Etiology of Acute Leukemia: A Review

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Simple Summary: Acute leukemias are some of the most common cancers affecting all age groups. Despite a significant improvement made in the treatment of acute leukemias, their cause remains unknown. A number of genetic and environmental factors for the development of acute leukemias have been proposed, but none have been proven. Undoubtedly, genetics have a major role in the development of these diseases. The effects of a variety of environmental factors, occupations and hobbies have been explored. A recent “two-hit” theory for the development of acute lymphoblastic leukemia has been proposed. This combines genetic factors and exposure to infections for the development of this disease. Several genetic factors are suggested. Most recently, for the infection portion, exposure to a virus containing Aspergillus Flavus has been proposed. This review summarizes what is currently known about the factors that are proposed for the development of acute leukemias.

Abstract: Acute leukemias constitute some of the most common malignant disorders. Despite significant progress made in the treatment of these disorders, their etiology remains unknown. A large and diverse group of genetic and environmental variables have been proposed. The role of a variety of factors, including pre-existing and acquired genetic mutations, exposure to radiation and various chemicals during preconception, pregnancy and throughout life, have been explored. The effects of inherited genetic variations and disorders, pre-existing diseases, infectious agents, hobbies, occupations, prior treatments, and a host of other factors have been proposed, but none is universally applicable to all cases. Variation in the incidence and prognosis based on the age, sex, race, type of the disease, geographic area of residence and other factors are intriguing but remain unexplained. Advances in genomic profiling, including genome-wide gene expression, DNA copy number and single nucleotide polymorphism (SNP) genotype, may shed some light on the role of genetics in these disparities. Separate two-hit hypotheses for the development of acute myeloblastic and lymphoblastic leukemia have been proposed. The latter combines genetics and infection factors resulting in leukemogenesis. A number of pre- and post-natal environmental conditions and exposure to infections, including a mycovirus infected Aspergillus flavus, have been suggested. The exact nature, timing, sequence of the events and mechanisms resulting in the occurrence of leukemia requires further investigations. This review summarizes some of the above factors in acute lymphoblastic and myeloblastic leukemias and the direction for future research on the etiology of these disorders.

Keywords: etiology; leukemia; acute lymphoblastic leukemia; acute myeloblastic leukemia; genetics; causes; occupations; hobbies; genetic; infections; mycovirus; Aspergillus

1. Background

Leukemia is one of the most common malignant disorders affecting the world population. Globally, in 2018, leukemia ranked as the fifteenth most common diagnosed cancer with 437,033 cases and 309,006 mortalities, amounting to the eleventh cause of death due to malignant disorders [1]. The geographic distribution of leukemia is universal, with higher prevalence and overall mortality in the more developed countries. The mortality rate, however, is higher in developing countries. A detailed pattern of the incidence of cancer in general, and leukemia in particular, is available [1]. Based on the Cancer Facts and Figures provided by the American Cancer Society, for the year 2020, it was estimated...
that 178,520 individuals were to be diagnosed with leukemia, lymphoma and myeloma in the United States. This accounts for 9.9 percent of the estimated 1,806,590 new cancer cases diagnosed in that year. While both sexes are affected, leukemia is more prevalent in males. The age-standardized incidence rates for leukemia in males and females in 2018 in the United States were 6.1 and 4.3 per 100,000, respectively. Likewise, the mortality rate of 4.2 per 100,000 population was higher for males compared to 2.8 per 100,000 in females [1].

Acute leukemias are malignant clonal disorders of blood-forming organs involving one or more cell-lines in the hematopoietic system. These disorders are marked by the diffuse replacement of bone marrow with abnormal immature and undifferentiated hematopoietic cells, resulting in reduced numbers of erythrocytes and platelets in the peripheral blood. Based on the origin of the abnormal hematopoietic cells involved, such as lymphoid, myeloid, mixed or undifferentiated, these disorders are classified accordingly. In contrast, chronic leukemias encompass a broad spectrum of diseases characterized by uncontrolled proliferation and expansion of mature, differentiated cells of the hematopoietic system. Thus, chronic leukemias are classified depending on the type of hemopoietic cells involved.

2. Age and Race

Age and race are important factors in the incidence of leukemias. For example, in the United Kingdom, 42.8% of all leukemias occur in individuals over 65 years of age [2]. A review of the subject in the United States reports that the overall age-adjusted leukemia incidence is highest in the White population at 15 per 100,000, followed by Blacks at 11 per 100,000, and Hispanics at 10.6 per 100,000 population [3]. The incidence among Asian/Pacific Islanders was 7.8 per 100,000 and in American Indian/Alaskan Natives, 8.3 per 100,000 population [3]. Similar racial and ethnic patterns were found for age-adjusted mortality rates per 100,000 population, which were 7 for Whites, 5.6 for Blacks, 4.8 for Hispanics, 3.8 for Asian/Pacific Islanders and 3.3 for Indian/Alaskan Natives [3].

While leukemia affects all age groups, its distribution varies based on the type of the disease. The age-adjusted incidence rate of leukemia from 2012 to 2016 in the United States in children, adolescents and young adults younger than 20 years was estimated to be approximately 4.6 per 100,000. Approximately 4.8 percent of all leukemia and lymphoma cases were diagnosed in individuals younger than 20 years of age. As such, it constituted approximately 20–30% of all cancers in this age group. Acute lymphoblastic leukemia (ALL), which is most common in childhood and adolescence, accounts for approximately 75% of all leukemia cases in individuals under 20 years of age and approximately one-quarter of all pediatric cancers. The peak incidence is in children ages 2–5 years. On the contrary, acute myeloblastic leukemia (AML), with an overall incidence of 3–5 cases per 100,000 in the general population, is far more prevalent in adults, with an incidence of only 7.7 per million between the ages of 0–14 years. Indeed, the median age at diagnosis for AML is 66 years with 54% of patients diagnosed after age 65 and 33% over age 75. It is of note that the incidence of acute lymphoblastic leukemia has increased over time, at least in the pediatric age group. This, in part, has been attributed to the improved accuracy of the diagnostic techniques and reporting. The incidence for AML appears to have been unchanged [4].

As noted above, racial differences in the incidence of and mortality caused by different types of acute leukemias have been reported. The incidence for some leukemias, such as ALL, is higher in the White population than the Black population. Based on a 2011 report by the American Association for Cancer Research, Hispanic children have the highest incidence of ALL and one of the lowest survival rates among pediatric patients diagnosed in the United States. In this regard, the report indicates that the overall mortality risk for ALL is 45 and 46 percent greater for Blacks and Hispanics than the White population, respectively. The rate of increase death in AML was 12 and 6 percent higher in these two groups than in the White population [5].

Despite reported differences in race and ethnicity in the incidence and outcome, the underlying causes for this disparities remain poorly understood [6–10]. While the role of the
financial and social structure versus genetic factors in the incidence and outcome in various populations have been considered, the underlying causes are poorly recognized. Advances in genomic profiling, including genome-wide gene expression, DNA copy number, and single nucleotide polymorphism (SNP) genotype, may shed some light regarding the roles of genetics in these disparities [11].

3. Genetics

Undoubtedly, genetics plays a major role in the etiology of leukemia. A vast body of new literature regarding the relation of genetic factors in normal hemopoiesis and transition to acute leukemias and mechanisms of leukemogenesis is available; however, a summary of this is well beyond the scope of this general review. The effects of genetics in the pathogenesis of acute leukemias are most evident in identical twins. If one of the identical twins develops the disease before the age of 7 years, the other has twice as much chance of developing this disease than the general population. The chance of developing leukemia then reduces in time. The twin who reaches age 15 years without developing leukemia appears not to have a higher risk of developing this disease than the average population [12,13].

While for the majority of leukemia cases there are no obvious known predisposing factors, some genetic and acquired germline mutations and clonal chromosomal abnormalities are associated with increased incidence of leukemia [14]. Increasingly, using genome-wide association studies, germline mutations that can cause leukemia prone changes have been identified. Patients with DNA repair disorders and constitutional chromosomal anomalies can be predisposed to the development of leukemia. Some inherited mutations have the potential to enhance the risk of developing leukemia, but this is in the absence of extramedullary phenotypes. Some families have an increased incidence of leukemia with no known inherited mutations [14]. The major inherited and genetic disorders resulting in a predisposition to acute leukemia are summarized in Table 1. The identified genes that can be inherited in an autosomal dominant fashion and potentially result in the development of leukemia include CEPBA, RUNX1 and GATA2. The CEBPα gene, located at chromosome 19q13.1, encodes granulocytic differentiation factor C/EBPα, a member of the bZIP family of proteins. The RUNX1 gene is located at 21q22.12 and is a transcription factor involved in hemopoiesis. The GATA2 gene is located at 3q21.3 and is involved in preserving the integrity of hematopoietic stem cells and regulating phagocytosis. Mutation of GATA2 has been associated with congenital neutropenia and MonoMAC syndrome, a disorder that frequently results in myelodysplastic syndrome (MDS), increased rate of infections and AML or chronic myelomonocytic leukemia [14]. Monosomy 7 has been reported in families with multiple members having MDS and AML. Likewise, inherited bone marrow failure syndromes with a variety of genetic abnormalities can lead to the development of leukemia [14].

DNA damage and impaired DNA damage repair capacity during proliferative DNA replication can result in mutations leading to the initiation of malignant transformation. Clonal hematopoiesis of indeterminate potential (CHIP) is a common asymptomatic condition that increases the risk of the development of hematological malignancies by the expansion of 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 pathogenesis of hematological malignancies. Recent progress in the study of cancer genomics and single-cell molecular analysis has made it possible to study the clonal population and their genetic and time-related sequences of genetic and epigenetic evolutions in detail. These may help to better understand the role of clonal evolution in lymphoid and myeloid leukemia as a principal driver in the disease initiation, progression and resistance. Genome-wide analysis has resulted in better understanding of various signaling pathways and their role in the development of leukemias. Further genomic and epidemiologic research will likely lead to the identification of new constitutional genetic mutations and their relation to the
environmental mutagens and pathogens in order to initiate malignant hematological clones and progress to full-fledged leukemia [15,16].

