A Narrative Review on Association of Smoking with Genetic Polymorphism Leading Different Life Threatening Diseases

By

Jinat Jahan
ID: 19346034

A thesis submitted to the Department of Pharmacy in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy

School of Pharmacy
BRAC University
April 2024

© 2024. BRAC University
All rights reserved.

Declaration

It is hereby declared that

1. The thesis submitted is my/our own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I/We have acknowledged all main sources of help.

Student's Full Name & Signature:

Student Full Name
Student ID

Approval

The thesis/project titled "A Review on Association of Smoking with Genetic Polymorphism" submitted by Jinat Jahan (19346034) of Summer 2019, has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy (Hons.).

Supervised By:

Dr. Md. Aminul Haque
Associate Professor,
School of Pharmacy
BRAC University

Approved By:

Program Director:

Professor Dr. Hasina Yasmin
Program Director and Assistant Dean
School of Pharmacy
BRAC University

Dean:

Professor Dr. Eva Rahman Kabir
Dean
School of Pharmacy
BRAC University

Ethics Statement

This study did not involve any human participants, human specimens or tissue, vertebrate animals or cephalopods, vertebrate embryos or tissues and field research.

Abstract

Genetic polymorphism has a very strong correlation with different kinds of diseases. Smoking causes genetic changes which are responsible for diseases like cancers, stroke, cardiovascular diseases, infertility etc. Mutations in the DNA sequence can alter the proteins, microRNAs, or other gene products. This might result in issues like the gene product experiencing loss or increase of function, affecting its linked processes. The variation in the nAChR subunit genes is the strongest genetic contribution for smoking-related traits, according to large genome-wide association study (GWAS) meta-analyses conducted in recent years. However, many other genes have also been associated by candidate gene studies, small-scale GWAS, and extensive animal studies. The aim of this review article is to overview the association of smoking with genetic polymorphism in various kinds of health hazards.

Keywords: Smoking, Nicotine, Genetic Polymorphism, Cancer, Cardiovascular Disease, Stroke, Infertility.

Dedication

This thesis project is dedicated to my beloved parents.

Acknowledgement

I am grateful to Allah for enabling me to choose Pharmacy as my field of study. Without His powerful blessings, I would be unable to finish this project and submit it to obtain my Bachelor's degree in Pharmacy.

This effort was made possible with the help of several individuals, all of whom are acknowledged below. I want to thank my supervisor, Dr. Md. Aminul Haque, for giving me the opportunity to study a fascinating issue. Thanks to his persistent effort and motivation, I was able to work more diligently. His words have motivated me to improve my ability to communicate thoughts efficiently. While overseeing the project, he regularly and articulately shown his sincere dedication, which further inspired me to complete the task. I want to express my gratitude to Eva Rahman Kabir, who is the Professor and Dean of the School of Pharmacy, and Dr. Hasina Yasmin, who is a Professor and Assistant Dean at the School of Pharmacy, for their help throughout my entire experience.

I want to sincerely thank them for their constant support and encouragement throughout my life. They have inspired me to work diligently and with greater patience. Their persistent prayers and unwavering love have been important in my progress.

I sincerely thank all those who helped me with this project.

Table of Contents

List of Figures

List of Acronyms

SNP	Single Nucleotide Polymorphism
GWAS	Genome-wide Association Study
PCR	Polymerase Chain Reaction
CVD	Cardiovascular Disease
IS	Ischemic Stroke
ICSI	Intracytoplasmic Sperm Injection
ASCVD	Atherosclerotic Cardiovascular Disease

Chapter 1

Introduction

1.1 Background

Inhaling smoke from burning tobacco, which is contained in pipes, cigarettes, and cigars, is known as smoking. The habit of smoking only rarely, usually for relaxation or in a social environment, is known as casual smoking. A physical dependency to tobacco products is a smoking habit. Nowadays regular smoking is considered as an addiction of psychology according to many healthcare professionals, with detrimental effects on one's health. No one ever smokes in order to develop a nicotine addiction. The amount of nicotine that can be ingested before the body develops an addiction is unknown. But if smoking develops into a routine, the smoker will always be at danger for health problems because smoking is one of the deadliest addictions ever discovered (Brian, 2012).

