ISSN: 2230-9926

Available online at http://www.journalijdr.com

IJDR

International Journal of Development Research
Vol. 15, Issue, 04, pp. 68293-68297, April, 2025
https://doi.org/10.37118/ijdr.29429.04.2025

RESEARCH ARTICLE OPEN ACCESS

UNRAVELING THE CAUSES OF ACUTE LEUKEMIA: A COMPREHENSIVE REVIEW OF GENETIC AND ENVIRONMENTAL FACTORS

Deepak Sharma[1], Alma Ruman Khan[2], Abhishek Mishra*[3]

[1]Research Scholar, Department Medical Laboratory Sciences, Faculty of Allied Health Sciences, Integral University, Lucknow, Uttar Pradesh, India; [2]Lecturer, Department of Medical Laboratory Sciences, Faculty of Allied Health Sciences, Integral University, Lucknow, Uttar Pradesh, India; [3]Lecturer, Department of Medical Laboratory Sciences, Faculty of Allied Health Sciences, Era University, Lucknow, Uttar Pradesh, India

ARTICLE INFO

Article History:
Received 14th January, 2025
Received in revised form
26th February, 2025
Accepted 08th March, 2025
Published online 30th April, 2025

Key Words:
AML, Epigenetics, Leukemia.

***Correspondingauthor:** **Abhishek Mishra**

ABSTRACT

Background: One of the most prevalent cancers afflicting people worldwide is leukemia. Leukemia was the eleventh leading cause of death from malignant illnesses worldwide in 2018, accounting for 437,033 cases and 309,006 fatalities, making it the fifteenth most prevalent diagnosed malignancy. Acute leukemias are malignant clonal illnesses of blood-forming organs that affect one or more hematopoietic system cell lines. These conditions are characterized by a broad substitution of aberrant immature and undifferentiated hematopoietic cells for bone arrow, which lowers the quantity of erythrocytes and platelets in the peripheral circulation. These illnesses are categorized according to the hematopoietic cells affected, such as lymphoid, myeloid, mixed, or undifferentiated. On the other hand, a wide range of illnesses known as chronic leukemias are distinguished by the unchecked growth and division of adult, differentiated hematopoietic system cells. Therefore, the type of hemopoietic cells involved determines the classification of chronic leukemias. Environmental factors that increase the risk of developing acute myeloid leukemia (AML) include smoking, benzene exposure, chemotherapy, and radiation treatment. AML is the most common acute leukemia in adults and accounts for 15–20% of cases in children. Acute myeloid leukemia (AML) is a genetically heterogeneous disease that is characterized by malignant clonal proliferation of immature myeloid cells in the bone marrow, peripheral blood, and occasionally other body tissues. AML can potentially originate from myeloproliferative neoplasm (MPN) or myelodysplastic syndrome (MDS). With an overall 5-year survival rate of about 25%, the prognosis for the majority of AML subtypes remains bleak despite their extreme variability. The risk of relapse and the possibility of remission are influenced by the genetic and epigenetic makeup of the cancerous cells. Gaining more knowledge about the underlying genetic and epigenetic mechanisms could help identify novel treatment targets, prognostic factors, and the mechanism of leukemogenesis in AML. Many molecular mutations in AML have well-documented prognostic effects. Less is known about the function of mutations in genes with epigenetic function, though.

Citation: Deepak Sharma, Alma Ruman Khan, Abhishek Mishra. 2025. *"*Unraveling the Causes of acute Leukemia: A Comprehensive review of Genetic and Environmental Factors*". International Journal of Development Research*, 15, (04), 68293-68297.

INTRODUCTION

One of the most prevalent cancers afflicting people worldwide is leukemia. Leukemia was the eleventh leading cause of death from malignant illnesses worldwide in 2018, accounting for 437,033 cases and 309,006 fatalities, making it the fifteenth most prevalent diagnosed malignancy (Bray, 2018). Acute leukemias are malignant clonal illnesses of blood-forming organs that affect one or more hematopoietic system cell lines. These conditions are characterized by a broad substitution of aberrant immature and undifferentiated hematopoietic cells for bone marrow, which lowers the quantity of erythrocytes and platelets in the peripheral circulation. These illnesses are categorized according to the hematopoietic cells affected, such as lymphoid, myeloid, mixed, or undifferentiated. On the other hand, a wide range of illnesses known as chronic leukemias are distinguished by the unchecked growth and division of adult, differentiated hematopoietic system cells. Therefore, the type of hemopoietic cells involved determines the classification of chronic leukemias (Tebbi, 2021).Environmental factors that increase the risk of developing acute myeloid leukemia (AML) include smoking, benzene exposure, chemotherapy, and radiation treatment. AML is the most common acute leukemia in adults and accounts for 15–20% of cases in children (Ferrara and Schiffer, 2013). Acute myeloid leukemia (AML) is a genetically heterogeneous disease that is characterized by malignant clonal proliferation of immature myeloid cells in the bone marrow, peripheral blood, and occasionally other