Table 1. Inherited predisposing syndromes to hematologic malignancy.

| Predisposing Disorder | Gene               | Inheritance | Type of Leukemia       |
|-----------------------|--------------------|-------------|------------------------|
| CEBPA                 | CEBPA              | AD          | MDS/AML                |
| Monosomy 7            | 7p/q               | AD          | MDS/AML/ALL            |
| Familial platelet disorder / AML | RUNX1 | AD          | MDS/AML/T-cell ALL |
| MonomAC Syndrome      | GATA2              | AD          | MDS/AML                |
| Familial AML with mutated DDX41 | DDX41 | AD          | MDS/AML/CML            |
| Thrombocytopenia 2    | ANKRD26            | AD          | MDS/AML                |
| Thrombocytopenia 5    | ETV6               | AD          | MDS/AML/CML, B-cell ALL|
| Familial MDS/AML with mutated GATA2 | GATA2 | AD          | MDS/AML/CML |
| Li-Fraumeni syndrome  | TP53               | AD          | ALL                    |
| Neurofibromatosis type 1 | NF1          | AD          | JMLM/MDM/AML |
| Noonan syndrome       | PTPN11             | AD          | JMLM/MDM/AML |
| CBL syndrome          | CBL                | AD          | JMLM |
| Familial aplastic anemia with mutated SRP72 | SRP72 | AD          | MDS/AML |
| Familial B- cell ALL with mutated PAX5 | PAX5 | AD          | ALL |
| Germine SH2B3         | SH2B3              | AR          | ALL                    |
| Telomere syndromes (dyskeratosis congenita) | TERC, TERT, CTC1, DKC1, NHP2, NOP10, RTEL1, TINF2, WRAP53, ACD, PARN | AD, AR | MDS/AML |
| Diamond Blackfan anemia | RPS19, RPL5, RPL11 | Sporadic, AD, AR, MDS/AML/ALL |
| Shwachman–Diamond syndrome | SBDS | AR          | MDS/AML/ALL |
| Amegakaryocytic thrombocytopenia | c-AML | AR          | MDS/AML |
| Thrombocytopenia with absent radii syndrome | RBMSA | AR, Sporadic | ALL/AML |
| Severe congenital neutropenia | ELA2, HAX1, G6PC3, WASP, Fanca, FANCb, FANCC, BRCA2, FANCD2, FANCE, FANCF, FANCG, FANCI, BRIP1, FANCL, FANCM, PALB2, RAD51C, SLX4 | AD, AR, X-linked | MDS/AML |
| Fanconi anemia         |                   | AR          | ALL/AML                |
| Mismatch repair Cancer syndrome | PMS2, MSH6, MLH1, MSH2 | AR          | ALL |
| Ataxia-telangiectasia  | ATM                | AR          | ALL                    |
| Nijmegen breakage syndrome | NBS1 | AR          | ALL                    |
| Bloom Syndrome        | BLM                | AR          | ALL                    |
| Werner Syndrome       | WRN (RECQL2)      | AR          | MDS/AML                |
| Rothmund–Thomson Syndrome | RECP4 | AR          | AML                    |
| Wiskott–Aldrich Syndrome | WASP | X-linked   | ALL                    |
| Burton’s agammaglobulinemia | BTK | X-linked | ALL |
| Trisomy 21 (Down Syndrome) | 21q | Sporadic | ALL/AML |

AD—autosomal dominant, AR—autosomal recessive, MDS—myelodysplastic syndrome, ALL—acute lymphoblastic leukemia, AML—acute myeloblastic leukemia, JMML—juvenile myelo-monocytic leukemia, CMML—chronic myelo-monocytic leukemia.

Events associated with leukemic transformation are often a multifactorial process. For example, the ETV6-RUNX1 fusion gene, which is found in approximately 25% of ALL cases in the pediatric age group, is acquired in utero; however, it needs a secondary somatic mutation to be activated. In one study, using exome and low-coverage whole-genome sequencing to evaluate the events culminating in this oncogenic rearrangement, RAG-mediated deletions emerged as the prominent driving force in this mutational process. Combining the data of point mutations and rearrangements identified ATF7IP and MGA as tumor-suppressor genes in ALL. Therefore, a multifactorial mutational process, targeting the promoters, enhancers and first exons of genes, which normally regulate B-cell differentiation, transforms ETV6-RUNX1-positive lymphoblasts [17,18].
Individuals with certain genetic disorders are known to have an increased rate of developing leukemia [14–27]. Persons with disorders such as Li Fraumeni syndrome, Down syndrome, Shwachman syndrome, Klinefelter syndrome and Diamond Blackfan anemia are at higher risk for the development of leukemia [19–27]. Point, missense or nonsense mutations can occur in the tumor suppressor genes, some of which encode for proteins with suppressive effects on the regulation of the cell cycle and ability to promote apoptosis. Disorders such as Noonan syndrome and CBL syndrome are associated with a high risk of leukemia [14]. Bone marrow failure syndromes such as thrombocytopenia with absent radius, amegakaryocytic thrombocytopenia, dyskeratosis congenita and severe congenital neutropenia, including Kostmann syndrome, are also associated with a higher risk of the development of leukemia [14]. Myelodysplastic syndrome, myelodysplasia, polycythemia vera and primary thrombocytopenia are also found to be associated with the increased rate of this disease [14]. DNA repair defects, such as mismatch repair deficiency syndrome, which involves sporadic mutations in genes responsible for DNA repair, as seen in some variants of Lynch syndrome, ataxia-telangiectasia, Nijmegen breakage syndrome, Bloom syndrome and Fanconi anemia, can be associated with hematological malignancies [14,19]. It is of note that approximately 33% of patients with Fanconi anemia develop a hematological malignancy by age 40. Germline polymorphisms in *IKZF1*, *CDKN2A*, *CEPBE* and *ARID5B* have been shown to be associated with increased risk of ALL [14].

Patients with various primary inherited immunodeficiency syndromes are predisposed to the development of malignant disorders, including leukemia [14]. These include Wiskott–Aldrich syndrome (an X-linked disorder with the triad of thrombocytopenia, immune deficiency and eczema) and Bruton agammaglobulinemia, which is due to the Bruton tyrosine kinase gene located at the chromosome Xq21.3-22 location.

As discussed in the AML and ALL sections of this review, two-hit theories involving genetics for the development of leukemias have been proposed.

4. Environment and Occupations

A large number of environmental causes for the development of leukemia have been suggested. These mostly involve exposure to cancer-causing agents, including chemicals, infections and radiation during various stages of life [28–37]. Certain exposures, occupations, industrial hazards, and hobbies have been implicated in a higher risk of leukemia [34–37]. There is a reported variation in the incidence of leukemia based on the type of industry (Table 2). The relation of certain occupations and the occurrence of acute leukemias is not certain and at times controversial. Occupations described to be associated with increased risk for leukemias include, but are not limited to, agricultural and forestry work and crop production [38–45] with exposure to pesticides and fertilizers [46–48], construction [33], animal slaughtering and poultry work [49,50], vocations in the oil/gas industries with exposure to benzene [40,48,51–57], oil refining and petrochemicals [58–64], automobile mechanic works [42,65], electrical utility careers, jobs with exposure to magnetic fields [66–71], works in the nuclear power industry/exposure to ionizing radiation [55,56,72–76], furniture manufacturing/repair [77] and nursing and health care positions with exposure to infectious agents/viruses [42,44,78–80]. Other occupations with increased risk of leukemia include hairdressing and hair dying [55,81], painting [82–85], laundry work, dry-cleaning with exposure to dry-cleaning chemicals [42,86,87], teachers [40,42], workers in the shoe and boot manufacturing industry [88] and taxi, bus, truck, and railway drivers and conductors [55,58,71,89,90]. Occupations with exposure to alkylating agents and formaldehyde [78,91,92], textile workers and manufacturers [55,93] and semiconductor workers [55,94] are also found to have a higher risk of leukemia. Increased risk of leukemia due to contact with workers in these industries is suggested [90]. With a few exceptions, such a diverse range of occupations, without a unifying element, lacks specificity (Table 3).
Table 2. Industries with Increased and Decreased Rate of Leukemia.

| Industries with Increased Rate of Leukemia |
|-------------------------------------------|
| Agriculture/Crop production and related ventures |
| Forestry |
| Fishing and Hunting |
| Construction and related services |
| Animal slaughtering/poultry processing |
| Oil refining and petrochemicals |
| Industries with Decreased Rate of Acute Leukemia |
| Professional, legal and technical services |
| Computer systems and related services |
| Business support, management and administrative services |
| Public administration |

Table 3. Occupations with an Increased and Decreased Risk of Acute Leukemia.

| Occupations Associated with Increased Risk of Acute Leukemia |
|-------------------------------------------------------------|
| Farmers, foresters, agriculture workers and related occupations |
| Fishing and related works |
| Construction, painting, maintenance and related occupations |
| Carpet, tile and floor installers |
| Building and ground cleaning, janitorial and maintenance workers |
| Healthcare workers |
| Workers exposed to solvents, chemicals and benzene |
| Electricians/electrical utility workers |
| Workers exposed to high doses of radiation/nuclear power industry |
| Automobile mechanics/drivers/rail conductors and pilots |
| Furniture manufacturers and repair personnel |
| Laundry workers, dry cleaners |
| Textile workers and manufacturers |
| Hairdressers |
| Teachers |
| Occupations Associated with Decreased Risk of Acute Leukemia |
| Attorneys and legal workers |
| Movers |

Direct and indirect exposure to chemicals and pesticides, in a variety of occupations, has been reported as a cause for the development of leukemia [95–97]. Likewise, exposure to hydrocarbon compounds, such as benzene, gasoline and trichloroethylene, in person or indirect, has been implicated in the development of leukemia [64,98]. Likewise, in children, a multiplicity of factors, including parental occupations, have been proposed to increase the risk of acute leukemia. A review of the subject is available [99].

5. Effects of Radiation

The effects of ionizing radiation in the development of leukemia at various phases of life, including preconception, in utero, and post-natal exposures, have been proposed, and various examples have been published. A correlation between the dose of irradiation and the occurrence of leukemia has been reported [100,101]. Following the bombing of Hiroshima and Nagasaki, Japan, the rate of occurrence of leukemia among survivors who were within 1000 meters of the explosions was 20-fold higher than the general population [101]. More recently, the consequences of the Chernobyl nuclear power plant accident have been studied [102–104].