Tobacco consumption has been considered one of the world's largest medical concerns for a long time. In the 20th century, it killed about 100 million people, most of them in the developed world's wealthier countries. High-income countries are already bearing a larger percentage of the health expenditures associated with smoking in low- to middle-income countries; estimates suggest that by the year 2150, tobacco use could threaten the existence of one billion people. The risks of coagulation of blood, cardiac illness, lung cancer, and oral cancer are increased by tobacco use. In addition, smoking tobacco raises the risk of heart attacks and strokes, damages teeth and gums, and wrinkles the skin (Duckworth & Lewis, 1999). Generally speaking, the highest smoking rates are seen in Southeastern Asia along with the European Balkan region. Chile has one of the highest rates of smoking worldwide, however that's not always the case. The smoking rates in West European and American countries are often lower. As of 2018, the

top five countries in the world for smoking rates are comprised of one Southeast Asian country, one South American country, and three Pacific Iceland Nations (Brian, 2012).

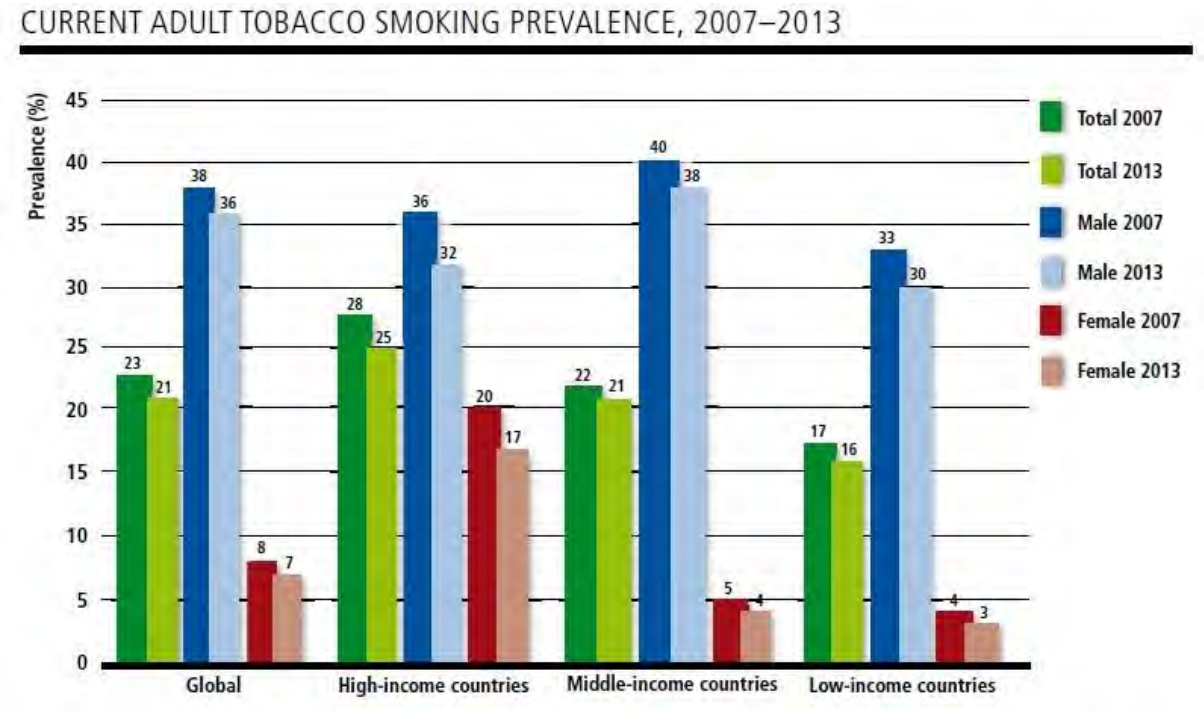

Figure1.1: Current adult tobacco smoking prevalence (2007-2013) (West, 2017)

This graph from the study illustrates how common smoking is worldwide. The apparent worry is that as the economies of low- and middle-income nations expand, the prevalence of smoking will increase. It is particularly concerning that over 30% of today's young adult smokers began smoking regularly before the age of sixteen in nearly two thirds of the world's countries. The majority of these nations have high or extremely high HDI scores, indicating that as economies grow, tobacco may become readily available to young people, enabling them to engage in smoking at a younger age. Furthermore, a quarter of young adolescent boys and females between the ages of 13 and 15 in over a third of nations have a tendency to start smoking as a result of peer pressure (Choudhury & Bhargava, 2007).

Smoking may boost your risk of cancer while additionally rendering it more: 1. Toxins in smoke from cigarettes can weaken the immune system, making it less able to kill cancer cells. Here the cancer cells expand the upregulated (Brian, 2012).

