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The Relationship between Cigarette Smoking and the Risk of Leukaemia: A Review of Epidemiological Evidence and Biological Mechanisms

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Abstract
Leukaemia comprises a number of haematological malignancies, being marked by the uncontrolled growth of abnormal blood-forming cells and as a result interfering with the normal production of blood cells. This review looks at the connection between cigarette smoking and leukaemia, with an emphasis on the epidemiological evidence and on the biological mechanisms by which tobacco smoke might lead to the development of the disease. Cigarette smoke includes a variety of harmful and carcinogenic substances such as benzene, tobacco-specific nitrosamines and polycyclic aromatic hydrocarbons. These substances can cause oxidative stress, damage to DNA, chromosomal abnormalities and genetic and epigenetic changes in haematopoietic stem and progenitor cells. Such alterations may interfere with normal cell differentiation, proliferation and apoptosis and could thus play a role in the development of leukaemia. The evidence reviewed shows that cigarette smoking is most consistently linked to acute myeloid leukaemia (AML), with various studies finding a higher risk among both current and former smokers. The evidence relating to acute lymphoblastic leukaemia (ALL), chronic myeloid leukaemia (CML) and chronic lymphocytic leukaemia (CLL) is less consistent, differing from study to study and according to the subtype of disease. The bone marrow toxicity related to benzene and the disruption of the bone marrow microenvironment offer plausible biological explanations for the associations observed. In general, the available literature supports an association between cigarette smoking and leukaemia, especially with regard to AML, even though more research is required to clarify the less well-established relationships. Continued efforts to prevent and help people to stop smoking should be considered major public health goals.

Keywords: Leukaemia, Cigarette Smoking, Acute Myeloid Leukaemia, Tobacco Carcinogens, Haematopoietic Stem Cells

Introduction

Leukemia is a hematological disorder characterized by uncontrolled proliferation of abnormal blood-forming cells, resulting in the accumulation of abnormal or immature leukocytes primarily within the bone marrow and blood, and impairment of normal blood-cell production [1]. It is commonly observed in children, accounting for 28% of pediatric cancer cases [2]. In the past, leukaemias have been divided according to the lineages of the altered cells either myeloid or lymphoid and on the basis of the clinical course of the disease, resulting in four main types: Acute myeloid leukaemia, acute lymphoblastic leukaemia, chronic myeloid leukaemia and chronic lymphocytic leukaemia [3].

Over the last twenty years, classification systems for these disorders have changed considerably. Instead of the earlier French-American-British morphological system, genetic based approaches have been gradually adopted, starting with the World Health Organization's classification and at the same time the European LeukaemiaNet guidelines [4]. In 2022, two new classifications were released at the same time the fifth edition of the WHO Classification of Haematolymphoid Tumours and the International Consensus Classification both of which defined new diseases mainly on the basis of genetic characteristics, replacing the previous morphological ones [5]. A major alteration in the fifth edition of the WHO classification was the removal of the 20% blast requirement for types of AML that have defining genetic abnormalities (except in the cases of AML with BCR::ABL1 fusion and AML with mutated CEBPA), so that now a defining molecular abnormality, together with the morphological features, is enough for a diagnosis [6]. This trend shows a wider move towards a multivariate classification that incorporates genetics, in which morphology, immunophenotype, cytogenetics and molecular abnormalities are all combined to

establish well-reasoned diagnostic categories [7]. The practical result of this is that thorough genetic analysis is now essential for the correct diagnosis and classification of AML and other myeloid neoplasms [8].

Leukaemia can be either lymphoid (or lymphoblastic, or lymphocytic) or myeloid (or myelogenous). The maturation stage of the altered cells can be used to differentiate leukaemias. Acute leukaemias are characterised by rapid growth of blast cells, particularly immature, young lymphocytes and myelocytes. Mature cells build up in chronic leukaemias, resulting in slowly spreading malignancies. Acute lymphoblastic leukaemia (ALL), chronic lymphocytic leukaemia (CLL), acute myelogenous leukaemia (AML), and chronic myelogenous leukaemia (CML) are the four distinct kinds of leukaemias [9]. It is unclear, nevertheless, if blood cancers maintain the hierarchical structure. In contrast to acute lymphoblastic leukaemias, myeloid leukaemias appear to be hierarchically arranged.

Leukaemia results from an abnormal change in haematopoietic stem cells or in those progenitor cells which have become committed during the process of blood cell formation. The malignant clone may then show either myeloid or lymphoid features, depending on the stage and the lineage involved. Acute myeloid leukaemia (AML) and chronic myeloid leukaemia (CML) are mainly linked with the myeloid lineage, while acute lymphoblastic leukaemia (ALL) and chronic lymphocytic leukaemia (CLL) affect the lymphoid lineage. In the case of AML and ALL there is mainly an accumulation of immature precursor cells, whereas in CML and CLL the cells involved are more highly differentiated. The relationship between haematopoietic stem/progenitor cells and the various types of leukaemia is given in Table 1 [10-12].

Table 1: Major types of leukaemia and their haematopoietic cell of origin

Type of leukaemia	Full name	Major lineage	Principal cell/stem-cell origin	Main abnormal cell produced
AML	Acute myeloid leukaemia	Myeloid	**Haematopoietic stem cell or myeloid progenitor/stem cell**	Abnormal myeloid blasts (myeloblasts and related precursors)
ALL	Acute lymphoblastic leukaemia	Lymphoid	**Lymphoid progenitor cell**, arising from the haematopoietic stem-cell lineage	Abnormal lymphoblasts, either B- or T-lineage
CML	Chronic myeloid leukaemia	Myeloid	**Haematopoietic stem cell (HSC)** with multilineage potential	Abnormal myeloid cells, particularly granulocytes
CLL	Chronic lymphocytic leukaemia	B-lymphoid	**Mature B lymphocyte** (arising from the lymphoid stem/progenitor lineage)	Abnormal mature B lymphocytes

Source: Adapted from [13, 6]

Major Types of Leukaemia and Their Peripheral Blood Film Features

Acute Myeloid Leukaemia (AML):

Acute myeloid leukaemia is an aggressive form of cancer which develops from myeloid precursor cells. The abnormal increase in myeloid blasts disrupts normal erythropoiesis, granulopoiesis and the production of platelets, causing anaemia, infection and bleeding. In a peripheral blood film, AML usually exhibits circulating myeloblasts, these being large cells with a high nuclear-to-cytoplasmic ratio (Fig 1), fine chromatin, obvious nucleoli and a moderate amount of cytoplasm [14]. The presence of Auer rods in the myeloblasts is a significant morphological indication of myeloid differentiation, even though Auer rods are not found in all cases of AML. The blood film may also reveal anaemia, thrombocytopenia and either a high or low white blood cell count [15].

Acute Lymphoblastic Leukaemia (ALL):

Acute lymphoblastic leukaemia is an aggressive disease of the lymphoid precursor cells, marked by the uncontrolled growth of immature lymphoblasts in the bone marrow. It can originate from either B-cell or T-cell precursors, B-cell ALL being the more common type [16]. Because of the proliferation of the lymphoblasts, normal haematopoiesis is suppressed and this leads to anaemia, thrombocytopenia and a decrease in the production of normal leukocytes. On examination of the peripheral blood smear the typical feature is the presence of lymphoblasts in circulation. These cells are generally of medium size, have a high nuclear-to-cytoplasmic ratio (Fig 1), show fine or relatively open chromatin, contain one or more nucleoli and have only a small amount of agranular cytoplasm [17]. Anaemia and thrombocytopenia are also frequently seen. Auer rods are not present, a feature that allows lymphoblasts to be differentiated from myeloblasts in AML [10].

