increasing number of medical specialties. The practice of radiotherapy has also been undergoing notable technical 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 normal tissue, but an overall reduction in the volume of normal structures receiving high doses. However, use of intensity modulated radiotherapy may include a larger volume of normal tissue within the irradiated field that receives low doses (Thariat J et al Diagn Intervent Imaging 2012) (see chapter 13).

Although most epidemiologic studies evaluating the association of diagnostic x-rays and risk of myeloid leukemia have relied on questionnaire data, a few have 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 (JD Boice et al JAMA 1991). In an interview and medical record-based study of AML 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 S and Pogoda JM Health Phys 2003), no association was observed between diagnostic x-rays and risk of adult AML among patients diagnosed during 1987-1994 (Pogoda JM et al Br J Cancer 2011). Radiographic procedures of the gastrointestinal tract and multiple spinal x-rays were linked with increased risk of chronic myeloid leukemia in a a case-control study in Los Angeles (Preston-Martin S et al Br J Cancer 1989). Three of four earlier studies of CML and diagnostic radiographic procedures (two based on medical records) reported small risks and one found a dose-response relationship with increasing numbers of x-ray films in the 20 years prior to diagnosis. Inconsistent findings in the limited numbers of epidemiologic studies along with the relatively small numbers of substantially exposed non-CLL leukemia cases preclude drawing firm conclusions (Linet MS et al CA Cancer J Clin 2012). Interpretation of findings must also consider potential methodologic limitations. Results linking diagnostic x-rays with risk of myeloid neoplasms may not reflect a causal relationship, but symptoms only recognized in retrospect as early clinical manifestations of myeloid leukemia (reviewed in Boice JD S & F 2006 and Linet et al S & F 2006). Patients developing myeloid neoplasms following standard radiographic or C-T x-ray examinations may be at high risk due to relatively rare genomic disorders such as Down syndrome (some of which are also characterized by radiation sensitivity) rather than x-ray exposures per se.

Risks of myeloid leukemias have been evaluated in relation to diagnostic radiologic examinations from 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/AML (IARC monograph 78 part 2, 2001; Travis LB et al Radiat Res 2003). During 1928-1954 between 2.5 and 10 million patients world wide were injected with Thorotrast. The estimated dose to bone marrow was 100 mGy from an injection of 25 ml. Elevated risk of MDS/AML persisted throughout the long 8-50 year latent period (Travis LB et al Radiat Res 2003), and cumulative risk ranged from 129-140 MDS/AML cases/104 persons per Gy (IARC monograph 78 part 2, 2001).

Elevated risks of myeloid neoplasms have been reported in patients with benign conditions who underwent radiation treatment. X-ray radiation treatment for anklylosing spondylitis was associated with a 7-fold increase in non-CLL leukemia during a period of 1-25 years after exposure to a uniform dose of 1 Gy; leukemia risk peaked within 10 years of exposure (Weiss HA et al Radiat Res 1995). 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 RR et al Rheumatology 2008). Somewhat lower AML excesses (relative risks ranging from 1.2 to 3.2) have been associated with x-ray radiation therapy treatments for benign gynecologic disorders (Sakata R et al Radiat Res 2012), peptic ulcer (Griem ML et al J Natl Cancer Inst 1994), and tinea capitis (Shore R et al Health Phys 2003). The ongoing use of radiotherapy to effectively 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 SR et al Br J Radiol 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 DGR et al J Med Genet 2006).

Radiation treatment-related AML (tAML) risks of about 2-fold have been described in patients treated for non-Hodgkin lymphoma, testicular cancer, uterine cervix cancer, uterine corpus cancer, Ewing’s sarcoma and total body irradiation for transplantation treatment (Wright JD et al Cancer 2010; NCRP Report 170 2011). In contrast, the elevated risks of t-AML associated with Hodgkin lymphoma and ovarian cancer are likely due to alkylating agents or other chemotherapy (Zeichner SB and Arellano ML Curr Treat Options in Oncol 2015). t-AML following treatment of testicular cancer has been linked with both radiotherapy and platinum chemotherapy (Travis LB et al Ann Epidemiol 2008). Similar to the temporal pattern for occurrence of AML among the Japanese atomic bomb survivors, t-AML following radiotherapy often appears within five years and most has arisen within 10-15 years (NCRP Report 170, 2011). Excess risks of 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 JD et al J Natl Cancer Inst 1987). See chapter 60 for more detail. Some evidence suggests that t-MDS/AML occurring among patients who receive more modern 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 V et al J Clin Oncol 2012).