2. Toxins incorporated into tobacco smoke have a capability to modify or degrade a cell's DNA. DNA is a cell's "instruction manual" that handles a cell's usual development and functionality. A DNA that is damaged molecule is susceptible to an uncontrolled cell division that develops into a tumor with a malignant cell. In the United States, twenty percent of diagnosed cancers and thirty percent of cancer related fatalities are directly tied to smoking. Eighty percent of the malignancy cases and lung cancer-related fatalities are caused by smoking. A further danger that rises up is acute myeloid leukemia. Cigars, pipes, and cigarettes may all trigger cancer. In regions with low tobacco taxes, the affordability of cigarettes is higher for children due to the lower prices (Sankaranarayanan, Sattar, & Lakshmanan, 2014). Many teenagers like experimenting with new experiences, although they may lack the maturity to consider the potential long-term outcomes. Nicotine is a psychoactive substance that induces pleasurable feelings without causing a drunken state. Most elementary and early middle school pupils have not experimented with smoking cigarettes. Most people will assert that they will never use tobacco cigarettes and they are sincere in their statement (Choudhury & Bhargava, 2007).However, as they age, some individuals may become more welcoming to the concept of smoking. Tobacco corporations design their marketing strategies to depict smokers as fashionable, alluring, self-reliant, entertaining, appealing, and daring, which resonate with several teenagers. Consequently, individuals experiment with smoking without realizing that they can develop an addiction after smoke as little as one hundred cigarettes (five packs). Merely 5% of high-school-age smokers expect to continue smoking five years post-graduation, however they underestimate the challenges of stopping. Studies indicate that 75 percent of

smokers continue to use tobacco in some capacity after eight years (Sankaranarayanan, Sattar, & Lakshmanan, 2014).

1.2 What is Nicotine?

Nicotine represents an alkaloid which is found naturally in high concentrations in tobacco leaves. It is also found in other plants like tomato and eggplant. The plant's toxicity serves as a defense mechanism against insects. Nicotine-containing products include cigarettes and smokeless alternatives. Some smoking cessation aids, such as nicotine replacement therapy, including tobacco chewing gum and nicotine patches. Nicotine can enter the body through inhalation, ingestion, or dermal penetration (Tulabandhula & Rudin, 2014).

1.3 How Nicotine is Absorbed into The Body

Nicotine is absorbed by the body within 10 seconds of a cigarette smoker inhaling it, passing through the epidermis and mucosal linings of the nose, mouth, and lungs, and then circulating via the bloodstream to reach the brain. It triggers the adrenal glands to secrete epinephrine, which is a neurotransmitter and hormone often known as adrenaline. This causes an elevation in heart rate and blood pressure, as well as the constriction of blood vessels (West, 2017). Additionally, it triggers the release of a chemical called dopamine that regulates the brain's pleasure center. Nicotine is rapidly absorbed when inhaled due to the presence of many alveoli in the lungs. Alveoli offer a very large surface area, around 40 times greater than that of the epidermis, which facilitates the efficient absorption of nicotine into the bloodstream. Nicotine has a short half-life of around one to two hours in the human body. Approximately 0.031 milligrams of the 1 mg of nicotine breathed from a cigarette remains in the body six hours after smoking (Verde, 2016).

1.4 How Nicotine Affects the Body

Many individuals develop a tolerance to nicotine over time. Increased exposure to the drug leads to a higher tolerance, requiring larger doses to have the same enjoyable effect. This reaction promotes nicotine addiction. Nicotine exposure alters brain regions involved in stress management, learning, and self-regulation. Nicotine can be detected in blood, urine, saliva, and breast milk. Nicotine can be transmitted from breastfeeding women to their infants. Mothers who are pregnant and have the nicotine compound in their bloodstream can give birth to offspring who are dependent on the drug. Newborns can produce withdrawal symptoms after being born (Mishra, 2015).

1.5 Benefits of Nicotine

Nicotine is commonly linked to the negative consequences of smoking but can also provide specific advantages. These consists of:

1.Elevated states of alertness, exhilaration and relaxation.

2.Enhanced focus and recollection resulting from heightened levels of acetylcholine and norepinephrine.

3.Decreased anxiety - caused by elevated beta-endorphin levels, resulting in less anxiety (Sankaranarayanan, Sattar, & Lakshmanan, 2014).

1.6 Side Effects of Nicotine

Nicotine can induce a variety of adverse effects in multiple various systems and organs of the body of a human being. These mostly affect the brain, heart, and gastrointestinal system, leading to a range of indications and symptoms that should be monitored closely (Verde, 2016).