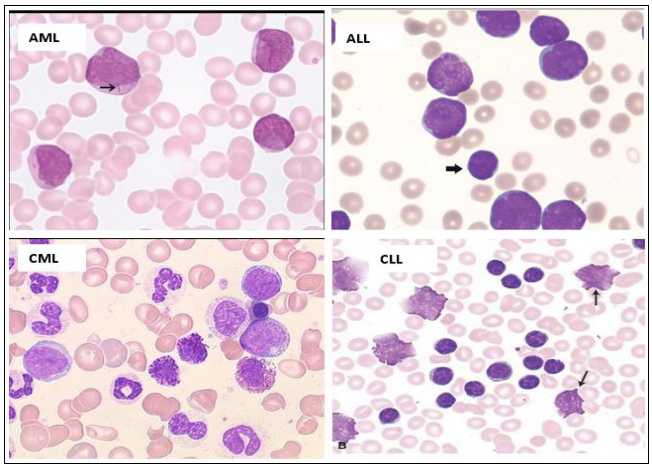
Chronic Myeloid Leukaemia (CML):

Chronic myeloid leukaemia is a disease of the myeloid line marked by an excessive growth of granulocytic cells and is closely linked to the BCR::ABL1 fusion gene which arises from the Philadelphia chromosome [18]. In a peripheral blood smear the typical finding is severe leukocytosis together with a left-shift in the granulocytic series, this showing an increased presence of neutrophils and their precursors such as myelocytes, metamyelocytes and, on occasion, promyelocytes [19]. Basophilia and eosinophilia are also frequently seen and these offer important indications for diagnosis. Different from acute leukaemias, in the chronic phase of CML the blood film mainly consists of maturing myeloid cells rather than having a majority of blasts (Fig 1) [20].

Chronic Lymphocytic Leukaemia (CLL):

Chronic lymphocytic leukaemia is a cancer of mature, generally B lymphocytes and is marked by the gradual build-up of abnormal lymphocytes in the blood, the bone marrow and the lymphoid tissues. It tends to progress slowly and mainly affects older people [21]. When examining the peripheral blood film the typical feature is a persistent lymphocytosis together with a higher number of small lymphocytes that look mature (Fig 1). These cells have a high ratio of nucleus to cytoplasm, dense or clumped chromatin and only a small amount of cytoplasm [22]. Another classic observation is the presence of smudge cells

(basket cells), which are caused by the fragility of the abnormal lymphocytes when the blood film is being prepared. Although smudge cells support a diagnosis of CLL they are not completely specific to it [23].



Leukaemia	Key feature to indicate
AML	Myeloblast with Auer rod
ALL	Lymphoblasts with high N:C ratio
CML	Granulocytes at different stages of maturation + basophilia

Source: Adapted from [24-27]

Fig 1: Characteristic peripheral blood-film morphology of the four major types of leukaemia

The global epidemiology and burden of leukaemia

Leukaemia represents a significant portion of the global cancer burden. The Global Burden of Disease Study 2021 shows that the number of new cases of leukaemia worldwide rose from 311,648 in 1990 to 461,423 in 2021 and is expected to increase further to 519,540 by 2050 [28]. In 2021, 57.15% (263,712 cases) of the new cases were in men and 70.88% (327,078 cases) were in people aged 45 years or over, while AML (144,656 cases, 31.35%) was the most common type 2050 [28]. Even though the total number of cases is increasing mainly because of population growth and ageing the age-standardised incidence rate for leukaemia fell significantly from 6.89 per 100,000 in 1990 to 5.63 per 100,000 in 2021 (average annual percentage change, AAPC −0.66), together with corresponding decreases in mortality (from 5.56 to 3.89 per 100,000; AAPC −1.16) and in disability-adjusted life years (from 266.31 to 136.94 per 100,000; AAPC −1.64) 2050 [28]. Incidence and mortality were always higher in men, and considerable regional disparities still exist: ALL is the main cause of the burden in areas with a low socio-demographic index, whereas AML is more common in areas with a higher SDI (Socio-demographic Index), and in some regions both incidence and mortality are projected to increase while global DALYs (disability-adjusted life years) are expected to decline by 2031 [2].

The impact is especially notable in children and young adults. All is the main cause of cancer-related death worldwide in people under the age of 20, representing 20.95% of all cancer deaths in this age group; between 1990 and 2021 the prevalence of ALL in this population increased by 60% while deaths decreased by 50%, the largest rises in both the number of cases (104%) and deaths (93%) occurring in Western Sub-Saharan Africa [29]. In 2021 there were an estimated 386,813 existing cases of ALL worldwide that is a 10.3% increase since 1990 and 71,221 deaths, the age-standardised prevalence rate rising from 4.1 to 5.4 per 100,000 [2]. Even though global deaths and DALY rates for childhood ALL have gone down, incidence rates remain variable, the burden on boys is greater than that on girls, and the disease burden in Sub-Saharan Africa and other low-SDI areas is increasing [30]. These trends highlight the urgent need for targeted prevention and care strategies, especially in low-resource areas [2, 28].

The epidemiology of leukaemia in Nigeria and in Africa

Reports from hospitals show that leukaemia is the most commonly diagnosed haematological malignancy in Nigeria, even though the proportion of cases differs from region to region. In a retrospective study spanning 16 years (2000 to 2015) at Jos University Teaching Hospital, haematological malignancies made up 19.3% of all cancers diagnosed, leukaemia being the most frequent (64.5%), then lymphoma (30%) and multiple myeloma (5.4%); chronic leukaemias were more common than acute leukaemias, there was a clear male majority (56.7%), and the number of cases of these malignancies increased during the period of the study [31]. The same results were found in Yola, in northeastern Nigeria, where leukaemia represented 58.9% of haematological malignancies, with CML being the most common type (23.3%), followed by AML (14.4%) and ALL (12.2%) [32]. In Kano, a three-year retrospective review (2017–2020) showed that CML was the most common haematological malignancy (45%), then CLL (24.2%) and AML (12.1%), with a mean age at presentation of 34.6 ± 14.9 years and a mean haemoglobin level of 8.4 ± 2.4 g/dl [33]. In Abakaliki, Ebonyi State, Ugwu *et al.*, (2021) [34] performed an eight-year retrospective analysis involving 135 persons diagnosed with haematological malignancies at Alex Ekwueme Federal University Teaching Hospital from May 2012 to April 2020. Leukaemias represented 48.2% of all haematological cancers, with lymphomas at 36.3% and multiple myeloma at 7.4%. Chronic leukaemias were more prevalent than acute leukaemias, with chronic lymphocytic leukaemia (CLL) being the predominant subtype (24.4%), succeeded by chronic myeloid leukaemia (CML; 12.6%), acute lymphoblastic leukaemia (ALL; 6.7%), and acute myeloid leukaemia (AML; 4.4%) [34].The fact that leukaemia was the predominant haematological malignancy in Jos & Ebonyi was in agreement with findings from Pakistan and Bangladesh but was in contrast to the results from Maiduguri (6.05%) and Benin City (17.4%) in Nigeria, where non-Hodgkin's lymphoma was the main type, thus confirming that there are significant variations in disease patterns even within the country [35].

The situation at the continental level is worrying since Africa is expected to see the greatest rise in the number of cases of AML over the next ten years, acute leukaemia being the most common form of leukaemia in adults and yet having the lowest survival rate of all types of leukaemia [36]. Because of the increasing incidence in Sub-Saharan Africa, the fact that cases are usually diagnosed late and because of the lack of both diagnostic and treatment facilities, it is essential to generate local epidemiological data, Nigerian researchers having specifically advised studies which assess the genetic and environmental risk factors linked to haematological malignancies in that area [31, 33].

Aetiology and Known Risk Factors

The causes of leukaemia are still not fully understood; even though there has been considerable progress in treatment, the origin of the majority of cases is unknown and a wide variety of genetic and environmental factors have been suggested [37]. The most well-established risk factors for acute leukaemia are old age, exposure to ionising radiation and genetic abnormalities such as LiFraumeni syndrome, Fanconi anemia, Bloom syndrome, and Down syndrome are correlated with a heightened risk of developing ALL and AML [38, 39]. Certain exposures have been related to distinct forms of leukemia; however, the most essential risk factors influence various subgroups. Ionising radiation which has been observed in Japanese survivors of the atomic bombs and among the clean-up workers at Chernobyl and exposure to benzene in the course of occupation are consistently regarded as the main environmental causes, together with exposure to pesticides, some chemotherapeutic agents and radiation therapy given for previous cancers [3, 40]. This significant amounts of ionizing radiation originating from the atomic bomb have been connected with a heightened death risk from all non-CLL leukemia among Japanese adults, notably affecting ALL, AML, and CML individually [38]. Additionally, exposure to formaldehyde, a chemical ubiquitous in several building materials, home products, and industrial disinfectants, has showed a strong relationship to myeloid leukemia. The fundamental mechanisms through which these shared risk factors contribute to oncogenic processes presumably display similarities.