**Atomic bomb survivors**

Long-term studies of the Japanese atomic bomb survivors have provided most important population-based quantitative risk assessment for the leukemias and other cancers. Studies of this population are the primary basis internationally of 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 JD S & F 2006; Linet MS et al S & F 2006; Mabuchi K et al 2011).

Leukemia incidence follow-up through 2001 among 113,011 Life Span Study cohort members ascertained 371 incident non-CLL leukemias, including 176 AML, 75 CML, and 43 ALL (Hsu et al, 2013). A nonlinear dose-response pattern observed for non-CLL leukemias derived primarily from results for AML, which demonstrated a nonlinear upward curving dose response. 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. 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 excess rates for ALL and CML accounted for 75% of the excess leukemias, but subsequently these two leukemia subtypes declined dramatically. Hsu et al (2013) speculated that CML and ALL rates may have been even higher within the first five years after the bombings (1945-1949), prior to availability of systematically ascertained data, and therefore the proportion of radiation-associated excess ALL and CML may have been even higher during the first decade after the bombings. The fraction of AML attributable to radiation among cohort members with >0.005 Gy was 38% for the entire period studied, although AML accounted for 80% of the excess leukemias during 1996-2001.

Leukemia mortality risks in atomic bomb survivors were first evaluated by subtype by Richardson and colleagues. The investigators followed up mortality among 86,611 survivors during 1950-2000 and identified 310 deaths from all forms of leukemia (Richardson et al Radiat Res 2009). 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 and recognition that a substantial proportion had MDS (Matsuo T et al, Jpn Journ Clin Oncol 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 Y et al Radiat Res 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% CI, 1.6 to 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 M et al J Clin Oncol 2011). Latency cannot be accurately determined prior to recognition of MDS in the mid-1980s, but the 40-year latency for the survivors after the mid-1980s is similar to that of *de novo* MDS cases, but differs from the median peak latency of 4-6 years observed for therapy-related MDS (Bhatia S Semin Oncol 2013). However, molecular characteristics of MDS in the atomic bomb survivors may resemble those of patients treated with alkylating agents since 6 of 13 patients with MDS in the atomic bomb survivors had *AML1* gene mutations compared with 5 of 13 patients treated with alkylating agents who developed therapy-related MDS/AML but only 2 of 27 patients with sporadic MDS (Harada H et al Blood 2003). Further study is needed to clarify the molecular features of MDS associated with different exposures.

**Military 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 JD S & F 2006). An excess of leukemia (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 GG et al JAMA 1980). Approximately 70,000 U.S. military who participated in one of five tests during the 1950s had a non-significant increase in risk for leukemia mortality (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 CR et al Occup Env 2003). None of these studies or others included estimated 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 doses in the various subsets of veterans to range from 9.5 to 24 mGy (Till J et al Radiat Res 2014).

Based on concerns raised about a possible association of leukemia among military exposed to ammunition reinforced by depleted uranium, Storm and colleagues followed up 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 HH Eur J Cancer 2006).

**Radiation workers**

Historically, 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 are the major categories of workers exposed to ionizing radiation (Wakeford J Radiol Prot 2009). Overall, iInterpretation of cancer risks and other serious disease findings of long-term studies of medical radiation workers is complicated due to dramatic ally declining radiation doses to workers over time (Linet MS et al Radiat Res 2010). As with most occupational epidemiologic studies of potentially leukemogenic exposures, information on potential confounders (worker’s 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). Studies quantifying risks of leukemia associated with protracted low-dose, low dose rate radiation exposures are important because: such radiation exposures are ubiquitous in the general population from personal medical radiologic procedures and the multiple sources of natural background radiation; very small risks could translate into meaningful numbers since millions of workers and most of the general population are exposed; and the findings from radiation worker studies contribute important information for recommendations about radiation protection measures (see chapters 13 and 16).

A large excess mortality risk (approximately 10-fold) of leukemia was initially reported among U.S. radiologists in 1944 (March HC et al, 1950). Eight major cohorts have been actively followed up for leukemia, other cancers, and chronic diseases (reviewed in Yoshinaga S et al Radiology 2004; Linet MS et al Radiat Res 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) risks ranging from 6- to 8.8-fold increased among those first joining professional societies (a proxy for first working) before 1940. Significantly elevated incidence risks of 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 who worked during 1950-1980. Leukemia risks declined notably over time, with no significant excesses observed in British radiologists entering the profession after 1921, in U.S. radiologists entering in 1940, or in U.S. radiologic technologists who first worked after 1950 (Yoshinaga S et al Radiology 2004; Linet MS et al Radiat Res 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 S et al Radiat Res 2014) will provide a useful basis for estimating risks per unit dose for hematologic malignancies, other cancers, circulatory diseases, and cataracts.