Most common side effects are: Feeling dizzy and arrhythmia, disrupted and erratic sleep patterns, disturbing sleep & night time terror, potential blood flow restriction, ulcer, dry mouth, vomiting and increased possibility of cardiovascular disease (Ware J. J., 2012).

1.7 Genetic Polymorphism

A modification in the DNA sequence of individuals, groups, or nations is known as genetic polymorphism. Sources consist of a sequence repeats, insertions, deletions, recombination and single nucleotide polymorphisms (SNPs). Mutations result in polymorphisms. A mutation may occur from an insertion, deletion, rearrangement, or modification of nucleotide types. Once generated, a polymorphism can be carried from parent to offspring just like every other DNA sequence. Genes and the proteins or microRNAs they produce can have their functions altered by DNA modification (Ismail, 2012).Lung cancer is thought to occur as a result of oncogenes promoting cancer being activated and tumor-suppressor genes being inactivated. For instance, the RB tumor-suppressor gene is no longer functional in 90% of individuals diagnosed with small-cell lung cancer and 15% of adults with non-small-cell lung cancer. In 50% of patients with non-small cell lung cancer and 70% of patients with small-cell lung cancer, the TP53 tumor-suppressor gene has been mutated and inactivated. KRAS oncogene activating mutations are hardly ever observed in lung cancers other than small cell malignancies in non-smokers (Mishra, 2015). The genetic susceptibility to environmental hazards or internally produced toxins is determined by genetic polymorphisms that are commonly found in the general population. This susceptibility involves a set of genes that are involved in the predisposition to specific diseases, the activation of metabolic processes or detoxification of genotoxins, and the regulation of DNA repair or cellular damage. Extensive research has been conducted on polymorphic genes that encode enzymes involved in the biotransformation of xenobiotics, specifically focusing on their significance as modifiers of cancer risk. Several

recent research have been examining the significance of these genes in the process of inflammation and in different autoimmune disorders such as multiple sclerosis, systemic lupus erythematosus, Guillain–Barré syndrome, and rheumatoid arthritis (Goeckenjan, 2015). Several substances that are of environmental significance have been proven to modify the body's immune system in several species. Exposure to natural xenobiotics, such as smoking, has been suggested as a potential cause for the loss of tolerance to self-proteins in genetically vulnerable individuals (Natássia E. Bufalo*, 2008).

1.8 Association of Smoking with Genetic Polymorphism Leads to Different Type of Diseases

Cancer

Smoking leads to cancer through various mechanisms. The primary method is through causing damage to the DNA within our cells. DNA regulates the growth and behavior of our cells. DNA damage leads to aberrant cellular behavior. Accumulation of DNA damage can eventually result in the development of cancer. Cigarette smoke contains more than 5000 compounds, including at least 70 known to be carcinogenic. Smoking introduces toxic substances into our lungs, impacting the entire body. These pollutants harm our DNA, including segments that provide protection against cancer. Cigarette smoke chemicals inhibit cellular DNA damage repair. This implies that DNA damage may develop. The accumulation of DNA damage within a single cell over time is what causes cancer (Goeckenjan, 2015).

Studies indicate that smoking leads to lung cancer through the formation of cell mutations. Cigarette smoke contains several compounds, a significant portion of which are carcinogenic. If the human body is unable to detoxify and eliminate carcinogens, they can lead to mutations in cells, potentially resulting in the development of malignant cells. Cell repair involves cells

continuously dividing until harm is fixed, and healthy cells have the ability to cease dividing when necessary. Cancerous cells fail the ability to regulate their division and growth, leading to continuous proliferation. Tobacco uses significantly increases the risk of developing lung, oral, throat, bladder, and various other types of cancers. Smoking is the direct cause of malignancies in 20% of those identified in U.S. (Ware J. J., 2012). All tobacco products for example cigarettes, pipes cigarette, nicotine gum *etc.* contain the following components:

1. Toxic substance like lead and arsenic
2. Carcinogens are agents which are known to cause cancer. Tobacco smoke contains a minimum of 70 carcinogens.
3. Nicotine which is the most addictive ingredient.

There is an Irish survey in 2015 stated that half number of all smokers are prone to die because of smoking related disease (Breitling, 2013). The data states that:

50% - due to cancers

14%- due to circulatory diseases

55% - respiratory disease

30% - other diseases (Breitling, 2013).

Heart Disease

The heart functions as the body's primary pump, circulating blood to essential organs. Smoking harms the engine through:

1.Raising heart rate increases the demand for oxygenation in the bloodstream. 2. Infusing carbon monoxide entering the bloodstream. This could lead to the onset of arterial heart diseases. These also cause potential heart attack.