body tissues (O'Donnell, 2012). AML can potentially originate from myeloproliferative neoplasm (MPN) or myelodysplastic syndrome (MDS). With an overall 5-year survival rate of about 25%, the prognosis for the majority of AML subtypes remains bleak despite their extreme variability (Estey, 2013). The risk of relapse and the possibility of remission are influenced by the genetic and epigenetic makeup of the cancerous cells. Gaining more knowledge about the underlying genetic and epigenetic mechanisms could help identify novel treatment targets, prognostic factors, and the mechanism of leukemogenesis in AML. Many molecular mutations in AML have well-documented prognostic effects. Less is known about the function of mutations in genes with epigenetic function, though (Lin, 2011; Abdel-Wahab, 2012; Okiand, 2010 and Shih, 2012). Therefore, the purpose of this review of the literature is to investigate the pathogenic function and prognostic significance of mutations in epigenetic modifying genes.

Genetics: The etiology of leukemia is unquestionably heavily influenced by genetics. A description of the large amount of recent research on the role of genetic variables in normal hemopoiesis, the transition to acute leukemias, and leukemogenesis pathways is well outside the purview of this comprehensive study. Identical twins exhibit the strongest genetic influences on the pathophysiology of acute leukemias. The other identical twin has twice the risk of getting the disease compared to the general population if one of them gets it before the age of seven. Over time, the likelihood of getting leukemia decreases. This illness compared to the general population. The twin who lives to be 15 years old without getting leukemia doesn't seem to be at a higher risk of getting it than the general population (Zipf, 2000 and Falletta, 1973). A higher prevalence of leukemia is linked to certain genetic and acquired germline mutations as well as clonal chromosomal abnormalities, even though there are no clear known predisposing factors for the majority of leukemia cases (Falletta, 1973).More and more germline mutations that can result in leukemia-prone alterations have been found through genome-wide association studies. Leukemia may be more likely to occur in patients with constitutional chromosomal abnormalities and DNA repair problems. Leukemia risk may be increased by some hereditary mutations, but only if extramedullary characteristics are not present. Leukemia is more common in some families even if there are no known inherited abnormalities. The genes CEPBA, RUNX1, and GATA2 have been found to be autosomal dominantly inherited and may contribute to the development of leukemia. A protein belonging to the bZIP family, granulocytic differentiation factor C/EBPa, is encoded by the CEBPA gene, which is found on chromosome 19q13.1 (Papaemmanuil, 2014). The transcription factor RUNX1, which is involved in hemopoiesis, is found at 21q22.12. The GATA2 gene, which is found at 3q21.3, controls phagocytosis and maintains the integrity of hematopoietic stem cells. Congenital neutropenia and MonoMAC syndrome, a condition that commonly leads to myelodysplastic syndrome (MDS), an elevated risk of infections, and AML, or chronic myelomonocytic leukemia, have been linked to GATA2 mutations (Falletta, 1973). There have been reports of monosomy 7 in families where several members have both AML and MDS. Leukemia can also arise from inherited bone marrow failure syndromes that have a number of genetic defects (Tebbi, 2021). Clonal hematopoiesis of indeterminate potential (CHIP) is a common asymptomatic condition that increases the risk of developing hematological malignancies by expanding age-related somatic mutations in the hematopoietic lineages of aging individuals. CHIP-associated mutations and genetic alterations in the hematopoietic stem cells and progenitors have the potential to redirect their development and result in the pathogenesis of hematological malignancies. Recent advancements in the study of cancer genomics and single cell molecular analysis have allowed for a detailed examination of the clonal population and their genetic and time-related sequences of genetic and epigenetic evolutions (Heuser, 2016). These could contribute to a better understanding of how clonal evolution plays a major role in the initiation, development, and resistance of lymphoid and myeloid malignancies. Many signaling pathways and their function in the development of leukemias have been better understood as a result of genome-wide study. New constitutional genetic mutations and their relationship to environmental mutagens and infections will probably be discovered through additional genomic and epidemiologic research to cause malignant hematological clones and eventually lead to full-fledged leukemia (Steensma, 2015). Leukemic transformation events can involve multiple factors. For instance, a secondary somatic mutation is required to activate the ETV6-RUNX1 fusion gene, which is acquired in utero and is present in about 25% of pediatric ALL cases. RAG-mediated deletions were found to be the main driver of this mutational process in one study that used exome and low-coverage whole genome sequencing to assess the events leading up to this oncogenic rearrangement (Papaemmanuil, 2014). ATF7IP and MGA were found to be tumor suppressor genes in ALL by combining the data of point mutations and rearrangements. Thus, ETV6-RUNX1-positive lymphoblasts undergo a multifactorial mutational process that targets the promoters, enhancers, and first exons of genes that typically govern B-cell development (Wang, 2011).