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. Results from individual and earlier studies can be found elsewhere (Boice JD S & F 2006; Polychronakis I et al J Occup Med Toxicol 2013). A 15-country study examining the relation between estimated cumulative occupational radiation dose and mortality risk of leukemia excluding CLL 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 E et al, BMJ 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 leukemias excluding CLL was significantly elevated (ERR per Gy = 2.96, 90% CI=1.17-5.21) based on 531 leukemia cases (Leuraud et al Lancet Haematol 2015). The mean cumulative occupational radiation dose across the three cohorts was estimated to be 15.9 (range 0.0-1217.5) mGy. The excess risk was primarily due to a significant increase of chronic myeloid leukemia (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 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. Radiat Res 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 than most nuclear workers (mean cumulative radiation dose of 92 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 LB et al, Environ Health Perspect 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 DF et al Ann Hematol 2015).

Radium dial painters, who experienced excess risks of osteosarcomas and cancers of the nasal sinuses, had no excess of myeloid malignancies (Boice JD S & F 2006). Epidemiologic studies of uranium miners (Tomasek L et al Lancet 1993; Darby S et al J Natl Cancer Inst 1995; Mc Laughlin J Radiat Prot Dosim 2012; Zablotska LB et al Environ Res 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 S et al J Natl Cancer Inst 1995). Studies of radium dial workers (Boice JD S & F 2006) have found no clear evidence of excess risk of myeloid neoplasms, although in males occupationally exposed to radium there is some evidence of an excess of leukemia, particularly the same form as seen in patients who received Thorotrast (Stebbings JH Health Phys 1998). The absence of radiation-induced leukemia in workers exposed to alpha-emitting radio-isotopes of radium and plutonium contrasts with the excess risk of MDS/AML observed in patients treated with Thorotrast (see below), although reasons are unclear (Harrison J J Radiol Prot 2009). Excess risks of acute myeloid leukemia were described in Canadian airline pilots (Band et al, AJE 1996) and in Danish cockpit crew flying more than 5,000 hours (Gundestrup M and Storm HH Lancet 1999), but pooled analysis of airline crew cohorts from 10 countries found no evidence of elevated myeloid leukemia risk (Hammer GP et al Occup Environ Med 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 deign, 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 RD and Schubauer-Berigan M Occup Environ Med 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 good agreement with the non-CLL leukemia risk from the Life Span Study of the atomic bomb survivors.

**Environmental radiation**

Although an ecological study suggested correlations between indoor radon and myeloid leukemia (Henshaw DL et al Lancet 1990), a comprehensive and critical review concludes that there was little evidence of a link (Laurier D et al Health Phys 2001). Fewer studies have examined natural background radiation and leukemia, although an intriguing evaluated approximately 80,000 stable residents residing in underground dwellings in China and experiencing about three-fold higher cumulative radiation levels (6.4 mSv) than the average worldwide found no evidence of an increase in leukemia (Wei L and Sugahara T J Radiat Res (Tokyo) 2000). Among the relatively 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 had individual measurements, and even those with measurements have been underpowered given the low radiation levels (Boice JD S & F 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 riskof 4.9 (95%CI=1.6-14.3) based on 70 non-CLL leukemia cases. No dose-response relationship was observed for CLL (Krestinina L et al Radiat Environ Biophys 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 D et al Radiat Prot Dosim 2008). A large ecologic investigation examined total and specific forms of adult cancers, including leukemia, but found no association (Jablon et al JAMA 1991). Limitations acknowledged by the authors include lack of measurements, no information about potential confounders, and likely underpowered nature of the study despite including a large population base and inclusion of more than 900,000 cancer deaths from 1950 through 1984 (Jablon S et al JAMA 1991). A borderline significant increase in risk of non-CLL leukemia and of acute lymphocytic leukemia 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 W et al JAMA 1990). Risks were significantly elevated for those exposed to fallout under age 20.

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

**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 energy produced by electromagnetic fields is too weak to break chemical bonds or cause translocations in DNA. The primary known biological effect is tissue heating. Electromagnetic fields generate energy that is proportional to the frequencies emitted; the frequencies are measured in hertz. 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 have mostly been studied in residential settings, in which most studies have assessed risks of pediatric leukemia and brain tumors (see chapters 15 and 59), or occupational settings.

**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 PK et al BMJ 1996) or Norway (Tynes T and Haldorsen T Cancer Causes Control 2003), but a borderline increase in risk of AML and CML among persons residing in homes in categories with the highest estimated fields in Sweden (Feychting M and Ahlbom A Epidemiology 1994). Risk of acute myeloid leukemia 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 United Kingdom (Elliott P et al Epidemiology 2013).