An individual's family history of haemopoietic cancers also increases their risk [3], and a germline predisposition is becoming more widely recognised through familial mutations in genes such as CEBPA and RUNX1, as well as through inherited syndromes such as Fanconi anaemia, Bloom syndrome and Down syndrome [41]. Furthermore, about 25% of the AML cases identified in large population-based studies are classified as secondary (being therapy-related or having developed from a previous myeloid disorder) and are linked to lower response rates and a worse prognosis than de novo AML [41].

Factors that are less well established include obesity, smoking (in the case of AML) and exposure to pesticides, since the available evidence is not yet sufficient to allow definite conclusions [40]. Nevertheless, a study based on data from the Global Burden of Disease identified cigarette smoking, a high body mass index, and occupational exposure to benzene and formaldehyde as the primary risk factors for death due to AML, the harmful effects of carcinogen exposure being notably greater in areas with a low socioeconomic development index [42]. With respect to acute leukaemia as a whole, two separate "two-hit" hypotheses have been put forward one combining genetic susceptibility with external exposures in the case of ALL and the other involving a sequence of acquired mutations in the case of AML in order to explain the development of leukaemia [37]. These findings provide a biologically plausible basis for the investigation into the causes of leukaemia, including the assessment of modifiable exposures such as tobacco smoking carried out in the present study.

Pathogenesis and Mechanisms of Leukaemogenesis

The development of leukaemia is a complicated, multistage biological process by which normal blood-forming cells come to have genetic and epigenetic abnormalities that gradually change their ability to proliferate, differentiate, survive and undergo apoptosis [43]. It is not the result of a single genetic mutation but rather arises from the stepwise accumulation of various abnormalities in haematopoietic stem cells (HSCs) or in committed progenitor cells. These abnormalities give the affected cells a selective advantage, enabling them to survive and multiply clonally at the cost of the normal blood-forming cells. The malignant clone that results may then acquire further abnormalities which in turn promote increased proliferation, hinder cellular differentiation and assist in the progression to clinically detectable leukaemia [44].

In normal physiological conditions, hematopoietic stem cells maintain a balance between self-renewal and differentiation to ensure a continuous supply of red blood cells, white blood cells and platelets [45]. This process is governed by complex interactions between transcription factors, signalling pathways, epigenetic mechanisms, cell-cycle regulators and tumour-suppressor proteins. If any of these regulatory mechanisms is disrupted, abnormally developed blood cells can occur. According to the lineage and the molecular abnormalities present, malignant transformation may lead to acute lymphoblastic leukaemia (ALL), acute myeloid leukaemia (AML), chronic lymphocytic leukaemia (CLL), or chronic myeloid leukaemia (CML). Even though these diseases differ in the cell from which they originate and in their molecular features, they all involve fundamental mechanisms such as abnormal clonal expansion, impaired regulation of cell survival and proliferation, and a disruption of normal haematopoiesis [46].

Genetic and epigenetic alterations

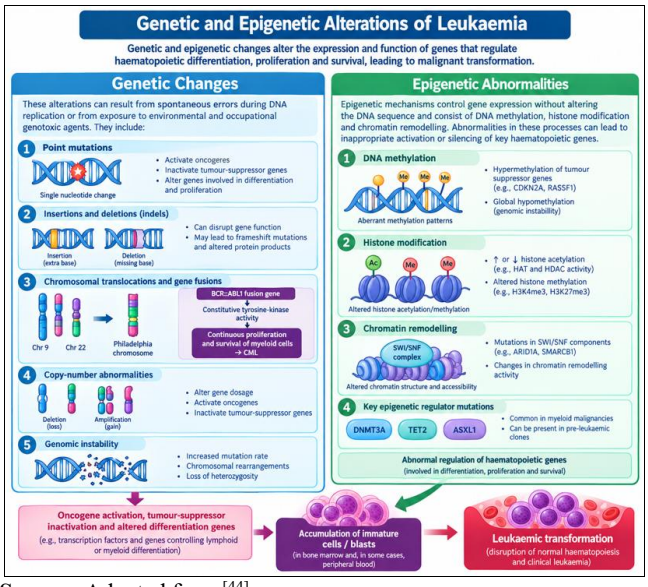
Genetic changes play a central role in the development of leukaemia; they can result from spontaneous errors that occur when DNA is replicated or from exposure to environmental and occupational genotoxic agents. The genetic abnormalities linked with leukaemia include point mutations, insertions and deletions, chromosomal translocations, gene fusions, copy-number abnormalities and other types of genomic instability (Fig 2). These abnormalities are capable of activating oncogenes, inactivating tumour-suppressor genes or modifying the genes which are responsible for normal differentiation and proliferation [44].

A key mechanism involves the activation of genes which encourage cellular proliferation and survival. For instance, the typical BCR::ABL1 fusion gene in CML is the product of a reciprocal translocation between chromosomes 9 and 22, leading to the formation of the Philadelphia chromosome. The BCR::ABL1 protein that results possesses constant tyrosine-kinase activity and therefore continuously triggers the intracellular signalling pathways responsible for cell proliferation and survival. This is what causes the uncontrolled growth of myeloid cells that is characteristic of CML [47].

In the same way, abnormalities in transcription factors and in genes responsible for lymphoid or myeloid differentiation can stop immature cells from undergoing proper maturation. If maturation is hindered but cell proliferation and survival go on, abnormal immature cells build up gradually in the bone marrow and, in certain instances, also in the peripheral blood. This process is especially significant in acute leukaemias since the accumulation of immature blast cells

disrupts the production of normal blood cells [46].

Epigenetic abnormalities also play a substantial role in the development of leukaemia. Epigenetic mechanisms control gene expression without altering the DNA sequence and consist of DNA methylation, histone modification and chromatin remodeling [44]. Abnormalities in the genes which are involved in these processes can lead to genes that regulate haematopoietic differentiation, proliferation and survival being activated or switched off in an inappropriate manner. Mutations in epigenetic regulators such as DNMT3A, TET2 and ASXL1 have been found especially in myeloid malignancies and can be present in pre-leukaemic clones. These results show that changes in gene regulation, together with direct changes in the DNA sequence, can contribute to malignant transformation [44, 48].



Source: Adapted from [44]

Fig 2: Genetic and Epigenetic Alterations Involved in the Pathogenesis of Leukaemia

Clonal expansion and evolution

A key feature of the development of leukaemia is clonal evolution. After a haematopoietic cell has acquired a favourable genetic change, it can undergo selective expansion and thus give rise to a group of cells that are genetically related. This group of cells may then obtain further mutations, each new mutation possibly providing additional advantages with regard to proliferation, survival or resistance to the normal regulatory mechanisms. As time goes on, the clone becoming more and more abnormal may end up becoming the dominant one in the bone marrow [46].

A good example of this process is clonal haematopoiesis, in which genetically modified blood cell clones can be found in people who do not have an obvious haematological malignancy [49]. Clonal haematopoiesis can remain stable for many years, but in certain individuals the gain of further genetic abnormalities may lead to progression to a myeloid malignancy, such as AML. Mutations in genes like DNMT3A, TET2 and ASXL1 are often linked with clonal haematopoiesis [46, 49]. Yet the occurrence of these mutations does not always result in leukaemia, which shows that further events are generally needed for malignant transformation.

The multistep model is especially applicable to environmental exposures like cigarette smoking. A person can at first have a small number of genetically altered haematopoietic cells without showing any clinical disease, and if they continue to be exposed to genotoxic substances this may lead to an increase in DNA damage and genomic instability, which could in turn help in the acquisition of further abnormalities. It follows that environmental exposures might function as initiating, promoting or accelerating factors at various stages of an already ongoing clonal evolution [49].