3.Arteriosclerosis causing decreased circulation to the heart.

4. Elevating the likelihood of blood clot formation

5. Artiosclerosis causing decreased circulation to the heart (Isordia-Salas, 2023).

Stroke

Smokers have a higher likelihood of experiencing a stroke (either due to a clog of blood flow to the spinal cord or bleeding in the brain) compared to non-smokers. Strokes are a significant contributor to mortality and long-term impairment (Orhan, 2016).

Fertility and birth problems

Smoking can decrease fertility and increase the risk of miscarriage, stillbirth, and early infancy sickness when done during pregnancy (Amor, 2023).

1.9 Purpose

Over the past three decades, gene polymorphisms have garnered significant attention in various scientific disciplines concerning public health and illness. Genetic polymorphisms are the predominant kind of variation in DNA in humans. They exist in human beings at a frequency above 1% and are distinct from DNA mutations, which are often found at very low rates and in a limited number of individuals (Chiarella P. C., 2023) . Genetic variations play a significant role in individual differences and have been studied as valuable indicators in medicine, pathological conditions, epidemiological study, pharmacological sciences therapeutic

immunology, and ethnicity. Biological mechanisms control the uptake of nicotine, its effects on the central nervous system, and its metabolism; some of these pathways are well-developed, while others are not. Through the use of various study methods to examine genetic variation, genetic studies provide a possible window into the genes that contribute to those functions (Munafò, 2004) .The variation in the nAChR subunit genes is the strongest genetic contribution for smoking-related traits, according to large genome-wide association study (GWAS) meta-analyses conducted in recent years. However, many other genes have also been associated by candidate gene studies, small-scale GWAS, and extensive animal studies. The goal of this review is to discuss current development in numerous of specific domains related to the genetics and different types of disease formation through genetic polymorphism associated with the addiction to smoking and nicotine dependency (West, 2017).

Chapter 2

Materials and Method

While working on my review, 30 different types of articles has been chosen which are suitable to the subject and it is trusted that doing this would better help me to analysis the whole scenario in depth and make me clear about the concept. All the relatable articles have been collected from reputed sources such as Google Scholar, PubMed, nature direct, Rochester, ResearchGate etc. are thoroughly searched in order to collect all the necessary informations. To ensure the reliability of my review inquiry, articles were included from the stated sources. For finding out the appropriate articles, the keywords were searched like smoking, generic polymorphism, Association of smoking and cancers, Association of smoking with other diseases, association of smoking with genetic polymorphism etc. to get my expected informations. All the necessary databases are gathered and analyzed the relationship between smoking and genetic polymorphism with all the diseases including cancer. APA 7th citation has been used in my review article and have given proper acknowledgment to the authors. While reading all the collected articles, knowledge has been enriched about the mechanism of nicotine in human body, how DNA polymorphism contributes in the formation of the smoking related diseases as well as the global condition of smokers. This review article has made me understand the fact that the key mechanism of all smoking related illness is genetic polymorphism. A number of articles explained different kind of genetic mutation occurred by smoking responsible for specific kind of illness. Some specific words have been searched to find out desirable articles for this topic. For example, appropriate articles have not been found if “Cancer and genetic polymorphism” is searched for different types of cancers associated with smoking and genetic polymorphism. The appropriate keywords should be “Cancer, smoking and genetic polymorphism.”

Chapter 3

Discussion

Mutations in the DNA sequence can alter the proteins, microRNAs, or other gene products. This might result in issues like the gene product experiencing loss or increase of function, affecting its linked processes. The primary cause of cancer is an accumulation of mutations in DNA that interfere with cellular activities like cell division, resulting in uncontrolled cell growth. Certain genes are highly influential in the development of cancer. Gene mutations are more prone to causing cancer (Breitling, 2013) .Oncogenes are mutated genes that promote the development of cancer. Tumor suppressor genes typically inhibit the development of cancer. Defects in tumor suppressor genes promote cancer development by decreasing their activity. Cigarette smoke contains several carcinogens with genotoxic properties. The molecular pathways through which these factors contribute to cancer development are intricate (Brian, 2012). Several complex biochemical pathways with shared characteristics lead to cancer development following being exposed to nicotine or cigarette smoke. DNA mutations have the potential to alter an aspect of genes and their resulting polypeptide or microRNA products. The deactivation of tumor-suppressor genes and the production of oncogenes that stimulate cancer growth are thought to play a role in the formation of lung cancer. For instance, 90% of small-cell lung cancer patients and 15% of non-small cell lung carcinoma patients have loss of functionality of the RB tumor-suppressor gene. TP53 tumor-suppressor gene has mutations and deactivated in 70% of small-cell lung cancer patients and 50% of non-small cell lung carcinoma patients. enabling alterations associated with the KRAS oncogene occur frequently in non-small cell carcinomas of the lungs, but seldom in malignancies of people who do not smoke(Yongtang Xu, 2010).