**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 (see chapter 16). A few studies that incorporated measurements as reviewed earlier reported inconsistent findings for AML (Linet MS et al S & F 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 (Kheifets L et al J Occup Environ Med 1997), was updated a decade later and reported a lower pooled estimate for AML (pooled RR = 1.09, 95% CI=0.98-1.21). Risk for CML was also lower in the more recent meta-analysis compared with the earlier one (original pooled RR = 1.24, 95% CI=0.98-1.57; new pooled RR=1.11, 95%CI=0.94-1.31) (Kheifets et al J Occup Environ Med 2008). 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 C et al Occup Environ Med 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 T Cancer Causes Control 2014).

**Radiofrequency exposures**

There is little evidence that myeloid neoplasms are increased among people using mobile telephones or living in proximity to base stations (IARC Monographs Vol 102 2013). There are few epidemiologic studies of workers exposed to radiofrequency fields, and some of these are difficult to interpret. In general leukemia and myeloid leukemia were not increased (IARC Monographs Vol 102 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 FD et al Am J Epidemiol 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.

**CHEMICAL EXPOSURES: MANUFACTURING, FARMING, MEDICATIONS**

**MANUFACTURING**

**Benzene**

Benzene has been used for more than a century as a key component in the manufacturing of shoes, leather, and rubber goods, paint, 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 monograph 100F, 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 acute myeloid leukemia (AML). The updated assessment by IARC noted that cohort studies in multiple industries and different countries demonstrated a dose-response pattern for AML (IARC monograph 100F 2012). Myeloid and lymphoid neoplasms as well as many other types of cancer have been described following benzene exposure to mice and rats (IARC Monograph 100F 2012). A systematic review and meta-analysis of four studies focusing on cumulative exposure to AML found evidence of a dose-response pattern with 3.2-fold relative risks for benzene exposure levels > 100 ppm-years although the trend was not statistically significant (Khalade A et al Environ Health 2010). Data on AML at low levels have been relatively limited due to small numbers of cases. 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 AML/MDS (2.7, 95%CI=0.8-9.5, based on 7 cases) were non-significantly increased (Hayes RB et al J Natl Cancer Inst 1997). In a pooled and updated analysis of three case-control studies carried out among petroleum distribution workers from Australia, Canada and the United Kingdom with low levels of benzene exposure, AML risks increased monotonically, but the trend was not significantly increased in relation to cumulative (<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) exposure (Schnatter AR et al J Natl Cancer Inst 2012; Rushton L et al Br J Cancer 2013). Dose-response trends were not as clearcut for other benzene exposure metrics in the 3-country study, although risks were highest in the top quartiles of average and maximum exposure and increased in those with peak exposure <3 ppm. Significantly elevated AML risks were observed those who worked as tanker drivers for at least one year compared with those who were never tanker drivers for a year. AML/MDS was associated with recent, but not distant exposure among Chinese benzene-exposed workers (Hayes RB et al J Natl Cancer Inst 1997). Data from the long-term follow-up of a cohort of U.S. pliofilm workers suggests that the excess risk of leukemia diminished with time since exposure (Rinsky R et al Am J Indus Med 2002). In addition to AML, benzene also causes hematotoxicity at very low measured levels in workers (Lan Q et al Science 2004). Some (Talbott EO et al Environ Res 2011; Raaschou-Nielsen O et al Int J Cancer 2016), but not all (Wilkinson P et al Occup Environ Med 1999) studies have reported increased risks of AML among community members exposed to gasoline vapors, traffic-related air pollution, or residence in proximity to oil refineries. Efforts are underway to understand mechanisms underlying leukemogenesis by identifying the critical genes and pathways that are involved in inducing genetic, chromosomal and epigenetic abnormalities and genomic instability in hematpoietic stem cells, altered proliferation and differentiation of the hematopoietic stem cells, and dysregulationof stromal cells (McHale et al Carcinogenesis 2012). These effects are likely modulated by benzene-induced oxidative stress, reduced immunosurveillance, and aryl hydrocarbon dysregulation.

Data are more limited for benzene and MDS. Risks of mortality from MDS were significantly increased among benzene-exposed (7 cases) compared with unexposed workers (0 cases) in the Chinese benzene exposed workers (Linet et al Int J Cancer 2015). Cumulative benzene exposure demonstrated a monotonic dose-response relationship and significant trend with increasing dose for MDS in the pooled 3-country (Australia, Canada, and United Kingdom) study of petroleum distribution workers (OR=4.33, 95%CI=1.31-14.3 at cumulative exposure >2.93 ppm-years, based on a total of 29 cases with all levels of cumulative exposure (Schnatter AR et al J Natl Cancer Inst 2012). Higher risks for MDS were observed among workers employed at terminal facilities and among tanker drivers employed for at least one year. 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.