Age and Ethnicity: After heart disease, cancer is the second leading cause of death worldwide. The COVID-19 pandemic had a major impact on cancer detection and treatment in 2020–2021. Closing healthcare facilities led to a temporary decrease in the prevalence of leukemia and cancer as well as decreased access to care (Cancer Statistics, 2021). But this was followed by a rise in advanced illness, which in turn led to higher death rates. Due to low cancer awareness, late leukemia discovery, and unequal or restricted access to reasonably priced treatment choices, cancer patients in low- and middle-income nations, like India, frequently have a worse prognosis than those in high-income nations (Molyneux, 2020). With 1.3 billion people spread throughout several states and territories, leukemia is distributed unevenly in India because of genetic heterogeneity in populations, environments, and lifestyles as well as different growth rates (Lancet Oncol, 2018).The Global Burden of Leukemia Injuries and Risk Factors Study and the India State-Level Illness Burden Initiative collaborated to develop subnational illness burden estimates for India. Variations in health status among Indian states from 1990 to 2016 were recently published using data from the Global Burden of Disease (GBD). 10,500 children (years 0–14) and 5,090 teenagers (ages 15–19) were predicted to receive a cancer diagnosis in 2016, with 1,190 and 590 of them passing away from the illness, respectively. These estimates, however, are based on 15 years of historical incidence data and do not include benign and borderline malignant brain tumors, which were not required to be reported to cancer registries until 2004. Leukemia is the most common type of cancer in children, making up 28% of cases. With 27% of cases, brain and other nervous system cancers rank second, with more than 25% of these being benign or borderline malignant. This study provides a comprehensive overview of the incidence and trends in health-related mortality for leukemia and cancer in India between 1990 and 2019 (Nalage, 2024).

Environment and Occupations: Numerous environmental factors have been proposed as contributing to the development of leukemia. These primarily entail exposure to substances that cause cancer at different periods of life, such as chemicals, infections, and radiation (Finch, 2007). Certain vocations, hobbies, industrial risks, and exposures have all been linked to an increased risk of leukemia (Kleinerman, 2006). There is uncertainty and even debate over the relationship between specific jobs and the incidence of acute leukemias. Jobs in the oil and gas industries with exposure to benzene, oil refining and petrochemicals, automobile mechanics, electrical utility workers, jobs with exposure to magnetic fields, jobs in the nuclear power industry with exposure to ionizing radiation, furniture manufacturing and repair, nursing and health care positions with exposure to infectious agents and viruses, and agricultural, forestry, and crop production jobs with exposure to pesticides and fertilizers are among the occupations linked to an increased risk of leukemias (Adegoke, 2003; Descatha, 2005; Brown, 1990; Wong, 2010; BeaneFreeman, 2012; DiGiacomo, 1997; Aksoy, 1985 and SenioriCostantini, 2003). Teachers, employees in the shoe and boot manufacturing business, drivers and conductors of taxis, buses, trucks, and railroads, hairdressers and hair dyers, painters, laundry workers, and dry cleaners who are exposed to dry cleaning chemicals

are among the other professions with a higher risk of leukemia. Jobs that expose workers to formaldehyde and alkylating chemicals, such as those in the textile and semiconductor industries, are also linked to an increased risk of leukemia. It is proposed that contact with employees in these industries increases the risk of leukemia (Guénel, 2002; Glass, Schwartz, 1987 and Bethwaite, 2001). In various vocations, leukemia development has been linked to direct and indirect exposure to chemicals and pesticides. Similarly, leukemia has been linked to direct or indirect exposure to hydrocarbon chemicals like trichloroethylene, gasoline, and benzene. Similarly, several variables, such as the jobs held by parents, have been suggested to raise the incidence of acute leukemia in children (Ahlbom, 2000; Kleinerman, 2000; Mahoney, 2004; Shu, 2002 and Belson, 2008).