There are conflicting data regarding the risk of the development of leukemia and exposure to diagnostic x-rays. Some studies have shown an elevated risk for childhood leukemia related to paternal diagnostic X-rays. An increased risk was found if two or
more X-rays of the lower abdomen were done. However, no increased risk was noted if the data were restricted to lower abdominal X-rays [105,106]. In one study, no increased risk of leukemia was found with maternal abdominal X-rays. Some evidence of increased risk in offspring was noted if the father had more than one abdominal X-ray done before conception or had a prior intravenous pyelogram [103].

In general, a correlation between diagnostic X-rays and the development of leukemia is inconsistent, inconclusive and subject to a number of variables, including time and reason for the procedure and statistical errors. Some studies have reported an increased rate of leukemia in individuals who have had diagnostic X-rays. For example, in one report, children having one or more computed tomography scans had an increased ratio of developing leukemia, indicating that even with low doses of ionizing radiation, there is an increased risk of this disease. However, others find no correlations between diagnostic X-ray tests and increased risk, especially if tests done close to the time of diagnosis of leukemia are subtracted.

Inconsistent results regarding exposure to nonionizing radiation as an etiological factor for the development of leukemia have been reported, and generally, the effects of such exposures in the development of this disease have been disputed [107–113].

6. Prior Immunosuppressive and Chemotherapy

Individuals who have received chemotherapy for the treatment of cancer, with or without radiation, have an increased risk of leukemia. A variety of immunosuppressive therapies can also increase the risk of developing acute leukemias. Certain chemotherapy agents, such as alkylating agents, platinum derivates and topoisomerase II inhibitors, are associated with higher risk for the development of this disease. The addition of radiation therapy to chemotherapy increases the risk involved [114,115]. In a study of 82,700 women with invasive breast cancer, the risk of acute nonlymphocytic leukemia was significantly higher for all types of therapy, including regional radiotherapy alone, alkylating agents alone and the combination of chemotherapy and radiation. The relative risk was 2.4 for radiotherapy, 10 for alkylating agents and 17.4 for the combination. The observed risk for the development of leukemia was dose- and treatment-dependent, with melphalan having ten times more leukemogenic effect than cyclophosphamide. With total cyclophosphamide doses of less than 20,000 mg, only a small increase in the risk of secondary leukemia was observed.

7. Parental and Residential Factors

In the pediatric age group, paternal hobbies and occupations, such as work involving contact with gasoline, paint, pigments, solvents, pesticide and plastics, jobs in metal, textile, pharmaceutical industries and professions requiring engine repair, have been investigated for the development of leukemia in children. Direct and indirect effects of chemical agents on children, including via breastfeeding and exposure to contaminated clothing or environment, have been implicated [64,95–97,110,116–122]. Likewise, household exposure to pesticides and insecticides has been found to be associated with a higher risk of leukemia in the pediatric age group [123].

The proximity of place of birth to the industrial sites with release of volatile organic compounds has been reported [124].

Children born through in vitro fertilization have a higher rate of acute leukemia and Hodgkin’s lymphoma [125,126].

Parental alcohol consumption and smoking during prenatal and neonatal periods and childhood have been suggested to contribute to the development of leukemia in their offspring. The risk may be related to the severity, frequency, duration and extent of the exposure [127–132]. Maternal use of marijuana during and after pregnancy has been reported to increase the risk of ALL and AML by 10-fold [133]. Effects of the chemico-biological interactions have been explored.
Several studies regarding the etiology of leukemia in childhood have examined the relation of the parent’s age, maternal history of fetal loss, birth characteristics and higher birth weight. A positive trend associating maternal and paternal age greater than 35 and 40 years, respectively, and the occurrence of ALL in the offspring was found. Maternal and paternal age exceeding 40 years has been reported to be associated with an increased the odd ratios of 1.95 and 1.45 for the development of childhood leukemia [134]. Maternal history of fetal loss and the risk of the development of ALL and AML is conflicting. This may reflect genetic predisposition or the effects of the environment [135–137]. Increased rate with the higher birth weight is presumed to reflect an increased ability for cell proliferation [138].

8. Infections

Infections, including bacterial, viral and fungal agents alone, and in conjunction with genetic mutations, have been implicated in leukemogenesis. Infective agents have been suspected to be associated with the development of cancer in general and acute leukemias in particular [139–142]. However, save for some recent reports [141,142], no consistent agent which can be uniformly applied to a group of patients is available. The impact of a variety of infectious organisms, 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), among others, in the development of leukemia have been hypothesized and explored [99,139,143–153].

Associations, such as that of EBV and Burkitt’s lymphoma in the endemic area of Eastern Africa, are well recognized. While such an association is strong, the findings are not entirely applicable to all cases; for example, the 8;14 chromosomal translocation resulting in constitutive activation of c-Myc oncogene, p53 mutations, variation in viral gene expression in some patients, actions of EBV oncoproteins and many other similar factors complicate such an association. During the first two years of life, exposure to EBV resulting in a positive serological response and the development of Burkitt’s lymphoma has been reported [139,149,154].

Human T-cell leukemia virus type 1, which is also known as human T-lymphotropic virus (HTLV-1) has been linked to adult T-cell leukemia/lymphoma (ATL), presumably due to the insertion of their DNA or RNA into the host cell. HTLV-I is proposed to cause ATL, after a latent period, in approximately 5% of carriers. It is hypothesized that post infection, HTLV-I advances the in vivo clonal proliferation of HTLV-I infected cells through the functions of encoded viral proteins, including Tax [155]. If exposed to pathogens, mice with monoallelic loss of the B-cell transcription factor PAX5 are predisposed to B-cell ALL [147,156].

Carcinogenic effects of fungal agents and aflatoxin are well established, but the mechanisms resulting in this phenomenon are not entirely clear. Few reports of fungal isolation from residences of patients with leukemia, including ALL, are available [157–160], and generally, their carcinogenic impacts are attributed to immunosuppression [158,159]. Mycotoxin-producing fungi, isolated from a residence associated with four patients with leukemia from three families has been reported and the leukemogenesis attributed to the mycotoxins’ immune depressive effects [158]. A published report is available regarding the isolation of fungal agents from a house where a husband had acute myelomonocytic and the wife had undifferentiated leukemia. The report indicates that the extract of the fungal isolates resulted in the depression of the phytohemagglutinin skin test in guinea pigs while the control was negative [159]. In another report, using the supernatant of the culture of Aspergillus and a modified microimmunodiffusion technique, sera from 36 patients with cancer, 15 of whom had leukemia or lymphoid tumors, positive results were found in 30% of the participants with cancer as compared to only 6% of the controls. This effect was attributed to a reaction to the aflatoxin produced by the fungi [158].

In recent reports, an Aspergillus Flavus species, isolated from the home of a patient with ALL by electron microscopy examination was found to contain a mycovirus within the body of the fungi and its culture supernatant [141,142]. This organism, by chemical analysis,
was reported not to produce any aflatoxin. Lack of production of aflatoxin, of course, is well known to occur in fungal organisms that host a virus, providing a stage for virus–virus and virus–host interactions, which results in blocking such production [161–163]. This study reports that using an ELISA technique, the plasma of patients with ALL in a complete remission, and long-term survivors, had antibodies to the products of this mycovirus containing *Aspergillus Flavus*. This test was reported to be able to recognize and differentiate patients with ALL in remission from those of normal controls, as well as individuals with sickle cell disease and solid tumors [141]. In a related study, exposure of the peripheral blood mononuclear cells (PMBC) from individuals with ALL in a complete remission to the products of the culture of the above mycovirus containing *Aspergillus Flavus* had resulted in the reproduction of genetic markers and cell surface phenotypes characteristic of ALL. Controls were found to be negative. A serial timeline evaluation to examine the time required for the development of ALL cell surface phenotypes, using flow cytometry, had revealed that the conversion from normal to leukemic cell surface markers had started shortly after incubation with the supernatant of the mycovirus containing *Aspergillus Flavus* and was completed over a 24-h period. The report indicates that the addition of EBV to the mixture had not altered the results. In these experiments, aflatoxin which was used as a positive control, indiscriminately had produced abnormal cell surface phenotypes in the PBMCs from normal controls as well as the ALL patients in a full remission. This study may indicate that mycovirus containing *Aspergillus Flavus* can directly affect cells of ALL patients in remission and alter and transform the genetic and cell surface markers of their presumably genetically susceptible cells, and not controls. The report also indicates that in limited studies, when cultures with and without EBV were irradiated, this had significantly increased the co-expression of CD10/CD19, which is considered as one of the characteristic cell surface phenotypes in the ALL [142]. Considering the two-hit theory for the development of acute lymphoblastic leukemia, it is postulated that the mycovirus containing *Aspergillus Flavus* may provide a consistent organism in the mechanism of leukemogenesis in acute lymphoblastic leukemia [141]. These experiments may give credence to the idea that a combination of pre-existing genetics/epigenetics background and exposure to infections in the environment may result in the development of ALL [142].

Mycotoxins produced by fungal agents, including aflatoxins, ochratoxin A, fumonisins, certain trichothecenes, and zearalenone, are known to be carcinogenic [164]. Some mycotoxins, such as Patulin and Gliotoxin, have a toxic epipolythiodioxopiperazine metabolite with substantial immunosuppressive effects. These agents can cause apoptosis in PBMC and have selective in vitro cytotoxicity, as compared to others that have suppressive effects on the immune response [165,166]. Gliotoxin, in vivo, is reported to inhibit the transcription of NF-κB in response to a number of stimuli in T and B cells. It is reported that in high concentrations, this agent is able to prevent the binding of NF-κB to DNA in vitro [167]. The presence of NF-κB p65 (Rel A) is required for protection from TNA-α. It is of note that constitutively activated NF-κB complexes have been reported in the majority (39/42) of the patients with ALL without any subtype restrictions [168].

The correlation between exposure to infections, including fungal organisms, and occupations with increased rate of leukemia, such as agricultural work, which potentially exposes the workers to fungal and other agents is not clear and requires future investigation.

As noted before, in recent years, two-hit hypotheses, indicating multifactorial causation for the development of acute leukemias, have been proposed [169,170]. The specifics for two major acute forms of the disease, i.e., acute lymphoblastic and myeloblastic leukemia, are described in the following sections.