In the relatively few studies that have examined CML, this hematopoietic disorder has not been consistently linked with benzene exposure (IARC monograph 100F 2012; Khalade A et al Environ Health 2010), although a meta-analysis found a moderate increase in CML in studies of benzene workers that commenced follow-up after 1970 (Vlaanderen J et al Am J Indus Med 2012). MPD has only been studied in the 3-country investigation. Dose-response trends for CML (based on 28 cases) and MPD excluding CML (based on 30 cases) were not statistically significant for cumulative, average, or maximum benzene exposure in the 3-country study, but risks rose notably with increasing cumulative dose experienced 2-20 years before diagnosis of CML and for MPD excluding CML (Glass DC et al Occup Environ Med 2014).

**Formaldehyde**

Concerns have arisen about health effects, including leukemia, associated with formaldehyde given the widespread exposures among workers in health care, embalming, and manufacturing as well as to the general population from increased indoor levels in new homes. In follow-up of 25,619 worked in 10 plants employed in manufacturing involving formaldehyde exposure during 1966-2004, risk of myeloid leukemia was associated with peak exposures. The myeloid leukemia risk appeared to be highest before 1980, but only achieved statistical significance in the mid-1990s when sufficient numbers of deaths had occurred. Risks were highest in the first 25 years following exposure, and declined with continuing follow-up (Hauptmann M et al J Natl Cancer Inst 2003; Beane Freeman L et al J Natl Cancer Inst 2009). The pattern was consistent with the wavelike exposures observed for myeloid leukemia seen for other chemical exposures (Linet MS et al S & F 2006).

Follow-up of a cohort of embalmers identified from national and state funeral directors’ associations and licensing boards, a nested case-control study was carried out that included embalmers who died from leukemia and selected other cancers during 1960-1986 (Hauptmann M et J Natl Cancer Inst 2009). Risk of myeloid leukemia rose significantly with increasing number of years of embalming, increasing number of embalming performed, increasing estimated lifetime formaldehyde exposure in ppm-years, and increasing peak formaldehyde levels. A study of 43 formaldehyde exposed vs 51 unexposed workers in China demonstrated numerical chromosomal aberrations in myeloid progenitor cells (including chromosome 7 monosomay and chromosome 8 trisomy) consistent with myeloid leukemia as well as other hematologic changes in peripheral blood that demonstrate effects on bone marrow (Zhang L et al CEBP 2010). Meta-analyses have provided evidence in favor (Schwilk E et al. J Occup Environ Med 2010) and against (Bachand AM et al Crit Rev Toxicol 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 Monographs Vol 100f 2012).

**Butadiene and rubber manufacturing**

Workers in butadiene manufacturing have been repeatedly found to have excess leukemia mortality, mostly due to CML and CLL. Large excesses were seen in workers employed in areas of the plants with higher exposures and in hourly workers, especially those hired in earlier years when exposures were higher. There are no measurements before the 1970s. Early measurements ranged from 8-20 mg/m3 while more recently exposures are generally <2 mg/ m3 (IARC Monographs Vol 100f 2012). Evidence of carcinogenicity was considered to be sufficient for leukemia in workers in butadiene manufacturing (IARC Monograph vol 100f 2012), but recent leukemia subtype-specific risks do not appear to be elevated for AML or CML from follow-up of workers in U.S. styrene butadiene rubber industry (Sielken RL Chem Biol Interact 2015). Excess risks of leukemia have been described in several cohorts of rubber manufacturing workers and the conclusion by an IARC Working Group that there was sufficient evidence linking rubber manufacturing with leukemia in 1982 was reaffirmed in the 2012 publication that also noted that the excess may be due to solvents, in particular benzene (IARC Monographs Vol 100f 2012).

**Farming, agricultural and related exposures**

As described previously, some studies of farmers and farm workers have shown modest excesses of AML as well as virtually all other subtypes of leukemia (risks ranging from 1.1-to-1.4-fold elevated), while others have shown no increase in risk of AML (Linet MS et al S & F 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 A and Zahm SH Environ Health Perspect 1995). Few earlier studies that reported increased risk of AML among those living on a farm (Sinner PJ et al CEBP 2005; Wong O et al Regul Toxicol Pharmacol 2009) evaluated specific pesticide exposures in relation to AML. In the Agricultural Health Workers cohort excess risk of leukemia has been associated with use of chlordane and heptachlor (Purdue MP Int J Cancer 2007), alachlor (Lee WJ et al Am J Epidemiol 2004), and the organophosphates fonofos (Mahajan R et al Environ Health Perspect 2006) and diazinon (Beane Freeman Am J Epidemiol 2005). Biomarkers are needed that provide information about long-term exposure and that assess chronic effects. Few studies have evaluated farming or agricultural work and risk of MDS or MPN (Anderson LA et al Am J Hematol 2012) and findings are inconsistent.