3.1 Association of Smoking with Genetic Polymorphism Leads to Lung Cancer

Lung cancer affects roughly one in ten smokers over their lifetime. This suggests that a person's vulnerability to tobacco smoke may vary depending on their host. Segregation analyses and familial clustering of the disease have suggested a potential role for genetic vulnerability in the creation of lung cancer. It's believed that inter-individual differences in the genetic components linked to cigarette smoking influence a person's genetic susceptibility to developing lung cancer (Zhou, 2003) .Thanks to developments in molecular biology, there is increasing interest in examining biological indicators that could either enhance or decrease a person's susceptibility to smoking-related carcinogenesis .Genetic variations are known to affect the compounds in tobacco smoke that are absorbed, how they are metabolized, and how they interact with receptors. It has been demonstrated that the CYP1A1 MspI polymorphism increases catalytic activity for the conversion of pro-carcinogens, such as PAH and aromatic amines (Ariyoshi, 2002) . Glutathione synthesis with carcinogens is catalyzed by GSTP1 and GSTM1, which results in detoxification. Numerous researches have examined the relationship between polymorphisms in genes and the risk of lung cancer. According to another research, Ras genes contain a variety of biological roles, mostly regulating cell development and proliferation. Cigarette smoke chemicals induce mutations in the Ras gene. Smoking leads to lung cancer due to the high binding of carcinogens to specific sites in the K-Ras gene (Helmut Nair, 2002). Large cohort studies have established a definitive link between cigarette smoking and lung cancer. Approximately 20% of individuals who smoke get pulmonary carcinoma, while around 90% of individuals diagnosed with lung disease are smokers. Merely 2% of individuals diagnosed with cancer of the lungs were individuals who did not engage in

smoking. The correlation between smoking and lung cancer is more pronounced for squamous cell cancer and small cell forms, as opposed to adenocarcinoma and large cellular carcinoma (Zhou, 2003). The correlation between smoking and lung cancer is more pronounced in males than in females. The incidence of lung cancer in individuals who smoke is directly correlated with the age at which smoking begins, the daily quantity of cigarettes ingested, and the extent of inhaling of cigarette smoke. The rate of lung cancer is influenced by geographical deviations and gender differences, which are also associated with the frequency of tobacco smoking (Ariyoshi, 2002).

The current study confirms the significant interaction observed among smoking cigarettes and CY1A1 or GSTM1 variants, which aligns with the findings of previous pooled analyses. These analyses revealed a greater relationship between the CYP1A1 MspI or GSTM1 null variants and lung cancer among smokers. However, it should be noted that Benhamou and colleagues reported a non-significant increased likelihood of interaction between the GSTM1 null genotype and lung cancer specifically among Asian individuals (Helmut Nair, 2002). Cigarette smoking has been established as a causal factor in the formation of BPDE-DNA adducts, which are higher in tissue in the lungs of smokers with the GSTM1 null genotype. This genotype has been discovered to trigger mutations in the active codons of the gene p53. Therefore, we hypothesized that the correlation between CYP1A1 or GSTM1 gene variations and lung cancer is linked to the exposure to polycyclic aromatic hydrocarbons, which are formed by smoking. This is because hydrocarbons that are polycyclic aromatic are predominantly broken down by the enzymes CYP1A1 and GSTM1 (Zhou, 2003). The significant impact reported among smokers provides further evidence for the smoking-related cause of lung cancer in the Chinese community. It is now understood that both inherited variations in DNA sequence (such as gene mutations) and epigenetic processes, like abnormal DNA methylation, are crucial in the initiation and progression of lung cancer. The most

extensively researched epigenetic occurrence in connection with lung cancer involves the hypermethylation of the promoters of the p16, DAPK, or RARb genes (Ariyoshi, 2002).