Dysregulation of cellular proliferation and survival

A major mechanism involved in the development of leukaemia is the disruption of the normal balance between cellular proliferation and apoptosis. Hematopoietic cells under normal conditions go through tightly regulated cycles of proliferation, maturation and programmed cell death. This keeps the number of blood cells in circulation at a level appropriate to the body's physiological needs.

In leukaemia, mutations in the growth-signalling pathways can lead to cells multiplying in the wrong way or surviving when they should normally undergo apoptosis [50]. Changes in the pathways involving RAS, PI3K/AKT, JAK/STAT and the tyrosine kinases, along with others, can result in continuous intracellular signalling and greater cellular survival [51]. Likewise, abnormalities in the tumour-suppressor pathways can decrease the cells' ability to respond properly to DNA damage or other cellular stresses. For instance, the TP53 tumour-suppressor pathway has a significant role in detecting DNA damage and in deciding whether a damaged cell should enter cell-cycle arrest, carry out DNA repair, become senescent or undergo apoptosis. If the normal function of TP53 is lost, then cells with considerable genetic abnormalities will be able to survive and multiply. The continued survival of such genetically damaged cells increases the chances of further mutations building up and may thus contribute to malignant progression [52].

Impaired differentiation and maturation

The normal process of blood cell formation depends on immature stem and progenitor cells differentiating in a well-regulated manner into mature myeloid and lymphoid cells. In the case of leukaemia, the transformation affects this process so that the cells stay in an immature or only partially differentiated state while still carrying on with their proliferation [9].

In acute leukaemias the bone marrow and the peripheral blood become filled with immature blast cells. These abnormal cells take up space in the bone-marrow microenvironment and prevent the production of normal erythrocytes, leukocytes and platelets. As a result the patients may suffer from anaemia, an increased susceptibility to infection and bleeding or bruising because of thrombocytopenia [53].

On the other hand, chronic leukaemias usually involve the buildup of more mature cells, even though these cells are still abnormal and are made in large numbers. The varying degrees of cellular maturation and differentiation are therefore responsible for the different clinical and biological features of acute and chronic leukaemias [54].

Genomic instability and DNA damage

Another important aspect of the development of leukaemia is genomic instability. The cells are constantly subjected to

DNA damage coming from endogenous sources such as oxidative metabolism, errors during replication and reactive oxygen species. Under normal conditions, the DNA repair systems either detect the damage and correct it or get rid of cells that are severely damaged by means of apoptosis. However, when the amount of DNA damage goes beyond what the protective mechanisms are able to handle, mutations and chromosomal abnormalities can build up [55]. Several environmental exposures can lead to an increased level of DNA damage. Ionising radiation, benzene, some cytotoxic drugs and tobacco smoke contain or produce agents which are capable of damaging DNA. If exposure continues, this raises the chance that mutations will take place in the genes that regulate haematopoiesis. When such changes occur in a haematopoietic stem or progenitor cell and give the altered cell a benefit in terms of survival or proliferation, that cell may expand and could thus play a role in the development of leukaemia [54].

Relationship between environmental exposure and leukaemogenesis

The fact that leukaemogenesis is a multistep process offers a solid framework for analyzing the possible role of environmental exposures. A person might at first have a small number of haematopoietic cells that have experienced genetic change, even if this does not result in any clinical disease. Subsequent exposure to genotoxic substances could therefore enhance DNA damage and oxidative stress and might thus help lead to the acquisition of subsequent abnormalities. Environmental exposures can therefore function as beginning, encouraging or accelerating variables at different phases in the overall process of malignant transformation.

The theory in question is especially pertinent to cigarette smoking, as it is the subject of the current study. The smoke from tobacco consists of a complex mixture of hazardous and carcinogenic chemicals, such as benzene, polycyclic aromatic hydrocarbons (PAHs), tobacco-specific nitrosamines, aromatic amines and other molecules which are able to form reactive oxygen species. Some of these chemicals have genotoxic effects and can lead to molecular damage in the tissues that are exposed [54].

Mechanisms Linking Smoking to Leukaemia (benzene, nitrosamines, oxidative DNA damage, micronucleus induction)

Benzene and Bone Marrow Toxicity

Benzene is one of the most prominent carcinogenic components with reference to the connection between tobacco smoke and leukemia. After it has been breathed, benzene is metabolised in the liver to create reactive metabolites such as phenol, hydroquinone and catechol. A number of these metabolites are able to reach the bone marrow, where additional metabolic events can lead to the creation of reactive intermediates that are capable of causing oxidative stress, DNA damage and chromosomal abnormalities. The bone marrow contains haematopoietic stem and progenitor cells which are in charge of producing all the major blood-cell lineages. The metabolites of benzene are able to disrupt the normal functioning and survival of these cells by influencing DNA repair, cell signalling, apoptosis, proliferation and differentiation [56]. Persistent genetic or epigenetic changes in the haematopoietic stem and progenitor cells, abnormal clones may be able to survive and grow, thus offering a possible route to leukaemic transformation. Benzene can also have an effect on the bone-marrow microenvironment, such as on the stromal cells that give structural and molecular support to the haematopoietic stem cells. Disruption of this supportive niche may interfere with normal hematopoiesis and may contribute to the survival or expansion of abnormal pre-leukaemic clones [56].

Tobacco-Specific Nitrosamines

Tobacco-specific nitrosamines (TSNAs) constitute a significant class of carcinogenic substances present in tobacco products and in tobacco smoke; among them are N-nitrosonornicotine (NNN) and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) [57]. These compounds are transformed by the body into active intermediates which are capable of reacting with DNA in cells and thus cause genetic damage. Both NNK and NNN are among the major carcinogenic components of cigarette smoke and tobacco-specific nitrosamines are able to cause DNA damage and mutagenesis [58].

The importance of the genotoxic effects of TSNAs lies in the fact that DNA damage in haematopoietic stem or progenitor cells can lead to mutations and genomic instability; if the abnormalities impact genes which control cell proliferation, differentiation, DNA repair or apoptosis, then the modified cells may gain a growth or survival advantage, and the ongoing accumulation of such changes can lead to clonal evolution and malignant transformation [59]. Moreover, tobacco smoke contains PAHs which can be metabolically activated and then interact with DNA, thus increasing the likelihood of genetic damage.

While the biological effects of TSNAs do offer a plausible mechanism by which tobacco exposure could lead to malignancy, their exact role in causing different types of leukaemia is less well established than the link between benzene exposure and myeloid malignancies. It follows that TSNAs should be seen as part of the wider range of genotoxic substances in tobacco smoke which may contribute to leukaemogenesis rather than as a sole cause of leukaemia.

Oxidative DNA Damage

Cigarette smoke is a major source of reactive oxygen species (ROS) and is also capable of triggering oxidative processes in cells; oxidative stress takes place when the amount of ROS produced goes beyond what the antioxidant and DNA-repair systems can handle, and this may result in damage to vital cellular components such as DNA, proteins and cell membranes [60]. When it comes to leukaemia, oxidative DNA damage is of particular significance if it takes place in haematopoietic stem and progenitor cells. Should damage cells survive rather than being properly repaired or undergoing apoptosis, the genetic abnormalities that they have acquired may then be passed on in later cell divisions. Because of this, repeated exposure to tobacco smoke may lead to an increased total amount of genetic damage in susceptible haematopoietic cells. This thus offers a possible explanation for how smoking could contribute to genomic instability and the development of leukaemia [61].

Oxidative damage to DNA may lead to base modifications, as well as to single- and double-strand breaks and errors in DNA replication. Generally, the DNA-repair systems are able to detect and repair most of this damage, and in the case

of severely damaged cells apoptosis occurs. But if the oxidative damage is persistent or excessive then these protective mechanisms can be overwhelmed and mutations and chromosomal abnormalities can build up.

Tobacco smoke has also an effect on raising the number of reactive oxygen species (ROS). When there is an excess of ROS, oxidative damage can occur to DNA, proteins and cellular membranes [62]. Oxidative damage to DNA may result in base changes, breakage in the DNA strands and replication mistakes. If this form of damage is not successfully repaired, it may be permanently included in the genome during later cell divisions. It follows that repeated exposure to tobacco smoke may thus lead to a bigger total amount of genetic damage in haematopoietic cells that are vulnerable to it [63].