### 9. Acute Myeloblastic Leukemia

Acute myeloblastic leukemia (AML) has two peaks in occurrence, during early childhood and later in adults. The median age for the newly diagnosed patients with AML is 66 years. While the disease can occur at any age, the diagnosis is relatively rare before 40 years of age. Based on the United States statistics obtained from 2000 to 2004, the
incidence in individuals under age 65 is 1.7 per 100,000, with the rate increasing to 16.8 per 100,000 in those aged 65 or older. The incidence of AML varies with gender and race. Overall, in the United States Surveillance Epidemiology and End Results Program (SEER) database for children aged 1-4 years, the recorded incidence rate is 0.9 per 100,000 for boys and 0.8 for girls [171].

During the first few years of life, the incidence of AML in Whites is three-fold higher than in blacks; however, black children have slightly higher rates of this disease after this age. In the United States between 2000 and 2004, with the rate of 3.7 per 100,000 population, AML was more common in Whites than Blacks who had a rate of 3.2 per 100,000 [171]. The increased incidence with age is partially suspected to be due to the progression of myelodysplastic syndromes (MDS) to AML. The MDS-related AML is characterized by common cytogenetic abnormalities, which is shared with MDS and has an increased frequency of unfavorable prognosis. In children, the incidence of acute myeloblastic leukemia between 2005 and 2009 was estimated to be 7.7 cases per million for ages 0–14 years. In the pediatric age group, the peak incidence rate occurs in the first year of life followed by a steady decline up to the age of 4 years. In infants less than one year of age, the incidence is 18.4 per million [2,172].

Other than MDS, in most cases, the etiology of AML is unclear. A significant amount of information and knowledge concerning leukemogenic agents, especially chemotherapy regimens used for the treatment of a variety of malignant disorders, has accumulated [114,115]. Associations of certain molecular pathogenesis such as t(8;21) translocation and inversion of chromosome 16 in AML have been reported. In addition to these genetic alterations, epigenetic changes, such as promoter silencing by hypermethylation of the p15/INK4b and other genes in the pathogenesis of AML, have been recognized. The association of certain genetic factors, including genetic defects, and AML, especially in children, is suggested. As noted above, patients with a variety of genetic disorders, such as Down’s syndrome, have a substantially higher potential for the development of malignant disorders, including AML. For example, children with Trisomy 21 have a 10- to 20-fold increased potential of developing acute leukemia, mostly AML [21,26,174,175].

Acquired genetic and clonal chromosomal abnormalities are found in 50–80% of AML patients, especially in older individuals and those with secondary leukemia. These abnormalities include loss or deletion of chromosomes 5, 7, Y and 9. Chromosome translocations, including those of t(8;21) (q22;q22), t(15;17) (q22;q11), trisomy 8 and 21, and abnormalities in the chromosomes 16, 9, and 11, have been reported [2,176–184]. Cases of tetraploid acute leukemia have been recorded. In one report, a pseudodiploid clone characterized by t(8;21) and a hypotetraploid clone with two t(8;21) and a loss of two Y chromosomes was recorded [185]. A report of specific associations between the most frequent balanced translocations in AML, such as AML with the (8;21) translocation and inversion of chromosome 16, and acute promyelocytic leukemia with the (15;17) translocation, is available. Regarding the pathogenesis of AML, in addition to these genetic alterations, epigenetic events such as promoter silencing by hypermethylation of the p15/INK4b and other genes have been reported.

A “two-hit-hypothesis” for the development of AML phenotype by class I and II mutations has been proposed. This two-hit hypothesis is different from that proposed for ALL. Among candidates for class I are mutations in FLT3, N-RAS or K-RAS. Class II mutations are exemplified by RUNX1-RUNXIT1 (also known as AML1-ETO, RUNX1-MTG8), CBF/SMMHC, PML/RAR, and MLL-related fusion genes. An example for this hypothesis is activating mutations in FLT3, which is seen in all subtypes of AML and can confer a proliferative advantage to the hematopoietic progenitors, (class I) and gene rearrangements affecting one of the hematopoietic transcription factors (class II). A combination of class I and class II mutations are necessary for the proposed theory to result in the development of AML [169,186]. This theory is in line with an increased rate in the development of AML in individuals treated for other malignant disorders [114,115].
Risk factors for the development of AML, as outlined before, include exposure to radiation, chemicals and engagement in various occupations and hobbies.

In some forms of acute promyelocytic leukemia (APML), distinct chromosomal and gene-rearrangement aberrations have been recognized. These may be different in various areas of the world. For example, while increased incidence of APML in adult patients originating from Latin America and in children in Southern Europe has been reported, the genetic rearrangement in these two localities is different. This may indicate that a particular breakpoint site may be responsible in various locations. It is known that certain polymorphisms in the genes metabolizing carcinogens are associated with an increased risk of AML. For example, NAD(P)H:quinone oxidoreductase 1 (NQO1) is a carcinogen-metabolizing enzyme that detoxifies quinones and reduces oxidative stress. A polymorphism at nucleotide 609 of the NQO1 complementary DNA decreases the activity of these enzymes and can result in therapy-related AML [169,187,188].

10. Acute Lymphoblastic Leukemia

Acute lymphoblastic leukemia (ALL) is the most frequently diagnosed cancer in the pediatric age group, amounting to approximately 25–30% of all childhood malignant disorders. The annual incidence of acute lymphoblastic leukemia in the United States is approximately 4.6 cases per 100,000 between the ages 0–14 years, with a peak incidence at age 2–5 years. The incidence of ALL during the first year of life is slightly higher in females than in males [189].

Similar to other leukemias, the role and possible effects of a number of factors, as outlined above, for the development of ALL have been proposed. The effects of various environmental factors, including parental preconception, in utero and post-natal exposure to ionizing radiation, have been explored. Likewise, the risks of nonionizing radiation, chemicals, infections, hydrocarbons and pesticides have been evaluated. The effects of parental alcohol, cigarette, and illicit drug use in the development of ALL in offspring have been examined.

Genetics play a major role in the development of leukemia in general and acute lymphoblastic leukemia in particular. The importance of genetics is most evident based on the concordance studies on identical twins with leukemia [12,190,191].

The concept that some cases of leukemia originate in utero by leukemogenic translocations or clonotypic gene fusion sequences is intriguing. Siblings of children with leukemia have a higher risk of developing this disease than others, albeit a relatively minimal risk [192,193].

It is well recognized that some genetic disorders, including Down syndrome [20,21], Shwachman syndrome [22], neurofibromatosis [23], Fanconi anemia [24], Bloom syndrome [25,26], and ataxia-telangiectasia [27], are associated with the increased rate of leukemia. Some of these syndromes, such as Down and Bloom syndromes and Fanconi anemia, have a higher incidence of AML than ALL. While genetic syndromes resulting in the development of ALL only accounts for a very small portion of the cases, the fact that they are associated with the increased rate of this disease points to the importance of genetics in the process of leukemogenesis. In B-cell ALL, genetic alterations, which are specific to each ALL immunophenotype, include hyperdiploidy, hypodiploidy, BCR-ABL1, ETV6-RUNX1 or TCF3-PBX1 fusions, PAX5 or ETV6 mutations, MLL rearrangements, or intrachromosomal amplification of chromosome 21 (iAMP21) specific for B-ALL. Alterations in LMO2, TAL1, TAL2, TLX1, TLX2, or HOXA are characteristics of T-cell ALL [186,194].

A revised taxonomy of B-ALL highlights the genetic heterogeneity of this disease by incorporating 23 subtypes, defined by chromosomal rearrangements, sequence mutations or heterogeneous genomic changes. Most of these molecular changes are acquired and not inherited [195]. Epigenetic priming in pediatric ALL has been suggested [196].

A recent two-hit theory combines genetic mutation and exposure to one or more infections for the genesis of ALL. The revised two-hit hypothesis for the development of precursor B-cell ALL hypothesizes that this disease arises through a two-step process. The
first step is a predisposing genetic mutation. The second step suggests exposure to one or more infections [170]. This proposal, therefore, hypothesizes that the process of developing ALL begins in utero by fusion gene formation or hyperdiploidy and preparation of pre-leukemic clone. It is estimated that step one of the process occurs in approximately 5% of newborns; however, only one percent of those that are predisposed progress to develop ALL. The hypothesis suggests that exposure to infections during early life can protect the individual from the development of precursor B-cell ALL. In the absence of early exposure, in a small fraction of the population, exposure to infection later in life triggers the critical secondary cellular mutations.

In western industrialized countries, approximately 80% of the cases of B-lineage ALL have either an \(ETV6/RUNX1\) translocation or a high-hyperdiploid leukemic clone. These are proposed to have been initiated in utero. Only one percent of healthy newborns have translocation \(t(12;21)\)\([\ ETV6/RUNX1\]\)-positive cord blood cells. In the developed countries, a lower chance of exposure to infections in early life is proposed to be the reason for a relatively higher rate of ALL in children. In contrast, in developing countries, a higher rate of exposure to infections, and possibly malnutrition, is suggested to contribute to a reduced rate of childhood ALL. These factors are proposed to increase the cortisol secretion during infections and the cellular response to cortisol [197].

Although the sequence of the events cannot be ascertained with any precision, and a number of alternatives exist, genetic predisposition along with random exposure to an infective agent can be plausible. While several genetic mutations have been suggested, no infection category or specific agent has been proposed. Recent reports suggest a mycovirus containing \(Aspergillus flavus\) as one of the possible candidates for the infection category [141,142].

11. Conclusions

Acute leukemias account for a significant portion of malignant disorders. These malignancies occur universally, albeit with different rates in various areas of the world, and affect all age groups, including children. While association of significant causative factors for the development of acute leukemias has been reported, the etiology of these disorders remains unclear. Recent advances in genetic and epigenetics provide indications for their involvement in leukemogenesis in acute leukemias. Likewise, the effects of environmental factors, including infections, have been explored. A recent finding of an antibody to a mycovirus containing \(Aspergillus flavus\) in patients with ALL in full remission and re-development of genetic and cell surface phenotypes, characteristic of ALL, upon exposure of PBMN cells from these patients, and not normal controls, to the products of this organism, may provide a new venue for research in leukemogenesis. More research to fulfill the required tenants of theories regarding the development of acute leukemias based on the combination of genetics and environment is needed.