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 Monographs Vol 100f 2012).

**MEDICATIONS**

**Cytotoxic chemotherapy**

***Overview***

Therapy-related myeloid neoplasms (t-MN), a new entity included in the 2008 WHO classification, includes therapy-related MDS (t-MDS) and therapy-related AML (t-AML). Therapy-related MDS occurs infrequently (0.8% - 6.8% in 20-year follow-up of patients treated with conventional chemotherapy), but is an often fatal complication of cytotoxic treatments for malignant and non-malignant diseases. t-MDS 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, t-MDS 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-AML than in *de novo* AML (Godley LA and Larson RA Semin Oncol 2008). Relative risks of developing t-MDS/AML following cytotoxic treatments are substantial (*e.g.*, ≥ 3-fold increased) and lifetime cumulative risks range from <1 to 10 % for t-AML (Leone G et al Chem Biol Interact 2010; Candelaria M and Duanes-Gonzalez A Exp Opin Drug Safety 2015). Although data are limited on changing occurrence of t-AML from cytotoxic therapy over calendar time, a 34-year assessment (1975-2008) of 426,068 adults treated with cytotoxic therapy for first primary cancers in the population-based SEER Program identified 801 t-AML (with nearly half occurring after breast cancer or non-Hodgkin lymphoma). The rate of t-AML was estimated to be 4.7-fold higher than the expected rate of AML in the general population (Morton LM et al Blood 2013). Based on data from the SEER population registries, the proportion of patients with non-Hodgkin lymphoma receiving chemotherapy increased during the period 1975-2008 and t-AML rates rose among these patients. However, t-AML declined for ovarian cancer and multiple myeloma during the same period, likely as a result of changes in treatments. t-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-AML were highest among those treated at younger ages, although elevated risks were apparent regardless of age at treatment. Excess absolute risks of t-AML were highest for Hodgkin lymphoma and multiple myelom; intermediate for lung and ovarian cancers and non-Hodgkin lymphoma; and lowest after breast cancer. Combination chemotherapy with radiotherapy non-significantly increased risks of t-AML after treatment of cancers of the lung, breast, and ovary, but not any of the lymphoproliferative malignancies.

***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 G Chem Biol Interact 2009). Nitrosoureas and procarbazine are associated with a higher risk of t-AML. Busulfan and melphalan are linked with higher risk of t-AML than cyclophosphamide. 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 the *RUNX1* gene (Leone G Chem Biol Interact 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.

***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 JL Nat Rev Cancer 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). More recently, other forms of chemotherapy that inhibit topoisomerase II may induce t-AML, including anthracyclines, anthracenedione, and bisdioxopiperazine derivatitives. 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 IG et al Proc Natl Acad Sci USA 2012). There are questions about whether there is a relationship between cumulative dose or with frequency of treatment with epipodophyllotoxins and risk of t-AML. 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. 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.

***Other chemotherapy agents used to treat cancer***

Increasing doses of platinum-based chemotherapy for ovarian (Travis LB et al N Engl J Med 1999) and testicular cancers (Howard R et al Ann Epidemiol 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 R et al Br J Cancer 2000). t-MDS/AML has also been associated with the intensity of pretransplantation chemotherapy (*e.g*., mechlorethamine (Metayer C et al Blood 2003) and/or conditioning treatments (*e.g*., total body irradiation (Pedersen-Bjergaard J et al Blood 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 treatment-related AML .

***Antimetabolites for treatment of malignant and non-malignant conditions***

Antimetabolites are used for some cancer treatments, as immunosuppressants in autoimmune diseases, or in recipients of organ transplants, the latter often including combination treatment withcyclosporine A and steroids. These agents include azothioprine, 6-thioguanine, and fludarabine. 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 P Br Med Bull 2006). Increased risks of AML have been reported in patients treated with azathioprine after organ transplantation or for autoimmune disease (Yenson PR et al Am J Hematol 2008).

***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 K et al Eur J Haematol 2009). There is variability in the risks of developing AML after different forms of MPN (Barbui T Semin Hematol 2004; Mesa RA et al Blood 2005; Passamonti F et al Haematologica 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 M et al J Clin Oncol 2011) and a significantly increased risk of developing MDS/AML was observed among MPD 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.