Moreover, tobacco smoke includes polycyclic aromatic hydrocarbons and tobacco-specific nitrosamines [64], which can be metabolically activated to produce reactive compounds able to interact with DNA; the DNA damage that results might lead to mutations or genomic instability, and if it happens in haematopoietic stem or progenitor cells this could lead to clonal evolution [65]. The biological plausibility of this mechanism is reinforced by the known carcinogenic and genotoxic effects of numerous components of tobacco smoke.

The formation of micronuclei and chromosomal damage

Another way in which exposure to tobacco smoke could be linked to the development of leukaemia is by causing the formation of micronuclei and chromosomal damage. Micronuclei are small structures located outside the nucleus which contain either fragments of chromosomes or entire chromosomes that do not get incorporated into the main nuclei of the daughter cells during cell division. The presence of micronuclei is a sign of genomic instability and can be due to chromosome breakage or mistakes in chromosome segregation [66].

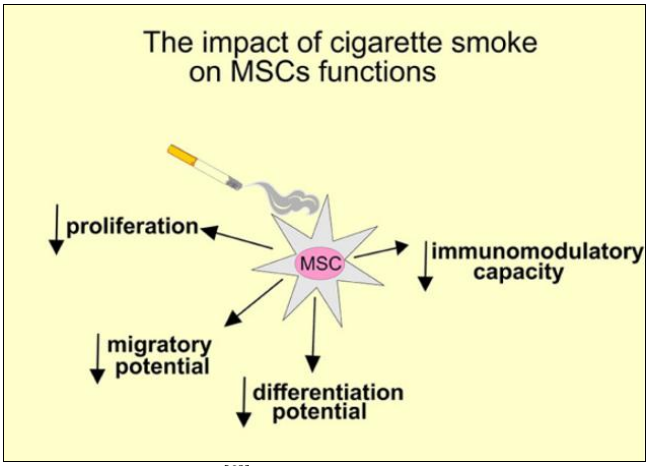
Several of the chemicals in tobacco smoke have genotoxic properties and may therefore lead to chromosomal abnormalities. Chemicals in tobacco smoke are able to cause the formation of micronuclei and chromatid exchange in myeloid tissue [67]. It is important because ongoing chromosomal damage can modify the structure or function of genes which are involved in the growth, differentiation and survival of haematopoietic cells.

As a result, chromosomal instability could increase the chance that a haematopoietic stem or progenitor cell accumulates a number of abnormalities over a number of successive cell divisions. Should these changes give the cell a selective advantage, then that cell might undergo clonal expansion and thus play a part in the multistep process of leukaemogenesis [68]. Hence, the formation of micronuclei and chromosomal damage offer another biologically reasonable route by which long-term exposure to tobacco smoke might contribute to the malignant transformation of blood-forming cells.

The effects of smoking on the bone-marrow microenvironment

Apart from damaging haematopoietic cells directly, cigarette smoke can also have an effect on the bone-marrow microenvironment, the cellular and molecular conditions needed for normal blood-cell production. This bone-marrow niche includes a number of supporting cell types, among them mesenchymal stromal cells (MSCs), which give structural support and control the maintenance, proliferation and differentiation of haematopoietic stem and progenitor cells (HSPCs) [69]. As shown in Fig 3, exposure to cigarette smoke hampers the functions of mesenchymal stromal cells (MSCs) by decreasing their ability to proliferate, migrate, differentiate and exert immunomodulatory effects [69]. Since MSCs are a key part of the bone marrow niche, they offer both structural and molecular support to haematopoietic stem and progenitor cells (HSPCs) which are responsible for the production of blood cells.

Because cigarette smoke is continuously inhaled, it can cause oxidative stress and trigger inflammatory reactions which disrupt the normal functions of the cells in this microenvironment. The evidence mentioned in your study shows that cigarette smoke can hinder the ability of bone-marrow MSCs to support HSPCs by means that involve ROS and the activation of the NLRP3 inflammatory pathway [70]; exposure can lead to a decrease in MSC proliferation, migration, differentiation and immunomodulatory functions, thus reducing their capacity to maintain normal haematopoiesis [56]. The balance between normal and abnormal blood-forming cells could therefore be altered by disruption of the bone-marrow niche. If the microenvironment is damaged or suffers from chronic inflammation it may interfere with the production of normal blood cells while at the same time producing conditions that are conducive to the survival and growth of abnormal or pre-leukaemic clones. This mechanism acts in addition to the direct genotoxic effects of tobacco smoke and indicates that smoking might affect the development of leukaemia both by damaging the haematopoietic cells and by altering their supporting microenvironment.



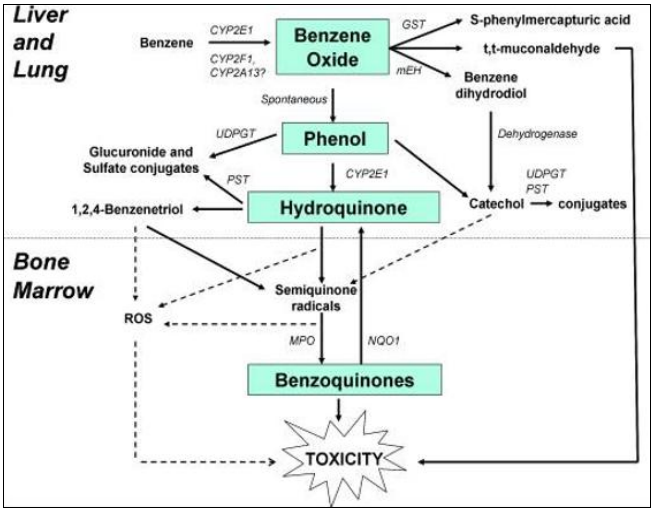
Source: Adopted from [69]

Fig 3: Effects of cigarette smoke exposure on mesenchymal stromal cell functions in the bone marrow microenvironment

Benzene in Cigarette Smoke and Leukaemia

Benzene is an aromatic hydrocarbon which is carcinogenic and found in cigarette smoke; it is a major toxic component that connects tobacco exposure with leukaemia. After cigarette smoke is inhaled, benzene passes into the blood and is mainly broken down in the liver into reactive metabolites such as benzene oxide, phenol, hydroquinone and catechol; these metabolites are able to reach the bone marrow, where they have toxic and genotoxic effects on the haematopoietic stem and progenitor cells (Fig 4) [56]. In the bone marrow, metabolites of benzene are able to cause

oxidative stress, result in DNA damage, produce chromosomal abnormalities and lead to epigenetic changes. They can also affect DNA repair, cell signalling, apoptosis and the normal proliferation and differentiation of haematopoietic stem cells. It is especially important that these cells be damaged since they are the ones that give rise to the different blood-cell lineages. If such genetic or epigenetic changes are persistent in these cells, this may lead to the survival and clonal expansion of abnormal cells, thus providing a route towards leukaemic transformation [56].
Benzene is also capable of disturbing the bone marrow microenvironment or stem-cell niche, this including the stromal cells which normally support the maintenance and differentiation of haematopoietic stem cells. This kind of disruption might hinder normal haematopoiesis and promote the expansion of abnormal or pre-leukaemic clones. As a result, exposure to benzene has been closely linked to acute myeloid leukaemia (AML) and myelodysplastic syndromes (MDS) [71].