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References

1. 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. \(CA Cancer J. Clin.\) \textbf{2018}, \textit{68}, 394–424. [CrossRef] [PubMed]
2. Deschler, B.; Lübbert, M. Acute myeloid leukemia: Epidemiology and etiology. \(Cancer\) \textbf{2006}, \textit{107}, 2099–2107. [CrossRef] [PubMed]
3. Bispo, J.A.B.; Pinheiro, P.S.; Kobetz, E.K. Epidemiology and Etiology of Leukemia and Lymphoma. \(Cold Spring Harb. Perspect. Med.\) \textbf{2020}, \textit{10}, a034819. [CrossRef] [PubMed]
4. Ries, L. SEER Cancer Statistics Review, 1975–2002. Available online: https://seer.cancer.gov/archive/csr/1975_2002/ (accessed on 23 February 2021).
5. American Association for Cancer Research. Death Rate Higher in Minorities with Acute Leukemia, s.f.S.S.D. Available online: www.sciencedaily.com/releases/2011/09/110919163952.htm (accessed on 19 September 2011).
6. Patel, M.I.; Ma, Y.; Mitchell, B.; Rhoads, K.F. How Do Differences in Treatment Impact Racial and Ethnic Disparities in Acute Myeloid Leukemia? *Cancer Epidemiol. Biomark. Prev.* 2015, 24, 344–349. [CrossRef]

7. O’Keefe, E.B.; Meltzer, J.P.; Bsethea, T.N. Health disparities and cancer: Racial disparities in cancer mortality in the United States, 2000–2010. *Front. Public Health* 2015, 3, 51. [CrossRef]

8. Pollock, B.H.; DeBaun, M.R.; Canvitt, B.M.; Shuster, J.J.; Ravindranath, Y.; Pullien, D.J.; Land, V.J.; Mahoney, D.H.; Lauer, S.J.; Murphy, S.B. Racial differences in the survival of childhood B-precursor acute lymphoblastic leukemia: A Pediatric Oncology Group Study. *J. Clin. Oncol.* 2000, 18, 813–823. [CrossRef] [PubMed]

9. Kadan-Lottick, N.S.; Ness, K.K.; Bhatia, S.; Gurney, J.G. Survival variability by race and ethnicity in childhood acute lymphoblastic leukemia. *JAMA* 2003, 290, 2008–2014. [CrossRef]

10. Bhatia, S.; Sather, H.N.; Heerema, N.A.; Trigg, M.E.; Gaynor, P.S.; Robison, L.L. Racial and ethnic differences in survival of children with acute lymphoblastic leukemia. *Blood* 2002, 100, 1957–1964. [CrossRef] [PubMed]

11. Aquino, V.M. Acute myelogenous leukemia. *Curr. Probl. Pediatr. Adolesc. Health Care* 2002, 32, 50–58. [CrossRef]

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

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

14. Stieglitz, E.; Loh, M.L. Genetic predispositions to childhood leukemia. *Ther. Adv. Hematol.* 2013, 4, 270–290. [CrossRef]

15. Heuser, M.; Thol, F.; Ganser, A. Clonal Hematopoiesis of Indeterminate Potential. *Dtsch. Arztebl. Int.* 2016, 113, 317–322. [CrossRef] [PubMed]

16. Steensma, D.P.; Bejar, R.; Jaiswal, S.; Lindesley, 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. [CrossRef]

17. 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. [CrossRef]

18. Wang, H.; Zhou, J.; Zhao, B.; Johanssone, 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. [CrossRef] [PubMed]

19. Swaminathan, M.; Bannour, S.A.; Routhbort, M.; Naqvi, K.; Kadia, T.M.; Takahashi, K.; Alvarado, Y.; Ravandi-Kashani, F.; Patel, K.P.; Champlin, R.; et al. Hematologic malignancies and Li-Fraumeni syndrome. *Cold Spring Harb. Mol. Case Stud.* 2019, 5. [CrossRef] [PubMed]

20. Dördelmann, M.; Schrappe, M.; Reiter, A.; Zimmermann, M.; Graf, N.; Schott, G.; Lampert, F.; Harbott, J.; Niemeyer, C.; Ritter, J.; et al. Down’s syndrome in childhood acute lymphoblastic leukemia: Clinical characteristics and treatment outcome in four consecutive BFM trials. Berlin-Frankfurt-Münster Group. *Leukemia* 1998, 12, 645–651. [CrossRef]

21. Robison, L.; Neglia, J. Epidemiology of Down syndrome and childhood acute leukemia. *Prog. Clin. Biol. Res.* 1987, 246, 19–32.

22. Woods, W.G.; Roloff, J.S.; Lukens, J.N.; Krivit, W. The occurrence of leukemia in patients with the Shwachman syndrome. *J. Pediatrics* 1981, 99, 425–428. [CrossRef]

23. Shearer, P.; Parham, D.; Kovnar, E.; Kun, L.; Rao, B.; Lobe, T.; Pratt, C. Neurofibromatosis type I and malignancy: Review of 32 pediatric cases treated at a single institution. *Med. Pediatr. Oncol.* 1994, 22, 78–83. [CrossRef]

24. Swift, M. Fanconi’s anaemia in the genetics of neoplasia. *Nature* 1971, 230, 370–373. [CrossRef]

25. Willis, A.E.; Lindahl, T. DNA ligase I deficiency in Bloom’s syndrome. *Nature* 1987, 325, 355–357. [CrossRef] [PubMed]

26. Miller, R.W. Relation between cancer and congenital defects: An epidemiologic evaluation. *J. Natl. Cancer Inst.* 1968, 40, 1079–1085. [PubMed]

27. Toledano, S.R.; Lange, B.J. Ataxia-telangiectasia and acute lymphoblastic leukemia. *Cancer* 1980, 45, 1675–1678. [CrossRef]

28. Brown, W.C.; Doll, R.; Hill, A.B. Incidence of leukaemia after exposure to diagnostic radiation in utero. *Br. Med. J.* 1960, 2, 1539. [CrossRef] [PubMed]

29. Stewart, A.; Webb, J.; Giles, D.; Hewitt, D. Malignant disease in childhood and diagnostic irradiation in utero. *Lancet* 1956, 268, 447. [CrossRef]

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

31. Gardner, M.J. Review of reported increases of childhood cancer rates in the vicinity of nuclear installations in the UK. *J. R. Stat. Soc. Ser. A* 1989, 152, 307–325. [CrossRef]

32. Meinert, R.; Kaletsch, U.; Kaatsch, P.; Schütz, J.; Michaelis, J. Associations between childhood cancer and ionizing radiation: Results of a population-based case-control study in Germany. *Cancer Epidemiol. Prev. Biomark.* 1999, 8, 793–799.

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

34. Bhatia, S.; Robison, L.L. Epidemiology of leukemia and lymphoma. *Curr. Opin. Hematol.* 1999, 6, 201. [CrossRef]

35. Zeeb, H.; Blettner, M. Adult leukaemia: What is the role of currently known risk factors? *Radiat. Environ. Biophys.* 1998, 36, 217–228. [CrossRef] [PubMed]

36. Sandler, D.P.; Ross, J.A. Epidemiology of acute leukemia in children and adults. *Semin. Oncol.* 1997, 24, 3–16.

37. Sandler, D.P. Epidemiology and etiology of acute leukemia: An update. *Leukemia* 1992, 6, 3–5.
67. Flodin, U.; Fredriksson, M.; Persson, B.; Hardell, L.; Axelson, O. Background radiation, electrical work, and some other exposures associated with acute myeloid leukemia in a case-referent study. *Arch. Environ. Health*. 1986, 41, 77–84. [CrossRef]

68. Brys, P.N.; Matanoski, G.M.; Elliott, E.A.; Francis, M.; Kaune, W.; Thomas, K. 60 Hertz magnetic field exposure assessment for an investigation of leukemia in telephone lineworkers. *Am. J. Ind. Med.* 1994, 26, 681–691. [CrossRef]

69. Matanoski, G.M.; Elliott, E.A.; Brys, P.N.; Lynberg, M.C. Leukemia in telephone linemen. *Am. J. Epidemiol.* 1993, 137, 609–619. [CrossRef]

70. Kheifets, L.I.; London, S.J.; Peters, J.M. Leukemia risk and occupational electric field exposure in Los Angeles County, California. *Am. J. Epidemiol.* 1997, 146, 87–90. [CrossRef]

71. Törnqvist, S.; Krave, B.; Ahlbom, A.; Persson, T. Incidence of leukaemia and brain tumours in some “electrical occupations”. *Occup. Environ. Med.* 1991, 48, 597–603. [CrossRef]

72. Carpenter, L.; Higgins, C.; Douglas, A.; Fraser, P.; Beral, V.; Smith, P. Combined analysis of mortality in three United Kingdom nuclear industry workforces, 1946–1988. *Radiat. Res.* 1994, 138, 224–238. [CrossRef]

73. Omar, R.Z.; Barber, J.A.; Smith, P.G. Cancer mortality and morbidity among plutonium workers at the Sellafield plant of British Nuclear Fuels. *Br. J. Cancer* 1999, 79, 1288–1301. [CrossRef]

74. Preston, D.L.; Kato, H.; Kopecky, K.; Fujita, S. Studies of the mortality of A-bomb survivors. 8. Cancer mortality, 1950–1982. *Radiat. Res.* 1987, 111, 151–178. [CrossRef] [PubMed]

75. Ritz, B.; Morgenstern, H.; Froines, J.; Young, B.B. Effects of exposure to external ionizing radiation on cancer mortality in nuclear workers monitored for radiation at Rocketdyne/Atomics International. *Am. J. Ind. Med.* 1999, 35, 21–31. [CrossRef]

76. Shilnikova, N.S.; Preston, D.L.; Ron, E.; Gilbert, E.S.; Vassilenko, E.K.; Romanov, S.A.; Kuznetsova, I.S.; Sokolnikov, M.E.; Okatenko, P.V.; Kreslov, V.V.; et al. Cancer mortality risk among workers at the Mayak nuclear complex. *Radiat. Res.* 2003, 159, 787–798. [CrossRef]