Radiation's Effects: There have been several hypotheses and published examples about the role of ionizing radiation exposure in the development of leukemia at different stages of life, such as preconception, in utero, and postnatal exposures. There has been evidence of a link between leukemia incidence and radiation dosage. After the bombings of Hiroshima and Nagasaki, Japan, survivors who lived within 1000 meters of the bombs had a 20-fold greater incidence of leukemia than the overall population (Sali, 1996). Regarding the danger of leukemia development with exposure to diagnostic X-rays, there are contradictory findings. Studies have indicated a link between paternal diagnostic X-rays and an increased incidence of juvenile leukemia. Two or more lower abdominal X-rays were observed to enhance the risk. However, if the data were limited to X-rays of the lower abdomen, no elevated risk was observed. In one investigation, maternal abdomen X-rays did not appear to enhance the risk of leukemia. If the father had previously undergone an intravenous pyelogram or had multiple abdominal X-rays performed before to conception, there was some indication that the offspring would be at higher risk (Infante-Rivard, 2003 and Ahlbom, 2000).

Infections: Leukemogenesis has been linked to infections, including bacterial, viral, and fungal agents both by themselves and in combination with genetic alterations (Tebbi, 2020). There is evidence linking infectious agents to the emergence of acute leukemias in particular and cancer in general (Tebbi, 2020). Nevertheless, there is currently no reliable agent that can be consistently administered to a group of patients, with the exception of a few recent findings. Numerous infectious organisms have been hypothesized and investigated in relation to the development of leukemia, including the Epstein-Barr virus (EBV), herpesvirus, human immunodeficiency virus (HIV), severe acute respiratory syndrome (SARS), COVID 19, and human T-lymphotropic virus (HTLV-1) (Lehtinen *et al*., 2003; Bartenhagen *et al*., 2017). It is commonly known that EBV and Burkitt's lymphoma are related in the endemic region of Eastern Africa. Even though there is a strong correlation, the results are not always applicable. For instance, the 8;14 chromosomal translocation, which causes constitutive activation of the c-Myc oncogene, p53 mutations, variations in viral gene expression in certain patients, the actions of EBV oncoproteins, and numerous other similar factors make the association more difficult to understand. There have been reports of EBV exposure within the first two years of life leading to a positive serological response and the emergence of Burkitt's lymphoma (Tebbi *et al*., 2020; Wiemels, 2012). Adult T-cell leukemia/lymphoma (ATL) has been associated with human T-cell leukemia virus type 1, commonly referred to as human T-lymphotropic virus (HTLV-1), most likely as a result of the virus's DNA or RNA being inserted into the host cell. It is estimated that HTLV-I causes ATL in about 5% of carriers following a latent period. Through the actions of encoded viral proteins, such as Tax (Matsuoka, 2003), it is postulated that HTLV-I promotes the in vivo clonal growth of HTLV-I infected cells. Mice with monoallelic deletion of the B-cell transcription factor PAX5 are more likely to develop B-cell ALL if they are exposed to infections (Hauer, 2015).

Acute Myeloblastic Leukemia: Acute Myeloblastic Leukemia (AML) has two peaks in occurrence, during early childhood and later in adults. The median age of newly diagnosed AML patients is 66 years old. Although the illness can strike at any age, it is somewhat uncommon to be diagnosed before the age of 40.The development of myelodysplastic syndromes (MDS) into AML is thought to be partially responsible for the rising incidence with aging. Common chromosomal abnormalities shared with MDS and a higher likelihood of an adverse prognosis are characteristics of MDS-related AML. According to estimates, there were 7.7 incidences of acute myeloblastic leukemia per million children aged 0–14 between 2005 and 2009. The incidence rate in the pediatric age group peaks during the first year of life and then steadily declines until the age of four. The incidence is 18.4 per million in infants under one year of age (Xie, 2003). Apart from MDS, the etiology of AML is mostly uncertain. There is a substantial body of knowledge and information about leukemogenic agents, particularly chemotherapy regimens used to treat a range of cancerous conditions. There have been reports linking AML to specific molecular etiology, including chromosomal 16 inversion and t(8;21) translocation. Alongside these genetic modifications, epigenetic modifications have also been identified in the pathophysiology of AML, including promoter silencing caused by hypermethylation of the p15/INK4b and other genes. There is evidence linking AML, particularly in youngsters, to certain hereditary variables, such as genetic abnormalities. Patients with certain genetic diseases, such as Down syndrome, are significantly more likely to acquire malignant conditions, including AML (Khan, 2011 and Lagunas-Rangel, 2017). It has been determined that certain types of acute promyelocytic leukemia (APML) exhibit unique chromosomal and gene-rearrangement abnormalities. These could vary depending on where you are in the world. For instance, there has been evidence of a higher occurrence of APML in children from Southern Europe and adult patients from Latin America, although the genetic rearrangement in these two regions differs. This might suggest that a certain breakpoint site could be in charge in several places. It is well established that an elevated risk of AML is linked to certain polymorphisms in the genes that metabolize toxins. For instance, the enzyme NAD(P)H:quinoneoxidoreductase 1 (NQO1) detoxifies quinones and lowers oxidative stress. It also metabolizes carcinogens. These enzymes' activity is reduced by a polymorphism at nucleotide 609 of the NQO1 complementary DNA, which may lead to therapy-related AML (Smith, 2001).