3.2 Association of Smoking with Genetic Polymorphism Leads to Breast Cancer

The third typically found cause of cancer-related death is breast cancer. Furthermore, among women under 50, breast cancer is particularly common type of cancer. Numerous studies have demonstrated a connection between smoking and a higher risk of breast cancer. It has been suggested that the carcinogens included in tobacco smoke enter the bloodstream through the lungs' alveolar membrane and may then be carried to the mammary by plasma lipoproteins (Kasajova, 2016). According to in vitro research, smoking cigarettes triggers epithelial cells to mesenchymal transition, which results in a more invasive phenotype. Women who smoke have been found to have breast tissue with higher prevalences of tobacco compounds and smoking-specific DNA adducts than non-smokers .Several studies have looked at the danger of breast cancer based on genes linked to DNA repair or genotypes that the body uses to metabolize tobacco chemicals, with varying degrees of success .It has been found that some genes, including NAT1, NAT2, CYP1A1, COMT, BRCA1, BRCA2, and DNA repair genes, can change the association between smoking and the risk of breast cancer (Dunning, 1999). Smoking is associated with several diseases and an increased likelihood of breast carcinoma in younger women who have not yet reached menopause. Research indicates a potential connection between extensive exposure to second-hand smoke and an increased risk of breast cancer in postmenopausal women. Smoking can also exacerbate issues arising from breast cancer medication, such as:

- It can cause damage to the lungs of the patient from radiation therapy
- Healing is more difficult after surgery and breast reconstruction

- Blood clotting possibility are higher while taking hormonal medication (Verde, 2016).

Alterations or faults in the DNA might be likened to typographical errors. They could give incorrect instructions, resulting in flawed cell development or function. If a gene contains an error in one person, that identical fault will be present in all cells that have that gene. It's like having a manual of instructions with the exact same typographical error in every copy (Kasajova, 2016). There are two categories of DNA alterations: inherited and acquired mutations. Hereditary genetic alterations are transmitted from one generation to the next. Germ-line modifications or mutations refer to inherited DNA modifications. Somatic alterations refer to changes in DNA that occur during an individual's lifetime due to normal aging events or exposure to environmental toxins like nicotine. Certain DNA alterations are benign, while others have the potential to induce disease or health complications. Mutations are DNA alterations that have a deleterious impact on health (Dunning, 1999).

Women who continue to smoke after being diagnosed with breast cancer experience worse overall survival rates compared to those who quit smoking upon obtaining their diagnosis. It should not be surprising that continued smokers have a higher risk of death from any cause, considering the well-documented negative effects of smoking (Verde, 2016). These effects include a higher likelihood of wound infections after lumpectomy and breast preserving surgery, as well as respiratory and cardiovascular diseases, additional cancer diagnoses, and a lower overall quality of life. Individuals who smoke have a higher probability of experiencing treatment-related problems, such as adverse impacts on the cardiovascular system, and may require premature cessation of treatment. Conversely, a disease-specific connection may suggest more direct impacts on the amount of tumors, potentially leading to a less effective outcome for endocrine therapy (Dunning, 1999).

3.3 Association of Smoking with Genetic Polymorphism Leads to Thyroid Cancer

Genetic susceptibility research focuses on the connection between gene variations and the risk of thyroid cancer. On the other hand, gene-environmental research examines how smoking affects the association with thyroid cancer risk. This type of research tests whether or not carrying wild-type homozygous or variant genotypes leads to significantly different associations (-Gutaj, 2014). Although there is a distinction, studies on genetic vulnerability may provide information that backing up hypotheses of effect modification. When genetically stratified relationships are contrasted with the unadjusted relationship between circumstances and outcomes, this comparison can shed light on the research of genetic vulnerability among specific subgroups of the population, such as smokers (Maha, 2009).

Various gene mutations associated with distinct kinds of thyroid cancer are identified and studied. Three subtypes of multiple endocrine neoplasia type 2 (MEN2), one type of hereditary condition, can be distinguished by a mutation in the RET proto-oncogene (MEN2A, hereditary medullary thyroid cancer (FMTC), and (MEN2B), all of which increase the risk of medullary thyroid carcinoma. The relationship between the BRAF gene alteration and papillary thyroid cancer has been extensively studied (Guo, 2016). Smoking tobacco may worsen thyrocyte oxidative stress and promote mutagenesis through thiocyanate-ion-induced iodine transport obstruction. High quantities of oxidized iodine and hydro peroxides are necessary for the biosynthesis of TSH. As hydro Peroxides produce highly potent hydroxyl radicals that can damage oxidized bases (Guo, 2016). In fact, a drop in iodine content can encourage the production of excess H2O2. Reduced thyroid function and indicators of low iodine levels point to the activation of H2O2 production, which may cause somatic mutation and DNA damage.