77. Miller, B.A.; Blair, A.; Reed, E.J. Extended mortality follow-up among men and women in a U.S. furniture workers union. *Am. J. Ind. Med.* 1994, 25, 537–549. [CrossRef]

78. Skov, T.; Maarup, B.; Olsen, J.; Reth, M.; Winthereik, H.; Lyng, E. Leukaemia and reproductive outcome among nurses handling antineoplastic drugs. *Br. J. Ind. Med.* 1992, 49, 855–861. [CrossRef]

79. Lie, J.A.; Kjaerheim, K. Cancer risk among female nurses: A literature review. *Eur. J. Cancer Prev.* 2003, 12, 517–526. [CrossRef]

80. Petralia, S.A.; Dosemeci, M.; Adams, E.E.; Zahm, S.H. Cancer mortality among women employed in health care occupations in 24 U.S. states, 1984–1993. *Am. J. Ind. Med.* 1999, 36, 159–165. [CrossRef]

81. Mele, A.; Szkoł, M.; Visani, G.; Stazi, M.A.; Castelli, G.; Pasquini, P.; Mandelli, F. Hair dye use and other risk factors for leukemia and pre-leukemia: A case-control study. Italian Leukemia Study Group. *Am. J. Epidemiol.* 1994, 139, 609–619. [CrossRef]

82. Morgan, R.W.; Claxton, K.W.; Kaplan, S.D.; Parsons, J.M.; Wong, O. Mortality of paint and coatings industry workers. A follow-up study. *J. Occup. Med.* 1985, 27, 377–378. [CrossRef] [PubMed]

83. Miller, B.A.; Silverman, D.T.; Hoover, R.N.; Blair, A. Cancer risk among artistic painters. *Am. J. Ind. Med.* 1986, 9, 281–287. [CrossRef] [PubMed]

84. Lindquist, R.; Nilsson, B.; Eklund, G.; Gahrton, G. Increased risk of developing acute leukemia after employment as a painter. *Cancer* 1987, 60, 1378–1384. [CrossRef]

85. Chen, R.; Seaton, A. A meta-analysis of painting exposure and cancer mortality. *Cancer Detect. Prev.* 1998, 22, 533–539. [CrossRef]

86. Blair, A.; Decoufle, P.; Grauman, D. Causes of death among laundry and dry cleaning workers. *Am. J. Public Health* 1979, 69, 508–511. [CrossRef] [PubMed]

87. McLean, D.; Mannetej, A.; Dryson, E.; Walls, C.; McKenzie, F.; Maule, M.; Cheng, S.; Cunningham, C.; Kromhout, H.; Boffetta, P.; et al. Leukaemia and occupation: A New Zealand Cancer Registry-based case-control study. *Int. J. Epidemiol.* 2009, 38, 594–606. [CrossRef]

88. Forand, S.P. Leukemia incidence among workers in the shoe and boot manufacturing industry: A case-control study. *Environ. Health* 2004, 3, 7. [CrossRef]

89. Flodin, U.; Törnqvist, S.; Stenlund, C. Incidence of selected cancers in Swedish railway workers, 1961–1979. *Cancer Causes Control.* 1994, 5, 189–194. [CrossRef]

90. Alfredsson, L.; Hammar, N.; Karlehaugen, S. Cancer incidence among male railway engine-drivers and conductors in Sweden, 1976–1990. *Cancer Causes Control.* 1996, 7, 377–381. [CrossRef] [PubMed]

91. Appelbaum, F.R.; Armitage, J.O.; Nierderhuber, J.E. (Eds.) *Abeloff’s Clinical Oncology*, 4th ed.; Churchill Livingstone: Philadelphia, PA, USA, 2008; pp. 2215–2234. [CrossRef]

92. Goldstein, B.D. Hematological and toxicological evaluation of formaldehyde as a potential cause of human leukemia. *Hum. Exp. Toxicol.* 2011, 30, 725–735. [CrossRef] [PubMed]

93. O’Brien, T.R.; Decouflé, P. Cancer mortality among northern Georgia carpet and textile workers. *Am. J. Ind. Med.* 1988, 14, 15–24. [CrossRef]

94. Kim, E.A.; Lee, H.E.; Ryu, H.W.; Park, S.H.; Kang, S.K. Cases series of malignant lymphohematopoietic disorder in Korean semiconductor industry. *Saf. Health Work* 2011, 2, 122–134. [CrossRef] [PubMed]

95. Freedman, D.M.; Stewart, P.; Kleinerman, R.A.; Wacholder, S.; Hatch, E.E.; Tarone, R.E.; Robison, L.L.; Linet, M.S. Household solvent exposures and childhood acute lymphoblastic leukemia. *Am. J. Public Health* 2001, 91, 564–567. [CrossRef] [PubMed]
96. Lowengart, R.A.; Peters, J.M.; Cicioni, C.; Buckley, J.; Bernstein, L.; Preston-Martin, S.; Rappaport, E. Childhood leukemia and parents' occupational and home exposures. *J. Natl. Cancer Inst.* 1987, 79, 39–46. [PubMed]

97. Buckely, J.D.; Robison, L.L.; Swotinsky, R.; Garabrant, D.H.; LeBeau, M.; Manchester, P.; Nesbit, M.E.; Odom, L.; Peters, J.M.; Woods, W.G. Occupational exposures of parents of children with acute nonlymphocytic leukemia: A report from the Childrens Cancer Study Group. *Cancer Res.* 1989, 49, 4030–4037. [PubMed]

98. Rinsky, R.A.; Young, R.J.; Smith, A.B. Leukemia in benzene workers. *Am. J. Ind. Med.* 1981, 2, 217–245. [CrossRef] [PubMed]

99. Belsey, M.; Kingsley, B.; Holmes, A. Risk factors for acute leukemia in children: A review. *Environ. Health Perspect.* 2007, 115, 138–145. [CrossRef]

100. Miller, R.W. Persons with exceptionally high risk of leukemia. *Cancer Res.* 1967, 27, 2420–2423. [PubMed]

101. Moloney, W.C. Leukemia in survivors of atomic bombing. *N. Engl. J. Med.* 1955, 253, 88–90. [CrossRef]

102. Sali, D.; Cardis, E.; Sztyaulik, L.; Auvinen, A.; Braitkova, A.; Dottas, 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. [CrossRef]

103. Ron, E. Ionizing radiation and cancer risk: Evidence from epidemiology. *Radiat. Res.* 1998, 150, S30–S41. [CrossRef]

104. 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. [CrossRef]

105. Shu, X.O.; Reaman, G.H.; Lampkin, B.; Sather, H.N.; Pendergrass, T.W.; Robison, L.L. Association of paternal diagnostic X-ray exposure with risk of infant leukemia. Investigators of the Childrens Cancer Group. *Cancer Epidemiol. Biomark. Prev.* 1994, 3, 645–653.

106. 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.

107. Hatch, E.E.; Linet, M.S.; Kleinerman, R.A.; Tarone, R.E.; Severson, R.K.; Hartsock, C.T.; Haines, C.; Kaune, W.T.; Friedman, D.; Robison, L.L.; et al. Association between childhood acute lymphoblastic leukemia and use of electrical appliances during pregnancy and childhood. *Epidemiology* 1998, 9, 234–245. [PubMed]

108. 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. [CrossRef] [PubMed]

109. Ahlbom, A.; Day, N.; Feychtling, 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 leukemia. *Br. J. Cancer* 2000, 83, 692–698. [CrossRef]

110. Savitz, D.A.; Chen, J.H. Parental occupation and childhood cancer: Review of epidemiologic studies. *Environ. Health Perspect.* 1990, 88, 325–337. [CrossRef]

111. 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. [CrossRef]

112. Linet, M.S.; Hatch, E.E.; Kleinerman, R.A.; Robison, L.L.; Kaune, W.T.; Friedman, D.R.; Severson, R.K.; Haines, C.M.; Hartsock, C.T.; Niwa, S.; et al. Residential exposure to magnetic fields and acute lymphoblastic leukemia in children. *N. Engl. J. Med.* 1997, 337, 1–7. [CrossRef]

113. Myers, A.; Clayden, A.D.; Cartwright, R.A.; Cartwright, S.C. Childhood cancer and overhead powerlines: A case-control study. *Br. J. Cancer* 1990, 62, 1008–1014. [CrossRef] [PubMed]

114. Smith, M.A.; McCaffrey, R.P.; Karp, J.E. The secondary leukemias: Challenges and research directions. *J. Natl. Cancer Inst.* 1996, 88, 407–418. [CrossRef]

115. Tebbi, C.K.; London, W.B.; Friedman, D.; Villaluna, D.; De Alarcon, P.A.; Constine, L.S.; Mendenhall, N.P.; Spoto, R.; Chauvenet, A.; Schwartz, C.L. Dexrazoxane-associated risk for acute myeloid leukemia/myelodysplastic syndrome and other secondary malignancies in pediatric Hodgkin’s disease. *J. Clin. Oncol.* 2007, 25, 493–500. [CrossRef]

116. Lin, C.K.; Hsu, Y.T.; Brown, K.D.; Pokharel, B.; Wei, Y.; Chen, S.T. Residential exposure to petrochemical industrial complexes and the risk of leukemia: A systematic review and exposure-response meta-analysis. *Environ. Pollut.* 2020, 258, 113476. [CrossRef]

117. Rushton, L.; Romanuik, H. A case-control study to investigate the risk of leukaemia associated with exposure to benzene in petroleum marketing and distribution workers in the United Kingdom. * Occup. Environ. Med.* 1997, 54, 152–166. [CrossRef] [PubMed]

118. Shu, X.O.; Stewart, P.; Wen, W.Q.; Han, D.; Potter, J.D.; Buckley, J.D.; Heineman, E.; Robison, L.L. Parental occupational exposure to hydrocarbons and risk of acute lymphocytic leukemia in offspring. *Cancer Epidemiol. Biomark. Prev.* 1999, 8, 783–791. [PubMed]

119. Zahm, S.H.; Ward, M.H. Pesticides and childhood cancer. *Environ. Health Perspect.* 1998, 106 (Suppl. 3), 893–908. [CrossRef]

120. Grossman, J. What’s hiding under the sink: Dangers of household pesticides. *Environ. Health Perspect.* 1995, 103, 550–554. [CrossRef]