Acute Lymphoblastic Leukemia: Acute lymphoblastic leukemia (ALL) accounts for around 25–30% of all children malignant diseases, making it the most common malignancy diagnosed in this age range. Between the ages of 0 and 14, the yearly incidence of acute lymphoblastic leukemia in the US is around 4.6 cases per 100,000, peaking between the ages of 2 and 5. In the first year of birth, girls are somewhat more likely than boys to have ALL (Gurney, 1995). Like other leukemias, ALL has been linked to the role and potential consequences of several factors, as mentioned above. The effects of environmental factors, such as parental preconception, ionizing radiation exposure during pregnancy and after delivery, the risks of nonionizing radiation, chemicals, infections, hydrocarbons, and pesticides, as well as the effects of parental alcohol, cigarette, and illicit drug use, have all been investigated in relation to the development of ALL in offspring. It is commonly known that a higher incidence of leukemia is linked to certain genetic abnormalities, such as Shwachman syndrome, Down syndrome, neurofibromatosis, Fanconi anemia, Bloom syndrome, and ataxia-telangiectasia. AML is more common in certain of these conditions than ALL, including Fanconi anemia and Down and Bloom syndromes. Although genetic disorders that cause ALL only make up a relatively tiny percentage of cases, the fact that they are linked to a higher incidence of the illness suggests that genetics plays a significant role in leukemogenesis (Pui, 2019). Hyperdiploidy, hypodiploidy, BCR-ABL1, ETV6-RUNX1 or TCF3-PBX1 fusions, PAX5 or ETV6 mutations, MLL rearrangements, or B-ALL-specific trachromosomal amplification of chromosome 21 (iAMP21) are among the genetic changes that are unique to each ALL immunophenotype in B-cell ALL. T-cell ALL is characterized by changes in LMO2, TAL1, TAL2, TLX1, TLX2, or HOXA (Andersen, 2001). About 80% of B-lineage ALL patients in western developed nations contain either a high-hyperdiploid leukemic clone or an

ETV6/RUNX1 translocation. It is suggested that they were started in utero. Only 1% of babies in good health have cord blood cells that are translocation t(12;21)[ETV6/RUNX1]-positive. It is suggested that a comparatively greater incidence of ALL in children in affluent nations is caused by a decreased likelihood of early infection exposure. Conversely, it is hypothesized that a lower incidence of pediatric ALL occurs in developing nations due to increased virus exposure and maybe malnutrition. These elements are thought to enhance the cellular response to cortisol and the release of cortisol during infections (Schmiegelow, 2008).

CONCLUSION

A large percentage of malignant illnesses are acute leukemias. These cancers impact all age groups, including children, and are found worldwide but at varying rates in different parts of the world. Although there have been reports linking important causal elements to the development of acute leukemias, the exact cause of these illnesses is still unknown. There are signs that recent developments in genetics and epigenetics contribute to leukemogenesis in acute leukemias. Similarly, research has been done on the impact of environmental variables, such as infections. Recent discovery of an antibody to a mycovirus containing Aspergillus flavus in ALL patients in complete remission, along with the reemergence of genetic and cell surface phenotypes typical of ALL when PBMN cells from these patients—rather than normal controls—are exposed to the organism's products, may open up new avenues for leukemogenesis research. There needs to be more study to support the necessary tenets of hypotheses on how acute leukemias form when genetics and environment interact.

Conflicts of Interest: The author declares no conflict of interest.

REFERENCES

Shih, A. H., O. Abdel-Wahab, J. P. Patel, and R. L. Levine, "The role of mutations in epigenetic regulators in myeloid malignancies," *Nature Reviews Cancer,*vol. 12,no.9,pp.599 612, 2012.

Adegoke, O.J.; Blair, A.; Shu, X.O.; Sanderson, M.; Jin, F.; Dosemeci, M.; Addy, C.L.; Zheng, W. Occupational history and exposure and the risk of adult leukemia in Shanghai. *Ann. Epidemiol.* 2003, 13, 485–494.