**Other medications**

***Chloramphenicol***

Use of chloramphenicol has long been linked with bone marrow depression and risk of aplastic anemia (Fraumeni JF Jr JAMA 1967). Some patients with this hematological disorder have developed acute myeloid leukemia (Cohen and Creger Am J Med), but risk of AML following use of chloramphenicol is unclear because rigorous epidemiological data are lacking (Fraumeni JF Jr JAMA 1967). A dose-response relationship was observed between use of chloramphenicol and risk of for childhood acute myeloid and acute lymphoblastic leukemia in Shanghai (Shu XO et al Lancet 1987), but studies in adults using medical or pharmacy records have shown no association (Doody MM et al Epidemiology 1996) or a non-significant excess risk of acute leukemia (Traversa G et al Pharmcoepidemiol Drug Safety 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 UK study, risk was non-significantly increased if topical chloramphenicol was used 3 or more times, but there was no significant dose-response relationship (Smith AG et al Pharmacoepidemiol Drug Safety 2000).

***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, but a non-significantly increased risk was observed for musculoskeletal disease at least 5 years before diagnosis of myelocytic leukemia (Friedman GD J Chron Dis 1982).

Limited data have linked use of non-steroidal anti-inflammatory drugs (NSAIDS) with risk of acute myeloid leukemia, but findings are inconsistent. A case-control study in Los Angeles reported that use of NSAIDS was associated with a decreased risk of AML (Pogoda JM et al Int J Cancer 2005). In case-control interview-based studies in Buffalo (Weiss JR et al Leuk Res 2006) and Minnesota (Ross JA et al CEBP 2011), aspirin was associated with a decreased risk and acetaminophen linked with increased risks of AML. Use of very high doses of NSAIDS was linked with a modest, non-significant reduction in risk of acute leukemia based on pharmacy records from the National Health System in the population-based case-control study in the Province of Rome (Traversa G et al Pharmacoepidemiol Drug Safety).

***Others***

An intriguing association was a reduced risk for AML linked with use of traditional Chinese medicines in a large hospital-based case-control study in Shanghai (Wong O et al Regul Toxicol Pharmacol 2009).

**LIFESTYLE FACTORS**

**SMOKING**

Since the early 1990s, a substantial number of studies have reported associations of cigarette smoking with AML. Recent meta-analyses have examined the relationship. A 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). Risks were notably higher for those who had smoked for 20 or more years than for those who smoked fewer than 20 years, and rose significantly with increasing number of cigarettes smoked per day and increasing number of pack-years smoked (Fircanis S et al Am J Hematol 2014). A growing number of studies have evaluated cigarette smoking and 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), along with higher risks among those who smoked for 20 or more years than for those who smoked fewer than 20 years, those who smoked 20 or more cigarettes per day than less than 20, and those with higher number of pack years of smoking (Tong H et al PLoS One 2013). Combining AML and MDS in a meta-analysis of 25 studies with 8,074 myeloid neoplasms case that overlapped with the above described meta-analyses, investigators found similar results as for AML alone. Risks for MDS/AML were significantly increased relative risks 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 more than 20 vs less than 20 years, more than 20 cigarettes per day than few than 20, and a greater number of pack years (Wang P et al PLoS One 2015). There have been fewer studies of cigarette smoking and CML, with some (Kinlen and Rogot BMJ 1988; Kabat GC et al CEBP 2013; Musselman JR et al Can Ep 2013), but not others (Bjork J et al Occup Environ Med 2001; Fernberg P et al Cancer Res 2007; Strom SS et al CEBP 2009; Richardson DB 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 AD et al Int J Cancer 2014). 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 JR et al Cancer Ep 2013).

**DIET AND ALCOHOL**

Overall, there have been relatively few studies of the possible role of diet in AML and even fewer for MDS and MPN. Two case-control (Li Y et al Leuk Res 2006; Yamamura Y et al Nutr Cancer 2013) and one cohort study (Ma X et al Am J Epidemiol 2010) have found that consumption of beef or meat in general increases risk of AML (Li Y et al Leuk Res 2006; Ma X et al Am J Epidemiol 2010; Yamamura Y et al Nutr Cancer 2013). Findings are inconsistent, however, as to whether those who consume high levels of vegetables or fruits experience reduced risks of AML (Ma X et al Am J Epidemiol 2010; Yamamura Y 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 P Br J Nutr 2015).