121. Daniels, J.L.; Olshan, A.F.; Savitz, D.A. Pesticides and childhood cancers. *Environ. Health Perspect.* 1997, 105, 1068–1077. [CrossRef]

122. Infante-Rivard, C.; Labuda, D.; Krajnovic, M.; Sinnott, D. Risk of childhood leukemia associated with exposure to pesticides and with gene polymorphisms. *Epidemiology* 1999, 10, 481–487. [CrossRef] [PubMed]

123. Meneghini, F.; Baruchel, A.; Bertrand, Y.; Lesceouer, B.; Leverger, G.; Nelken, B.; Sommelet, D.; Hémon, D.; Clavel, J. Household exposure to pesticides and risk of childhood acute leukaemia. *Occup. Environ. Med.* 2006, 63, 131–134. [CrossRef] [PubMed]

124. Knox, E. Childhood cancers and atmospheric carcinogens. *J. Epidemiol. Community Health* 2005, 59, 101–105. [CrossRef]
125. Petridou, E.T.; Sergentanis, T.N.; Panagopoulou, P.; Moschovi, M.; Polychronopoulou, S.; Baka, M.; Poursidis, A.; Athanassiadou, F.; Kalmanit, M.; Sidi, V.; et al. In vitro fertilization and risk of childhood leukemia in Greece and Sweden. Pediatr. Blood Cancer 2012, 59, 930–936. [CrossRef] [PubMed]

126. Reigstad, M.M.; Larsen, I.K.; Myklebust, T.A.; Robsham, T.E.; Oldereid, N.B.; Brinton, L.A.; Storeng, R. Risk of Cancer in Children Conceived by Assisted Reproductive Technology. Pediatrics 2016, 137, e20152061. [CrossRef] [PubMed]

127. Ji, B.T.; Shu, X.O.; Linet, M.S.; Zheng, W.; Wacholder, S.; Gao, Y.T.; Ying, D.M.; Jin, F. Paternal cigarette smoking and the risk of childhood cancer among offspring of nonsmoking mothers. J. Natl. Cancer Inst. 1997, 89, 238–244. [CrossRef]

128. Stjernfeldt, M.; Ludvigsson, J.; Berglund, K.; Lindsten, J. Maternal smoking during pregnancy and the risk of childhood cancer. Lancet 1986, 2, 687–688. [CrossRef]

129. John, E.M.; Savitz, D.A.; Sandler, D.P. Prenatal exposure to parents’ smoking and childhood cancer. Am. J. Epidemiol. 1991, 133, 123–132. [CrossRef]

130. Sorahan, T.; Prior, P.; Lancashire, R.J.; Faux, S.P.; Hultén, M.A.; Peck, I.M.; Stewart, A.M. Childhood cancer and parental use of tobacco: Deaths from 1971 to 1976. Br. J. Cancer 1997, 76, 1525–1531. [CrossRef]

131. Shu, X.O.; Ross, J.A.; Pendergrass, T.W.; Reaman, G.H.; Lampkin, B.; Robison, L.L. Parental alcohol consumption, cigarette smoking, and risk of infant leukemia: A Childrens Cancer Group study. J. Natl. Cancer Inst. 1995, 88, 34–31. [CrossRef]

132. Pang, D.; McNally, R.; Birch, J.M. Parental smoking and childhood cancer: Results from the United Kingdom Childhood Cancer Study. Br. J. Cancer 2003, 88, 373–381. [CrossRef]

133. Robison, L.L.; Buckley, J.D.; Daigle, A.E.; Wells, R.; Benjamin, D.; Arthur, D.C.; Hammond, G.D. Maternal drug use and risk of childhood nonlymphoblastic leukemia among offspring. An epidemiologic investigation implicating marijuana (a report from the Childrens Cancer Study Group). Cancer 1989, 63, 1904–1911. [CrossRef]

134. Dockerty, J.D.; Draper, G.; Vincent, T.; Rowan, S.D.; Bunch, K.J. Case-control study of parental age, parity and socioeconomic level in relation to childhood cancers. Int. J. Epidemiol. 2001, 30, 1428–1437. [CrossRef]

135. Kaye, S.A.; Robison, L.L.; Smithson, W.A.; Gunderson, P.; King, F.L.; Neglia, J.P. Maternal reproductive history and birth characteristics in childhood acute lymphoblastic leukemia. Cancer 1991, 68, 1351–1355. [CrossRef]

136. Ross, J.A.; Davies, S.M.; Potter, J.D.; Robison, L.L. Epidemiology of childhood leukemia, with a focus on infants. Epidemiol. Rev. 1994, 16, 243–272. [CrossRef]

137. Yeazel, M.W.; Buckley, J.D.; Daigle, A.E.; Wells, R.; Benjamin, D.; Arthur, D.C.; Hammond, G.D. Maternal drug use and risk of childhood nonlymphoblastic leukemia among offspring. An epidemiologic investigation implicating marijuana (a report from the Childrens Cancer Study Group). Cancer 1989, 63, 1904–1911. [CrossRef]

138. Westergaard, T.; Andersen, P.K.; Pedersen, J.B.; Olsen, J.H.; Frisch, M.; Sørensen, H.T.; Wohlforth, J.; Melbye, M. Birth characteristics, sibling patterns, and acute leukemia risk in childhood: A population-based cohort study. J. Natl. Cancer Inst. 1997, 89, 939–947. [CrossRef] [PubMed]

139. Smith, M. Considerations on a possible viral etiology for B-precursor acute lymphoblastic leukemia of childhood. J. Immunother. 1997, 20, 89–100. [CrossRef]

140. Wiemels, J. Perspectives on the causes of childhood leukemia. Chem. Biol. Interact. 2012, 196, 59–67. [CrossRef] [PubMed]

141. Tebbi, C.K.; Badiga, A.; Sahakian, E.; Arora, A.I.; Nair, S.; Powers, J.J.; Achille, A.N.; 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. [CrossRef]

142. 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. [CrossRef] [PubMed]

143. Greaves, M.F. Speculations on the cause of childhood acute lymphoblastic leukemia. Leukemia 1988, 2, 120–125. [PubMed]

144.栈, J.E.; Castella, A.; Zalusky, R. B-cell acute lymphocytic leukemia in HIV-antibody-positive patients. Am. J. Hematol. 1989, 32, 200–204. [CrossRef]

145. Fantanowitz, L.; Schlecht, H.P.; Dezube, B.J. The growing problem of non-AIDS-defining malignancies in HIV. Curr. Opin. Oncol. 2006, 18, 469–478. [CrossRef]

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

147. Bartenhagen, C.; Fischer, U.; Korn, K.; Pfister, S.M.; Gombert, M.; Opara, 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. [CrossRef]

148. Martin-Lorenzo, A.; Hauer, J.; Vicente-Dueñas, C.; Auers, E.; González-Herrero, I.; García-Ramírez, I.; Ginzel, S.; Thiele, R.; Constantinescu, S.N.; Bartenhagen, C.; et al. Infection Exposure is a Causal Factor in B-cell Precursor Acute Lymphoblastic Leukemia as a Result of Pax5-Inherited Susceptibility. Cancer Discov. 2015, 5, 1328–1343. [CrossRef]

149. Rowe, M.; Fitzsimmons, L.; Bell, A.I. Epstein-Barr virus and Burkitt lymphoma. Chin. J. Cancer 2014, 33, 609–619. [CrossRef] [PubMed]

150. Li, C.; Zee, B.; Lee, J.; Chik, K.; Ha, S.; Lee, V. Impact of SARS on development of childhood acute lymphoblastic leukemia. Leukemia 2007, 21, 1353–1356. [CrossRef] [PubMed]
151. Taub, J.W.; Ge, Y.; Xavier, A.C. COVID-19 and childhood acute lymphoblastic leukemia. *Pediatr. Blood Cancer* 2020, 67, e28400. [CrossRef] [PubMed]

152. Greaves, M. COVID-19 and childhood acute lymphoblastic leukemia. *Pediatr. Blood Cancer* 2020, 67, e28481. [CrossRef]

153. Maia, R.A.R.; Wünsch Filho, V. Infection and childhood leukemia: Review of evidence. *Rev. Saúde Pública* 2013, 47, 1172–1185. [CrossRef]

154. Chabay, P.A.; Preciado, M.V. EBV primary infection in childhood and its relation to B-cell lymphoma development: A mini-review from a developing region. *Int. J. Cancer* 2013, 133, 1286–1292. [CrossRef]

155. Matsuoka, M. Human T-cell leukemia virus type I and adult T-cell leukemia. *Oncogene* 2003, 22, 5131–5140. [CrossRef] [PubMed]

156. Hauer, J.; Martín-Lorenzo, A.; Sánchez-García, I. Infection causes childhood leukemia. *Aging* 2015, 7, 607–608. [CrossRef] [PubMed]

157. Wray, B.B.; O’Steen, K.G. Mycotoxin-producing fungi from house associated with leukemia. *Arch. Environ. Health* 1975, 30, 571–573. [CrossRef]

158. Wray, B.B.; Harmon, C.A.; Rushing, E.J.; Cole, R.J. Precipitins to an aflatoxin-producing strain of Aspergillus flavus in patients with malignancy. *J. Cancer Res. Clin. Oncol.* 1982, 103, 181–185. [CrossRef]

159. McPhedran, P.; Heath, C.W. Multiple cases of leukemia associated with one house. *JAMA* 1969, 209, 2021–2025. [CrossRef] [PubMed]

160. Wray, B.B.; Rushing, E.J.; Boyd, R.C.; Schindel, A.M. Suppression of phytohemagglutinin response by fungi from a "leukemia" house. *Arch. Environ. Health* 1979, 34, 350–353. [CrossRef]

161. Hisano, S.; Zhang, R.; Faruk, M.I.; Kondo, H.; Suzuki, N. A neo-virus lifestyle exhibited by a (+)ssRNA virus hosted in an unrelated dsRNA virus: Taxonomic and evolutionary considerations. *Virus Res.* 2018, 244, 75–83. [CrossRef] [PubMed]

162. Schmidt, F.R. The RNA interference-virus interplay: Tools of nature for gene modulation, morphogenesis, evolution and a possible mean for aflatoxin control. *Appl. Microbiol. Biotechnol.* 2009, 83, 611–615. [CrossRef]