Ahlbom, A.; Day, N.; Feychting, M.; Roman, E.; Skinner, J.; Dockerty, J.; Linet, M.; McBride, M.; Michaelis, J.; Olsen, J.H.; *et al*. A pooled analysis of magnetic fields and childhood leukaemia. *Br. J. Cancer* 2000, 83, 692–698.

Ahlbom, A.; Day, N.; Feychting, M.; Roman, E.; Skinner, J.; Dockerty, J.; Linet, M.; McBride, M.; Michaelis, J.; Olsen, J.H.; *et al*. A pooled analysis of magnetic fields and childhood leukaemia. *Br. J. Cancer* 2000, 83, 692–698.

Aksoy, M. Malignancies due to occupational exposure to benzene. *Am. J. Ind. Med.* 1985, 7, 395–402.

Andersen, M.K.; Christiansen, D.H.; Jensen, B.A.; Ernst, P.; Hauge, G.; Pedersen-Bjergaard, J. Therapy-related acute lymphoblastic leukaemia with MLL rearrangements following DNA topoisomerase II inhibitors, an increasing problem: Report on two new cases and review of the literature since 1992. *Br. J. Haematol.* 2001, 114, 539–543.

Bartenhagen, C.; Fischer, U.; Korn, K.; Pfister, S.M.; Gombert, M.; Chen, C.; Okpanyi, V.; Hauer, J.; Rinaldi, A.; Bourquin, J.P.; *et al*. Infection as a cause of childhood leukemia: Virus detection employing whole genome sequencing. *Haematologica* 2017, 102, e179–e183.

BeaneFreeman, L.E.; Deroos, A.J.; Koutros, S.; Blair, A.; Ward, M.H.; Alavanja, M.; Hoppin, J.A. Poultry and livestock exposure and cancer risk among farmers in the agricultural health study. *Cancer Causes Control.* 2012, 23, 663–670.

Belson, M.; Kingsley, B.; Holmes, A. Risk factors for acute leukemia in children: A review. Environ. Health Perspect. 2007, 115, 138–145.

Bethwaite, P.; Cook, A.; Kennedy, J.; Pearce, N. Acute leukemia in electrical workers: A New Zealand case-control study. Cancer Causes Control 2001, 12, 683–689.

Bray, F.; Ferlay, J.; Soerjomataram, I.; Siegel, R.L.; Torre, L.A.; Jemal, A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J. Clin.* 2018, 68, 394–424.

Brown,L.M.; Blair, A.; Gibson, R.; Everett, G.D.; Cantor, K.P.; Schuman, L.M.; Burmeister, L.F.; Van Lier, S.F.; Dick, F. Pesticide exposures and other agricultural risk factors for leukemia among men in Iowa and Minnesota. *Cancer Res.* 1990, 50, 6585–6591.

Cancer Statistics, 2021. Siegel RL, Miller KD, Fuchs HE, Jemal A. *CA Cancer J Clin.* 2021;71:7–33. doi: 10.3322/caac.21654.

Descatha, A.; Jenabian, A.; Conso, F.; Ameille, J. Occupational exposures and haematological malignancies: Overview on human recent data. *Cancer Causes Control.* 2005, 16, 939–953.

DiGiacomo, R.F.; Hopkins, S.G. Food animal and poultry retroviruses and human health. *Vet. Clin. N. Am. Food Anim. Pract.* 1997, 13, 177–190.

E.H.Estey, "AcutemyeloidLeukemia: 2013updateonrisk stratification and management," *American Journal of Hematology,* vol. 88, no. 4, pp. 318–327, 2013.

F. Ferrara and C. A. Schiffer, "Acute myeloid Leukemia in adults," The Lancet, vol. 381, no.9865, pp.484–495, 2013.

Falletta, J.M.; Starling, K.A.; Fernbach, D.J. Leukemia in twins. Pediatrics 1973, 52, 846–849

Finch, S.C. Radiation-induced leukemia: Lessons from history. Best *Pract. Res. Clin. Haematol*. 2007, 20, 109–118.

Glass, D.C.; Gray, C.N.; Jolley, D.J.; Gibbons, C.; Sim, M.R.; Fritschi, L.; Adams, G.G.; Bisby, J.A.; Manuell, R. Leukemia risk associated with low-level benzene exposure. *Epidemiology* 2003, 14, 569–577.

Guénel, P.; Imbernon, E.; Chevalier, A.; Crinquand-Calastreng, A.; Goldberg, M. Leukemia in relation to occupational exposures to benzene and other agents: A case-control study nested in a cohort of gas and electric utility workers. *Am. J. Ind. Med.* 2002, 42, 87–97.