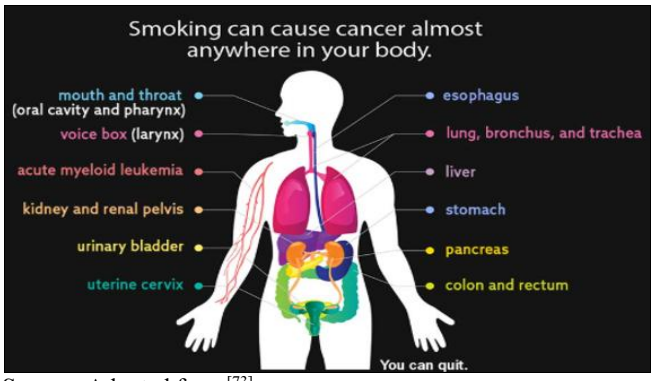


Cigarette smoke → Benzene → Benzene oxide → Phenol/Hydroquinone/Catechol → Bone marrow activation → Benzoquinones + ROS → DNA/cellular damage → Bone marrow toxicity → Abnormal haematopoiesis → Leukaemogenesis
Source: Adopted from [56]

Fig 4: Metabolic activation of benzene and its contribution to bone marrow toxicity and leukaemogenesis

Tobacco Smoking

Tobacco smoking is still the leading cause of preventable morbidity and premature death in the world. About 80% of the 1.3 billion tobacco users in the world are in low- and middle-income countries [72]. Understanding the global and national burden of smoking, the carcinogenic composition of tobacco smoke, and the mechanisms through which its constituents initiate malignant transformation is central to appreciating its contribution to leukaemia risk.
As demonstrated in Fig 5, cigarette smoking is connected with malignancies of the mouth and throat, larynx, oesophagus, lung, bronchus and trachea, liver, stomach, pancreas, colon and rectum, kidney and renal pelvis, urinary bladder and uterine cervix. Importantly, the image also identifies acute myeloid leukaemia (AML) as a smoking-associated cancer. This is particularly significant to the present study because it reveals that the potential carcinogenic consequences of tobacco smoking extend beyond solid tumours to encompass malignancies of the haematopoietic system.



Source: Adopted from [73]

Fig 5: Cancers associated with cigarette smoking at different anatomical sites, including acute myeloid leukaemia

Global and country-wide prevalence of tobacco smoking

Tobacco smoking remains a major health problem affecting a large proportion of the adult population worldwide. According to the Global Burden of Disease Study 2019, there were 1.14 billion (95% UI 1.13–1.16) current smokers worldwide in 2019, with age-standardised prevalence rates of current smoking tobacco use among individuals aged 15 years and older estimated at 32.7% (95% UI 32.3–33.0) among males and 6.62% (95% UI 6.43–6.83) among females [74]. The same analysis documented wide geographical variation, with male prevalence ranging from 7.33% in Peru to 64.6% in Timor-Leste, and female prevalence from 0.70% in Eritrea to 42.3% in Greenland; smoking prevalence exceeded 20% among males in 151 countries and among females in 42 countries [74]. Earlier estimates similarly found that approximately 23% of adults globally smoke tobacco, equating to around one billion people, with marked sex differences (32% of males versus 7% of females) [75]. Although prevalence has begun to decline in several regions the age-standardised prevalence of smoking among adults aged over 30 years was 19.4% in 2016, with a reference forecast of 14.5% by 2040 [76] the absolute burden remains enormous. A 2024 WHO report nevertheless forecasts that global smoking prevalence will remain high, at 30.6% among males and 5.7% among females, in 2030 [77].
At the national level, Nigeria exemplifies the pattern observed across sub-Saharan Africa, where data on smoking remain comparatively sparse and heterogeneous. A systematic review and meta-analysis of 64 studies (n = 54,755) conducted between 1990 and 2018 estimated the pooled crude prevalence of current smokers in Nigeria at 10.4% (95% CI 9.0–11.7) and of ever smokers at 17.7% (95% CI 15.2–20.2), with higher rates among men than women and considerable variation across geopolitical zones from 5.4% in the North-west to 32.1% in the North-east for current smoking and a median age at smoking initiation of 16.8 years [78]. Data from the Global Adult Tobacco Survey reported in Nigeria show that 10.0% of men, 1.1% of women and 5.6% overall (4.5 million adults) currently use tobacco products, while 7.3% of men, 0.4% of women and 3.9% overall (3.1 million adults) currently smoke tobacco [79]. Previous GATS data from 2012 had also reported overall currently smoking cigarettes at 3.7% (3.1 million adults; 7.2% males and 0.3% females) [80]. Recent spatial analyses estimated around 20 million active smokers in the country. More than 80% of them were male, and most of them were young adults aged 20-39 [72]. These figures

indicate that although smoking prevalence in Nigeria remains below the global average, a large and predominantly young male population is exposed to the carcinogenic constituents of tobacco smoke, with important implications for the future burden of smoking-related cancers, including leukaemia.

Harmful and Carcinogenic Substances in Cigarette Smoke

Tobacco smoke is an extraordinarily complex chemical mixture containing thousands of constituents distributed between a particulate ("tar") phase and a vapour phase. Cigarette smoke contains over 7,000 identified compounds, of which over 70 components of tobacco smoke are considered carcinogenic to laboratory animals or humans according to the International Agency for Research on Cancer (Table 2), of which 16 are recognised as carcinogenic to humans [81]. Approximately 60 known carcinogens have been identified in tobacco smoke, with the strongest activity attributed to polycyclic aromatic hydrocarbons, N-nitrosamines and aromatic amines, while the most prevalent carcinogens in the vapour phase include aldehydes, benzene and butadiene [82]. The particulate phase contains nicotine, the tobacco-specific nitrosamines 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone and N-nitrosonornicotine, metals such as cadmium, nickel, zinc and polonium-210, PAHs and carcinogenic aromatic amines such as 4-aminobiphenyl; the vapour phase contains carbon monoxide, carbon dioxide, benzene, ammonia, formaldehyde, hydrogen cyanide, N-nitrosodimethylamine and N-nitrosodiethylamine [82]. Mainstream smoke additionally contains gases such as ozone, formaldehyde, ammonia, carbon monoxide, toluene and benzene, together with roughly 10^{10} particles of varying sizes in each milliliter [64]. Several constituents are of particular toxicological significance. Benzene is classified by IARC as a Group 1 (confirmed human) carcinogen, as are 1,3-butadiene and benzo[a]pyrene, while styrene is classified as Group 2A and toluene as Group 3 (IARC, 2026). Over 500 distinct PAHs occur in tobacco smoke, of which BaP is regarded as the most potent carcinogen [83]. Many of these agents notably the PAHs and tobacco-specific nitrosamines are formed predominantly when tobacco is burned, whereas others, including nitrosamines such as N-nitrosodimethylamine, arise during processing, preservation and storage [81]. Among the constituents with the strongest carcinogenic activity are benzene, dimethylnitrosamine, ethylmethylnitrosamine, diethylnitrosamine, nitrosopyrrolidine, hydrazine and vinyl chloride [81]. Of these, benzene is the constituent most directly implicated in the induction of haematological malignancy, providing a mechanistic bridge between smoking and leukaemia.

Table 2: Major Harmful Substances in Cigarette Smoke and Their Effects

Harmful substance	Chemical class/type	Major harmful effects	Relevance to cancer/leukaemia
Benzene	Volatile organic compound	Bone-marrow toxicity; oxidative stress; DNA and chromosomal damage	Strongly associated with haematotoxicity and myeloid malignancies, particularly AML
Formaldehyde	Aldehyde	Irritates tissues; causes DNA and protein damage	Carcinogenic; may contribute to DNA damage and mutation
Acetaldehyde	Aldehyde	Irritation and oxidative stress; DNA damage	Carcinogenic and capable of forming DNA adducts
Tobacco-specific nitrosamines (TSNAs) e.g., NNK, NNN	Nitrosamines	DNA damage and mutagenesis	Important tobacco-related carcinogens associated with cancer development
Polycyclic aromatic hydrocarbons (PAHs) e.g., benzo[a]pyrene	Organic compounds produced during combustion	Oxidative stress and DNA adduct formation	Potent carcinogens that can induce mutations
Carbon monoxide (CO)	Toxic gas	Reduces oxygen-carrying capacity of blood by forming carboxyhaemoglobin	Causes tissue hypoxia and contributes to cardiovascular toxicity
Hydrogen cyanide	Toxic gas	Interferes with cellular respiration and oxygen utilization	Major systemic toxicant in cigarette smoke
1,3-Butadiene	Volatile organic compound	Genotoxicity and cellular toxicity	Carcinogenic; associated with DNA and chromosomal damage
Aromatic amines e.g., 4-aminobiphenyl	Aromatic compounds	DNA damage and formation of DNA adducts	Carcinogenic; particularly implicated in bladder cancer
Cadmium	Heavy metal	Kidney and lung toxicity; oxidative stress; DNA damage	Carcinogenic and may cause genomic damage
Arsenic	Metalloid/heavy metal	Oxidative stress, DNA damage and impaired cellular repair	Established human carcinogen
Chromium	Heavy metal	Oxidative stress and DNA damage	Certain chromium compounds are carcinogenic
Nickel	Heavy metal	Oxidative stress and cellular damage	Certain nickel compounds are carcinogenic
Lead	Heavy metal	Neurotoxicity, haematological and renal effects	Can contribute to oxidative stress and genomic damage
Ammonia	Irritant gas	Respiratory irritation and mucosal damage	Enhances toxicity of tobacco smoke; not a principal carcinogen
Nicotine	Alkaloid	Dependence; cardiovascular and neurological effects	Primarily responsible for addiction; facilitates continued exposure to tobacco carcinogens
Tar	Complex particulate mixture	Deposits numerous toxic chemicals in respiratory tissues	Contains PAHs and other carcinogenic compounds
Reactive oxygen species (ROS)	Reactive chemical species	Oxidative stress and lipid, protein and DNA damage	Can produce oxidative DNA damage and genomic instability
Polonium-210	Radioactive substance	Internal radiation exposure following inhalation	Can cause DNA damage and contribute to carcinogenesis