163. Hisano, S.; Zhang, R.; Faruk, M.I.; Kondo, H.; Suzuki, N. A neo-virus lifestyle exhibited by a (+)ssRNA virus hosted in an unrelated dsRNA virus: Taxonomic and evolutionary considerations. *Virus Res.* 2018, 244, 75–83. [CrossRef] [PubMed]

164. Kotta-Loizou, I.; Coutts, R.H.A. Mycoviruses in Aspergilli. A comprehensive review. *Front. Microbiol.* 2017, 8, 1699. [CrossRef] [PubMed]

165. Schmidt, F.R. The RNA interference-virus interplay: Tools of nature for gene modulation, morphogenesis, evolution and a possible mean for aflatoxin control. *Appl. Microbiol. Biotechnol.* 2009, 83, 611–615. [CrossRef]

166. Kotta-Loizou, I.; Coutts, R.H.A. Mycoviruses in Aspergilli. A comprehensive review. *Front. Microbiol.* 2017, 8, 1699. [CrossRef] [PubMed]

167. Piumala, S.E.; Ross, J.A.; Aplenc, R.; Spector, L.G. Epidemiology of childhood acute myeloid leukemia. *Cancer* 2001, 97, 2229–2235. [CrossRef] [PubMed]

168. Greaves, M. Author Correction: A causal mechanism for childhood acute lymphoblastic leukemia. *Nat. Rev. Cancer* 2018, 18, 526. [CrossRef] [PubMed]

169. Reilly, J.T. Pathogenesis of acute myeloid leukaemia and inv (16) (p13; q22): A paradigm for understanding leukaemogenesis? *Br. J. Haematol.* 2005, 128, 18–34. [CrossRef] [PubMed]

170. Kordes, U.; Krappmann, D.; Heissmeyer, V.; Ludwig, W.D.; Scheidereit, C. Transcription factor NF-kappaB is constitutively activated in acute lymphoblastic leukemia cells. *Leukemia* 2000, 14, 399–402. [CrossRef] [PubMed]

171. Kordes, U.; Krappmann, D.; Heissmeyer, V.; Ludwig, W.D.; Scheidereit, C. Transcription factor NF-kappaB is constitutively activated in acute lymphoblastic leukemia cells. *Leukemia* 2000, 14, 399–402. [CrossRef] [PubMed]

172. Pitt, J.I. Toxigenic fungi: Which are important? *Med. Mycol.* 2000, 38 (Suppl. 1), 17–22. [CrossRef]

173. Klein, K.R.; Woodward, C.S.; Waller, E.K.; Lechowicz, M.J.; Rosenthal, H. *Effects of Mycotoxins on Mononuclear Cells (MNCs) in Normal Blood, T-Cell Leukemia and Lymphoma Cell Lines*; American Society of Hematology: Washington, DC, USA, 2005.

174. Konstantinovas, C.; de Oliveira Mendes, T.A.; Vannier-Santos, M.A.; Lima-Santos, J. Modulation of Human Immune Response by Fungal Biocontrol Agents. *Front. Microbiol.* 2017, 8, 39. [CrossRef] [PubMed]

175. Pahl, H.L.; Krauss, B.; Schulze-Osthoff, K.; Decker, T.; Traenckner, E.B.; Vogt, M.; Myers, C.; Parks, T.; Warring, P.; Mühlbacher, A.; et al. The immunosuppressive fungal metabolite gliotoxin specifically inhibits transcription factor NF-kappaB. *J. Exp. Med.* 1996, 183, 1829–1840. [CrossRef] [PubMed]

176. Kordes, U.; Krappmann, D.; Heissmeyer, V.; Ludwig, W.D.; Scheidereit, C. Transcription factor NF-kappaB is constitutively activated in acute lymphoblastic leukemia cells. *Leukemia* 2000, 14, 399–402. [CrossRef] [PubMed]

177. Reilly, J.T. Pathogenesis of acute myeloid leukaemia and inv (16) (p13; q22): A paradigm for understanding leukaemogenesis? *Br. J. Haematol.* 2005, 128, 18–34. [CrossRef] [PubMed]

178. Greaves, M. Author Correction: A causal mechanism for childhood acute lymphoblastic leukemia. *Nat. Rev. Cancer* 2018, 18, 526. [CrossRef] [PubMed]

179. Ries, L.A.G.; Melbert, D.; Krapcho, M.; Mariotto, A.; Miller, B.A.; Feuer, E.J.; Clegg, L.; Horner, M.J.; Howlader, N.; Eisner, M.P.; et al. (Eds.) *SEER Cancer Statistics Review, 1975–2004*; National Cancer Institute: Bethesda, MD, USA, 2007. Available online: https://seer.cancer.gov/csr/1975_2004/ (accessed on 23 February 2021).

180. Puumala, S.E.; Ross, J.A.; Aplenc, R.; Spector, L.G. Epidemiology of childhood acute myeloid leukemia. *Pediatr. Blood Cancer* 2013, 60, 728–733. [CrossRef]

181. 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. [CrossRef] [PubMed]

182. Fong, C.T.; Brodeur, G.M. Down’s syndrome and leukemia: Epidemiology, genetics, cytogenetics and mechanisms of leukemogenesis. *Cancer Genet. Cytogenet.* 1987, 28, 55–76. [CrossRef]

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

184. 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. [CrossRef]

185. Heim, S.; Mitelman, F. Cytogenetic analysis in the diagnosis of acute leukemia. *Cancer* 1992, 70, 1701–1709. [CrossRef]

186. Khwaja, A.; Björkholm, M.; Gale, R.E.; Levine, R.L.; Jordan, C.T.; Ehninger, G.; Bloomfield, C.D.; Estey, E.; Burnett, A.; Cornelissen, J.J.; et al. Acute myeloid leukemia. *Nat. Rev. Dis. Primers* 2016, 2, 16010. [CrossRef]

187. Moorman, A.V.; Roman, E.; Willett, E.V.; Dovey, G.J.; Cartwright, R.A.; Morgan, G.J. Karyotype and age in acute myeloid leukemia. Are they linked? *Cancer Genet. Cytogenet.* 2001, 126, 155–161. [CrossRef]

188. Bloomfield, C.D.; Lawrence, D.; Byrd, J.C.; Carroll, A.; Pettenati, M.J.; Tantravahi, R.; Patil, S.R.; Davey, F.R.; Berg, D.T.; Schiffer, C.A.; et al. Frequency of prolonged remission duration after high-dose cytarabine intensification in acute myeloid leukemia varies by cytogenetic subtype. *Cancer Res.* 1998, 58, 4173–4179. [PubMed]
181. Grimwade, D.; Walker, H.; Oliver, F.; Wheatley, K.; Harrison, C.; Harrison, G.; Rees, J.; Hann, I.; Stevens, R.; Burnett, A.; et al. The importance of diagnostic cytogenetics on outcome in AML: Analysis of 1612 patients entered into the MRC AML 10 trial. The Medical Research Council Adult and Children’s Leukaemia Working Parties. Blood 1998, 92, 2322–2333. [CrossRef] [PubMed]

182. Mauritzson, N.; Johansson, B.; Albin, M.; Billström, R.; Ahlgrén, T.; Mikoczy, Z.; Nilsson, P.G.; Hagmar, L.; Mitelman, F. A single-center population-based consecutive series of 1500 cytogenetically investigated adult hematological malignancies: Karyotypic features in relation to morphology, age and gender. Eur. J. Haematol. 1999, 62, 95–102. [CrossRef] [PubMed]

183. Rossi, G.; Pelizzari, A.M.; Bellotti, D.; Tonelli, M.; Barlati, S. Cytogenetic analogy between myelodysplastic syndrome and acute myeloid leukemia of elderly patients. Leukemia 2000, 14, 636–641. [CrossRef] [PubMed]

184. Bacher, U.; Schnittger, S.; Haferlach, T. Molecular genetics in acute myeloid leukemia. Curr. Opin. Oncol. 2010, 22, 646–655. [CrossRef]

185. Abe, R.; Raza, A.; Preisler, H.D.; Tebbi, C.K.; Sandberg, A.A. Chromosomes and causation of human cancer and leukemia. LIV. Near-tetraploidy in acute leukemia. Cancer Genet. Cytogenet. 1985, 14, 45–59. [CrossRef]

186. 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. [CrossRef] [PubMed]

187. Larson, R.A.; Wang, Y.; Banerjee, M.; Wiemels, J.; Hartford, C.; Le Beau, M.M.; Smith, M.T. Prevalence of the inactivating 609C→T polymorphism in the NAD(P)H:quinone oxidoreductase (NQO1) gene in patients with primary and therapy-related myeloid leukemia. Blood 1999, 94, 803–807. [CrossRef]

188. 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. [CrossRef] [PubMed]

189. 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. [CrossRef]

190. Clarkson, B.D.; Boyse, E.A. Possible explanation of the high concordance for acute leukaemia in monozygotic twins. Lancet 1971, 1, 699–701. [CrossRef]

191. Greaves, M.F.; Maia, A.T.; Wiemels, J.L.; Ford, A.M. Leukemia in twins: Lessons in natural history. Blood 2003, 102, 2321–2333. [CrossRef] [PubMed]

192. Heath, C.W.; Moloney, W.C. Familial leukemia; Five cases of acute leukemia in three generations. J. Med. Genet. 1965, 14, 81–90. [CrossRef]

193. Draper, G.J.; Heaf, M.M.; Kinnier Wilson, L.M. Occurrence of childhood cancers among sibs and estimation of familial risks. J. Med. Genet. 1977, 14, 81–90. [CrossRef]

194. 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. [CrossRef]

195. Gu, Z.; Churchman, M.L.; Roberts, K.G.; Moore, I.; Zhou, X.; Nakitandwe, J.; Hagiwara, K.; Pelletier, S.; Gingras, S.; Berns, H.; et al. PAX5-driven subtypes of B-progenitor acute lymphoblastic leukemia. Nat. Genet. 2019, 51, 296–307. [CrossRef]

196. Raboso-Gallego, J.; Casado-García, A.; Isidro-Hernández, M.; Vicente-Dueñas, C. Epigenetic Priming in Childhood Acute Lymphoblastic Leukemia. Front. Cell Dev. Biol. 2019, 7, 137. [CrossRef]

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