Gurney, J.G.; Severson, R.K.; Davis, S.; Robison, L.L. Incidence of cancer in children in the United States. Sex-, race-, and 1-year age-specific rates by histologic type. *Cancer* 1995, 75, 2186–2195.

Hauer, J.; Martín-Lorenzo, A.; Sánchez-García, I. Infection causes childhood leukemia. Aging 2015, 7, 607–608.

Heuser, M.; Thol, F.; Ganser, A. Clonal Hematopoiesis of Indeterminate Potential. Dtsch. Arztebl. Int. 2016, 113, 317–322.

Infante-Rivard, C.; Deadman, J.E. Maternal occupational exposure to extremely low frequency magnetic fields during pregnancy and childhood leukemia. *Epidemiology* 2003, 14, 437–441.

Khan, I.; Malinge, S.; Crispino, J. Myeloid leukemia in Down syndrome. *Crit. Rev. Oncog.* 2011, 16, 25–36.

Kleinerman, R.A. Cancer risks following diagnostic and therapeutic radiation exposure in children. *Pediatr. Radiol.* 2006, 36, 121–125.

Kleinerman, R.A.; Kaune, W.T.; Hatch, E.E.; Wacholder, S.; Linet, M.S.; Robison, L.L.; Niwa, S.; Tarone, R.E. Are children living near high-voltage power lines at increased risk of acute lymphoblastic leukemia? *Am. J. Epidemiol.* 2000, 151, 512–515.

Lagunas-Rangel, F.A.; Chávez-Valencia, V.; Gómez-Guijosa, M.; Cortes-Penagos, C. Acute Myeloid Leukemia-Genetic Alterations and Their Clinical Prognosis. *Int. J. Hematol. Oncol. Stem Cell Res.* 2017, 11, 328–339.

Lehtinen, M.; Koskela, P.; Ogmundsdottir, H.M.; Bloigu, A.; Dillner, J.; Gudnadottir, M.; Hakulinen, T.; Kjartansdottir, A.; Kvarnung, M.; Pukkala, E.; *et al*. Maternal herpesvirus infections and risk of acute lymphoblastic leukemia in the offspring. *Am. J. Epidemiol.* 2003, 158, 207–213.

M. R. O'Donnell, C. N. Abboud, J. Altman *et al*., "Acute myeloid Leukemia," Journal of the National Comprehensive Cancer Network,vol.10,no.8,pp.984–1021,2012.

Mahoney, M.C.; Moysich, K.B.; McCarthy, P.L.; McDonald, R.C.; Stepanenko, V.F.; Day, R.W.; Michalek, A.M. The Chernobyl

childhood leukemia study: Background & lessons learned. Environ. Health 2004, 3, 12.

Matsuoka, M. Human T-cell leukemia virus type I and adult T-cell leukemia. Oncogene 2003, 22, 5131–5140.

Molyneux E, Israels T, Howard SC. Oxford Textbook of Cancer in Children. Oxford University Press; 2020. Cancer Treatment in Low- and Middle-Income Countries.

Nalage DN, Kudnar PS, Langhe R, Ughade B, Sontakke T, Biradar A, Nalage D, Kudnar PS. Leukemia in India: Insights Into Incidence, Prevalence, Mortality, and Disability-Adjusted Life Years. Cureus. 2024 Jun 17; 16(6).

O. Abdel-Wahab andA. T. Fathi, "Mutations inepigenetic modifiers in myeloid malignancies and the prospect of novel epigenetic-targeted therapy," *Advances in Hematology*, vol. 2012, Article ID 469592, 12 pages, 2012.

Papaemmanuil, E.; Rapado, I.; Li, Y.; Potter, N.E.; Wedge, D.C.; Tubio, J.; Alexandrov, L.B.; Van Loo, P.; Cooke, S.L.; Marshall, J.; *et al*. RAG-mediated recombination is the predominant driver of oncogenic rearrangement in ETV6-RUNX1 acute lymphoblastic leukemia. Nat. Genet. 2014, 46, 116–125.

Pui, C.H.; Nichols, K.E.; Yang, J.J. Somatic and germline genomics in paediatric acute lymphoblastic leukaemia. Nat. Rev. Clin. Oncol. 2019, 16, 227–240.

Sali, D.; Cardis, E.; Sztanyik, L.; Auvinen, A.; Bairakova, A.; Dontas, N.; Grosche, B.; Kerekes, A.; Kusic, Z.; Kusoglu, C.; *et al*. Cancer consequences of the Chernobyl accident in Europe outside the former USSR: A review. Int. J. Cancer 1996, 67, 343–352.