Source: Adapted from [84]

Smoking and the Risk of Leukaemia: Evidence from Epidemiological Studies

Leukaemia consists of a diverse group of haematological cancers in which the causes, cell lines involved, and natural courses vary considerably, and the same applies to their association with tobacco exposure [85]. Since studies that regard leukaemia as a single disease tend to blur or weaken the relationships specific to each subtype, the epidemiological literature should be assessed on the basis of subtype.

Smoking and Acute Myeloid Leukaemia

Research shows that smoking raises the risk of developing acute myeloid leukaemia, or AML. The chemicals in tobacco smoke can damage DNA in blood-forming cells. This damage may lead to changes in the cells that cause AML. The link between cigarette smoking and acute myeloid leukaemia (AML) is the most clearly established of all the major types of leukaemia [85]. AML results from the malignant transformation and clonal expansion of myeloid precursor cells in the bone marrow. Since cigarette smoke contains benzene and other carcinogens which are able to form reactive metabolites and cause DNA damage in haematopoietic cells, frequent exposure can therefore lead to genetic and epigenetic changes that cause abnormally rapid proliferation and faulty differentiation of myeloid progenitor cells [44]. Studies have found that people who smoke have a higher chance of getting AML compared to those who do not smoke. The risk increases with the number of cigarettes smoked each day and the number of years a person has smoked. Quitting smoking may lower this risk over time, but it does not return to the level of someone who has never smoked.

AML is the subtype most closely and consistently associated with cigarette smoking. The most extensive meta-analysis carried out so far combined data from 23 observational studies published between 1993 and 2013, involving 7,746 adult cases of AML, and showed that current smokers had a 40% higher risk of AML and ever smokers a 25% higher risk compared to non-smokers, the increased risk remaining the same regardless of sex, the type of study, the geographical area, or the quality of the study [86]. A meta-analysis from the same group that was carried out a little earlier, using data from 16 case–control and 6 cohort studies, gave very similar pooled odds ratios of 1.26 for ever smoking and 1.42 for current smoking, with a higher odds among men (ever smokers: OR 1.45 compared to 1.14 in women) and no clear geographical difference [87]. Later systematic reviews and updated meta-analyses have confirmed these results, verifying the link between cigarette smoking and susceptibility to AML especially in people of Caucasian descent [88], and further reviews of the literature on smoking and AML also reached the same conclusions [89]. With respect to the four main subtypes of leukaemia, the evidence showing a link between cigarette smoking and AML is the strongest and most consistent. This association is biologically plausible since carcinogens derived from tobacco, especially benzene and its reactive metabolites, are capable of causing toxicity to the bone marrow, leading to oxidative damage to DNA, producing chromosomal abnormalities, and disrupting normal haematopoiesis [88].

Smoking and acute lymphoblastic leukaemia

Acute lymphoblastic leukaemia (ALL) is a disease of the lymphoid precursor cells, characterised by the abnormal multiplication of immature B- or T-lymphoblasts [90]. In contrast to AML, the evidence showing a direct link between cigarette smoking and ALL is fairly limited and inconsistent. Even though tobacco smoke contains carcinogens which can cause DNA damage, epidemiological studies have not consistently shown that cigarette smoking is an independent risk factor for ALL [91]. The risk of ALL varies depending on the age at which it first appears and on when exposure occurred. In the case of adult ALL, a large case–control study found that the risk of ALL caused by tobacco was no different from the risk of AML, although the small number of cases made it difficult to arrive at a precise estimate; a similar study of comparable size gave an odds ratio of 1.3, indicating that the increased risk from smoking of ALL may be about the same as that for AML [92]. Yet other pooled analyses have not revealed a consistent association for adult ALL, which can be attributed to the relatively low incidence of the disease and the variety of study designs.

By contrast, research into childhood ALL has mostly focused on parental smoking. In the Northern California Childhood Leukemia Study (which included 327 cases of childhood leukaemia, comprising 281 cases of ALL and 46 cases of AML, and 416 matched controls), maternal smoking was not found to increase the risk of either ALL or AML; nevertheless, paternal smoking before conception was significantly linked to more than a threefold increased risk of childhood AML, with a suggestive but not statistically significant rise in the risk of ALL, and the risk of ALL was higher when paternal preconception smoking was combined with either maternal postnatal smoking or postnatal exposure to passive smoke [93]. It cannot be said on the basis of the current evidence that cigarette smoking is a clearly established risk factor for ALL to the same degree as it is for AML. The possibility on a biological level still exists since carcinogens from tobacco can lead to genetic damage in haematopoietic cells, but more epidemiological research is needed to determine whether smoking has a direct and independent role in the development of ALL [91].

Smoking and chronic myeloid leukaemia

Chronic myeloid leukaemia (CML) is a type of myeloproliferative neoplasm which is marked by the uncontrolled growth of myeloid cells and is closely linked to the BCR::ABL1 fusion gene caused by the Philadelphia chromosome [94]. Although similar to AML, the connection between cigarette smoking and CML is not as well established. CML has not been studied as extensively as AML, but the evidence available suggests the same conclusion. In the population-based Iowa/Minnesota study, both AML and CML risk increased as cigarette smoking intensity rose in both men and women; yet while the risk of AML decreased in a straightforward manner with the length of time since quitting, the reduction in CML risk was more gradual, and for both diseases the risk among long-term quitters (those who had quit for 30 years or more) was similar to that of people who had never smoked [95]. A meta-analysis of epidemiological studies found that smoking might significantly raise the risk of CML in a dose-dependent way, and it called for further well-designed prospective cohort studies to confirm this finding [96]. The burden-of-disease data are in agreement with a real contribution: In the GBD analysis of CML from 1990 to

2017, smoking was consistently the leading potential factor responsible for CML deaths and disability-adjusted life years, even though its contribution ratio fell over the course of the study period, especially in the higher SDI quintiles [97]. The pattern of a modest but dose-responsive increase in risk that lessens after long-term cessation is very similar to what would be expected for a malignancy of the myeloid compartment exposed to benzene and other leukemogens in tobacco smoke.