Older studies generally have not supported a role for alcohol consumption in the etiology of adult AML (Williams RR and Horm JW J Natl Cancer Inst 1977; Blackwelder WC et al Am J Med 1980; Hinds MW et al Br J Cancer 1980; Carstensen JM et al Int J Cancer 1990; LM Brown et al, 1992a). Hospital-based case control studies assessing alcohol consumption and MDS have shown conflicting results (Ido M et al Leuk Res 1996; Liu P et al Cancer Causes Control 2016), while a large cohort study found no association (Ma X et al Am J Epidemiol 2009). 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 Y et al Leuk Res 2009). No association was observed between alcohol consumption and MPN in two cohort studies of women (Kroll ME et al Br J Cancer 2012; Leal AD et al Int J Cancer 2014).

**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 JJ et al Leuk Res 2012). A large cohort study found increasing risk of MDS with increasing level of BMI (Ma X et al Am J Epidemiol 2009). The Iowa Women’s cohort study found that BMI was associated with increased risk of ET, but not PV (Leal AD et al Int J Cancer 2014).

**HAIR DYE USE**

Hair dye use, particularly dark hair dyes for longer duration, has been weakly linked with adult AML in a large case-control study(Rauscher GH et al Am J Epidemiol 2004), but not in a large cohort study (Altekruse S et al Cancer Causes Control 1999). Weak associations have been reported in some case-control studies of MDS (Ido et al Leuk Res 1996), CML (Cantor KP et al Am J Publ health 1988) and essential thrombocythemia (Mele A et al Cancer 1996) based on small numbers of exposed cases and limited exposure data (Correa A et al Cancer Investig 2000; IARC Monograph 99 2010).

**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 MM et al Cancer Causes Control 1992; Zheng W et al Cancer Causes Control 1993). An intriguing finding was a positive association between an early age at onset of childhood viral infections and risk of AML (Cooper GS et al Cancer Epidemiol Biomark Prev 1996). Excess risk of myeloid leukemia has also been reported in patients with AIDS (Shiels and Engels Cancer 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, cytomegalo virus and cellulitis (with individual risk estimates ranging from 1.2-5.6, but the majority <2-fold elevated) (Kristinsson SY et al J Clin Oncol 2011;29:2897-2903). 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 for a 3 year latency. The Swedish linked registry analysis was based on infections treated on an inpatient basis, there was no specific validation of the infectious disease diagnoses,and treatment and other potentially confounding information was not available. If these associations are confirmed with adequate latency periods and potential confounders appropriately evaluated, potential mechanisms would need to be identified.

**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 acute myeloid leukemia 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 JN et al Br J Cancer 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.

**MEDICAL CONDITONS**

**AUTOIMMUNE DISORDERS**

A limited number of case-control studies have examined risk of autoimmune disorders and risk of myeloid disorders and found inconsistent findings for rheumatoid arthritis (Severson RK et al J Coin Epidemiol 1989; Cartwright RA et al Leuk 1988; Zheng W et al Cancer Causes Control 1993; Cooper GS et al Cancer Epidemiol Biomark Prev 1996). Cohort studies in the Nordic countries have used linkage of hospital discharge data with population-based cancer registry incidence data to assess 25 (Kristinsson SY et al J Clin Oncol 2011;29:2807-2903) and 33 (Hemminki K Br J Haematol 2013;161:677-87) autoimmune disorders with systemic involvement, specific organ involvement and diseases without autoantibodies and risk of AML and MDS for the former study, and also CML, other myeloid and myelofibrosis for the latter study. For all autoimmune disorders combined, Kristinsson and colleagues found risk of AML to be increased 1.7-fold based on 359 patients with any autoimmune diseases out of 9,468 AML cases (or 1.4-fold for latency of at least 3 years) and risk of MDS to be increased 2.1-fold based on 133 patients with any autoimmune disease out of 1,662 cases (or 1.7-fold for latency of at least 3 years). Since the data sets were overlapping, it is not surprising that Hemminki and colleagues reported similar significantly elevated risks for all autoimmune diseases and risk of AML, but these investigators reported risks of similar magnitude for CML (standardized incidence ratio [SIR] was 1.68), other myeloid (SIR was 2.20) and myelofibrosis (SIR was 1.36). A U.S . study based on a linkage of the population-based Surveillance Epidemiology and End Results cancer registries with Medicare data evaluated the relationship of 27 autoimmune diseases and risk of myeloid neoplasms among 13,486 patients aged 67-99 years old, including 7,824 with AML, 2,174 with CML, 2,471 with MDS, and 1,017 with MPN diagnosed durin 1987-2002 (Anderson LA et al Br J Cancer 2009;100:822-8).

**ALLERGIC DISORDERS**

**OTHER DISORDERS**

**MOLECULAR AND GENETIC FACTORS**

**FAMILIAL AGGREGATION**

**GENETIC SYNDROMES**