Schmiegelow, K.; Vestergaard, T.; Nielsen, S.M.; Hjalgrim, H. Etiology of common childhood acute lymphoblastic leukemia: The adrenal hypothesis. Leukemia 2008, 22, 2137–2141.

Schwartz, E. Proportionate mortality ratio analysis of automobile mechanics and gasoline service station workers in New Hampshire. Am. J. Ind. Med. 1987, 12, 91–99.

SenioriCostantini, A.; Quinn, M.; Consonni, D.; Zappa, M. Exposure to benzene and risk of leukemia among shoe factory workers. Scand J. Work Environ. Health 2003, 29, 51–59.

Shu, X.O.; Potter, J.D.; Linet, M.S.; Severson, R.K.; Han, D.; Kersey, J.H.; Neglia, J.P.; Trigg, M.E.; Robison, L.L. Diagnostic X-rays and ultrasound exposure and risk of childhood acute lymphoblastic leukemia by immunophenotype. Cancer Epidemiol. Biomark. Prev. 2002, 11, 177–185.

Smith, M.T.; Wang, Y.; Kane, E.; Rollinson, S.; Wiemels, J.L.; Roman, E.; Roddam, P.; Cartwright, R.; Morgan, G. Low NAD(P)H:quinone oxidoreductase 1 activity is associated with increased risk of acute leukemia in adults. Blood 2001, 97, 1422–1426.

Steensma, D.P.; Bejar, R.; Jaiswal, S.; Lindsley, R.C.; Sekeres, M.A.; Hasserjian, R.P.; Ebert, B.L. Clonal hematopoiesis of indeterminate potential and its distinction from myelodysplastic syndromes. Blood 2015, 126, 9–16.

T. L. Lin and B. D. Smith, "Prognostically important molecular markers in cytogenetically normal acute myeloid Leukemia," *American Journal of the Medical Sciences,* vol. 341, no.5, pp.404 408, 2011.

Tebbi CK. Etiology of acute leukemia: A review. Cancers. 2021 May 8; 13(9):2256.

Tebbi, C.K.; Badiga, A.; Sahakian, E.; Arora, A.I.; Nair, S.; Powers, J.J.; Achille, A.N.; Jaglal, M.V.; Patel, S.; Migone, F. Plasma of Acute Lymphoblastic Leukemia Patients React to the Culture of a Mycovirus Containing Aspergillus Flavus. J. Pediatr. Hematol. Oncol. 2020, 42, 350–358

Tebbi, C.K.; Badiga, A.; Sahakian, E.; Powers, J.J.; Achille, A.N.; Patel, S.; Migone, F. Exposure to a mycovirus containing Aspergillus Flavus reproduces acute lymphoblastic leukemia cell surface and genetic markers in cells from patients in remission and not controls. Cancer Treat. Res. Commun. 2020, 26, 100279.

The burden of cancers and their variations across the states of India: the Global Burden of Disease Study 1990-2016. Lancet Oncol. 2018;19:1289–1306. doi: 10.1016/S1470-2045(18)30447-9.

Wang, H.; Zou, J.; Zhao, B.; Johannsen, E.; Ashworth, T.; Wong, H.; Pear, W.S.; Schug, J.; Blacklow, S.C.; Arnett, K.L.; *et al*. Genome-wide analysis reveals conserved and divergent features of Notch1/RBPJ binding in human and murine T-lymphoblastic leukemia cells. *Proc. Natl. Acad. Sci. USA* 2011, 108, 14908–14913.

Wiemels, J. Perspectives on the causes of childhood leukemia. Chem. Biol. Interact. 2012, 196, 59–67.

Wong, O.; Harris, F.; Armstrong, T.W.; Hua, F. A hospital-based case-control study of acute myeloid leukemia in Shanghai: Analysis of environmental and occupational risk factors by subtypes of the WHO classification. *Chem. Biol. Interact*. 2010, 184, 112–128.

Xie, Y.; Davies, S.M.; Xiang, Y.; Robison, L.L.; Ross, J.A. Trends in leukemia incidence and survival in the United States (1973–1998). Cancer 2003, 97, 2229–2235.

Y. Okiand J. P. Issa, "Epigenetic mechanisms in AML—atarget for therapy," *Cancer Treatment and Research,* vol.145,pp.19–40, 2010.

Zipf, T.; Berg, S.; Roberts, W.; Poplack, D.; Steuber, C.; Bleyer, W. Childhood Leukemias. Clinical Oncology, 2nd ed.; Churchill Livingstone: New York, NY, USA, 2000; pp. 2402–2434.

****