Smoking and chronic lymphocytic leukaemia

Chronic lymphocytic leukaemia (CLL) is a type of cancer marked by the gradual build-up of mature but abnormal B lymphocytes in the peripheral blood, in the bone marrow, in the lymph nodes, and in other lymphoid tissues [98]. Similarly, the connection between cigarette smoking and CLL is no clearer than the one seen in the case of AML. CLL has a unique place in this area of research since it is a mature B-cell neoplasm and not a malignancy arising from stem or progenitor cells. Smoking has not usually been regarded as a risk factor for CLL [99], and a review from 2002 found little support for an association, there being only one later study which indicated a small, statistically non-significant increase in risk for people who had smoked at least 42 years before their CLL was diagnosed [100]. The pooled analyses carried out by the InterLymph consortium are noteworthy in that they showed a modest inverse association a protective odds ratio of 0.91 for cigarette smoking, while the results for most occupational and chemical exposures were null or inconsistent, and CLL/SLL is generally regarded as nonradiogenic, lifestyle factors being among the least consistent of the possible risk areas [101]. Yet, the GBD 2019 study found that both a high body mass index and smoking were the main contributors to deaths and DALYs from CLL worldwide [102], and the UK Million Women Study, which followed about 1.3 million middle-aged women and recorded 9,162 cases of haematological malignancies (7,047 lymphoid and 2,072 myeloid), specifically looked at the associations by subtype of tobacco consumption, in line with the hypothesis that greater tobacco consumption is linked to an increased risk of haematological malignancy [103]. The apparent contradiction between the inverse or null associations found in the pooled case–control data and the positive findings in the GBD analyses probably stems from the very small size of any real effect, the possibility of residual confounding, and differences in the methods of analysis; overall, the full body of evidence shows that any causal role of smoking in CLL is at most weak and is certainly much smaller than that for the myeloid leukaemias [101].

Dose Response Relationships

Dose response analysis plays a key role in causal inference in this area, and the most clear-cut gradients are found in the AML meta-analyses. In the combined analysis of 23 studies, smoking intensity categorised as less than 10, 10–20, 20–30 and more than 30 cigarettes per day was linked to relative risks of 1.27, 1.36, 1.55 and 1.77 respectively; duration of smoking defined as less than 20 and more than 20 years was associated with relative risks of 1.07 and 1.44; and cumulative exposure grouped as less than 10, 10–20, 20–30 and more than 30 pack-years was connected with relative risks of 1.13, 1.23, 1.39 and 1.71 [86]. When the different measures are compared, it appears that intensity may be a greater factor in increasing AML risk than duration: those who smoked more than 20 cigarettes a day had an odds ratio of 1.76 compared with 1.38 for those who smoked fewer than 20 cigarettes, while smoking for more than 20 years was associated with an odds ratio of 1.35 and smoking for fewer than 20 years was not at all significantly related to AML [87]. Early research in the field also assessed dose–response in terms of the number of cigarettes smoked per day, the number of years smoked, and pack-years, thus setting the measurement standards that are still in use today [92].

The evidence showing a dose response relationship goes beyond acute myeloid leukaemia (AML). With regard to myelodysplastic syndromes (MDS), risk rose with both the intensity and the duration of smoking and then fell within a few years of stopping [104]; for chronic myeloid leukaemia (CML), meta-analytic evidence shows that the risk increases in a dose-dependent manner [96]; and at the molecular level, the mutation burden in MDS increases in a graded way as pack-years increase, with statistically significant trends observed for the chromatin-modification and RNA-splicing pathways as well as for the genes ASXL1 and ETNK1 [105]. Just as important is the reduction in risk following cessation: The risk of AML decreased in a monotonic fashion as the time since quitting increased and reached the level seen in people who have never smoked after 30 years [95], and the risk of acute leukaemia was also found to fall after cessation in the UK case–control study [92]. The fact that this effect is reversible and shows clear gradients risk increasing with greater exposure and decreasing after exposure stops meets the classic criteria for causality and forms the basis of the public health argument for promoting smoking cessation as a means of preventing leukaemia.

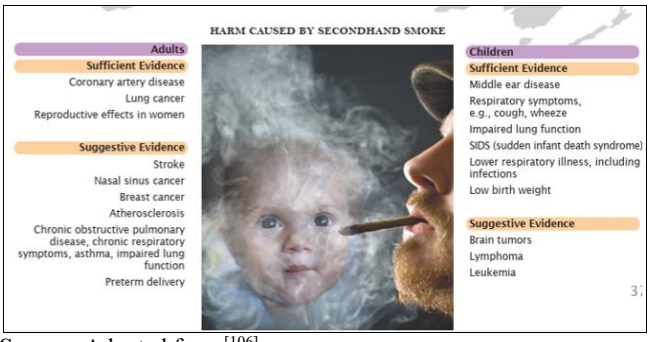
Passive Smoking and Secondhand Smoke Exposure (Secondary smoke exposure)

Passive smoking, also referred to as secondhand smoking, secondhand smoke (SHS) exposure, involuntary smoking, or exposure to environmental tobacco smoke (ETS), occurs when a non-smoker unconsciously inhales the tobacco smoke produced by another person who is smoking. In **Secondhand smoke,** the smoke a non-smoker inhales are from **two sources**; smoke exhaled by the smoker and smoke released directly from the burning cigarette. This secondhand smoke is made up largely of sidestream smoke, which is emitted directly from the burning end of a cigarette, and of mainstream smoke, which is exhaled by the smoker. Passive smoking therefore does not mean that a person starts to smoke themselves, but rather that one is exposed to tobacco smoke in the surrounding environment [106].

Secondhand smoke consists of a complex mixture of thousands of chemical substances, some of which are toxic and carcinogenic; this mixture includes benzene, tobacco-specific nitrosamines, polycyclic aromatic hydrocarbons, carbon monoxide, formaldehyde, and nicotine [107]. A number of these compounds can cause oxidative stress, DNA damage, inflammation, and other changes to cells. Because of this, the IARC has deemed involuntary exposure to tobacco smoke as carcinogenic to humans, the evidence in the case of lung cancer being established [108]. People may find themselves exposed to secondhand smoke in many situations, in particular in houses, at work, in public areas, in vehicles, in bars, and in other enclosed spaces where smoking happens. The extent and duration of this exposure

will vary according to the number of people who are smoking, how frequently smoking takes place, the ventilation of the area, the size of the enclosed space, and the length of time during which the exposure occurs [109]. As cotinine which is a metabolite of nicotine can be detected in biological samples such as blood, urine, and saliva, it is possible to use biomarkers such as cotinine to objectively measure exposure to secondhand smoke [110].

Passive smoking is linked to a number of harmful health effects (Fig 6). In adults, being exposed to secondhand smoke raises the chance of suffering from coronary heart disease, a stroke, respiratory disease and lung cancer, while exposure during pregnancy and in childhood is connected with bad developmental and respiratory results. The World Health Organization says that there is no safe level of exposure to secondhand tobacco smoke and that such exposure contributes greatly to premature death among non-smokers all over the world [111].



Source: Adopted from [106]

Fig 6: Harm caused by second hand smoke

Exposure to Passive Smoke and Leukaemia Risk

The link between passive smoking and leukaemia is biologically reasonable since secondhand smoke includes many of the same carcinogenic substances found in tobacco smoke that is actively inhaled. Particularly relevant to the development of leukaemia is benzene, a substance known to be haematotoxic and carcinogenic that is present in tobacco smoke [44]. After it has been inhaled, benzene is converted into reactive compounds which can reach the bone marrow and interfere with normal haematopoiesis. This kind of exposure may lead to oxidative stress, DNA damage, chromosomal abnormalities and a disruption of the normal development and survival of haematopoietic cells [65]. These mechanisms therefore offer a biological basis for examining whether long-term exposure to tobacco smoke by people who do not smoke could play a role in the development of haematological malignancies.

The health effects of environmental tobacco smoke are especially worrying for children since they have no say in regard to the level of exposure they suffer at home and because their developing blood-forming systems might be particularly susceptible. A meta-analysis of the evidence concerning maternal smoking during pregnancy which is the exposure that has been studied most frequently shows only a slight rise in the risk of all childhood cancers with no significant increase in the case of childhood leukaemia, and there is no clear dose–response relationship [112]. On the other hand, paternal exposure has been linked to childhood brain tumours and to lymphomas, though the data for other types of cancer were too limited to allow definite conclusions to be drawn, and it was not possible to rule out the possibility of bias and confounding [112].

Systematic reviews of paternal smoking and childhood ALL, which include 18 studies, confirm this pattern [113], and more comprehensive reviews of the causes of cancer list maternal and paternal smoking, together with in-utero exposure to alcohol, tobacco and pesticides, as recognised environmental risk factors for childhood leukaemia [114]. The idea that paternal rather than maternal smoking is the more important factor suggests that the cause lies in preconception germline damage or in early post-conception mechanisms rather than merely in transplacental exposure, and this provides additional justification for protecting households from tobacco smoke.

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