Various investigations have demonstrated that cigarette smoking has numerous impacts on the activity of the thyroid gland. Smoking appears to alter thyroid function testing by reducing TSH levels and elevating thyroid hormone levels (Maha, 2009) .Nevertheless, these changes are typically minor. Tobacco smoking may contribute to thyroid autoimmunity. Several studies have shown a strong correlation between smoking and Graves' hyperthyroidism, especially in relation to Graves' orbitopathy. Smoking can elevate the likelihood of illness progression, diminish treatment efficacy, and potentially trigger a relapse (-Gutaj, 2014) .

Smoking in current population surveys is linked to a small decrease in serum TSH levels, which is likely caused by an increase in serum FT4 and FT3 levels due to the production of the nervous system's sympathetic nervous system. This effect is not influenced by iodine intake. On the other hand, the slightly larger gland growth in smokers is only seen in places with insufficient iodine, not in areas with abundant iodine (Maha, 2009). This increase in size is due to the blocking of thyroidal absorption of iodide by thiocyanate, which competes with iodide. Individuals who smoke are more likely to have a higher occurrence of nontoxic goiter and thyroid related illness, particularly in regions where there is a lack of iodine. Smoking at the present time decreases the danger of thyroid cancer in a manner that is dependent on the amount smoked. This effect is more noticeable for the papillary type of thyroid cancer compared to the follicular type (-Gutaj, 2014) .The probability of thyroid cancer in those who used to smoke is similar to that of individuals who have never smoked. Smokers may have a decreased chance of developing certain conditions due to their lower levels of TSH and decreased body mass index. Smoking at present reduces the likelihood of acquiring peroxidase and thyroglobulin antibodies, as well as preclinical and overt autoimmune hypothyroidism (Guo, 2016).This impact is influenced by the amount of smoking, but ceases within 3 years after stopping. The living being model of therapeutic autoimmune thyroiditis provides evidence that the anti-inflammatory properties of nicotine play a role. Smoking is a risk factor for Graves'

hyperthyroidism and particularly for Graves' ophthalmopathy. The risk increases with the amount of smoking (-Gutaj, 2014).

3.4 Association of Smoking with Genetic Polymorphism Leads to Cardiovascular Disease

Smoking raises the risk of death from all causes and plays a significant influence in arterial cardiovascular disease (ASCVD). Active smoking and exposure to secondhand smoke contribute to almost 30% of deaths from coronary heart disease (CHD). The specific causes of cardiovascular damage are not fully understood, although the harmful impact of smoking on the condition of endothelial cells has been acknowledged for a long time (Bazo, 2011). Smoking triggers oxidative processes that harm platelet function, fibrinolysis, inflammation, and vasomotor function. These effects increase a ten-year of fatal events in smokers compared to non-smokers. One interesting aspect of smoking is the susceptibility of the feminine sex. Females who smoke have a higher death rate from cardiovascular illnesses (CVDs) compared to male smokers (Breitling L. P., 2013) .Female smokers also have a 25% greater chance of developing coronary heart disease (CHD) than male smokers with similar experiences with tobacco smoke. This sensitivity in females appears to be linked to genes associated with thrombin signaling. Research on the impacts of quitting smoking has been well examined. Stopping at a young age (40 years) results with a significant 90% decrease in the additional risk of death. This review presents latest information on the direct connection between smoking and cardiovascular diseases, as well as the advantages of quitting smoking (Breitling L. P., 2013).

Genetic and epigenetic components have a significant role in coronary biology and illness. Smoking tobacco is a significant risk factor for cardiovascular issues and is influenced by hereditary variables, leading to changes in epigenetic patterns. The epigenetics and genetic of

smoking-related heart disease illustrate environmental epigenetics and recent multimodal analysis methodologies (Munafò, 2004). A strong correlation between smoking-related variations in methylation in the F2RL3 chromosome and survival in patients with chronic coronary artery disease has been recently reported. However, there is a lack of particular information regarding the impact of genetic variations and epigenetic modifications on the growth of cardiovascular illnesses in smokers. Gene-environment interactions are thought to be involved in tobacco-related coronary artery disease and have been observed for different genetic variations (Bazo, 2011).One well-researched instance is the relationship between smoking and apolipoprotein E variations. The E protein, isoform ε4 has lower antioxidant properties compared to other variations and has been linked to a change in lipoprotein distribution that promotes the generation of oxidized lipoproteins. The genetic difference in antioxidative resilience does not have clinical cardiovascular repercussions on its own. However, when combined with the increased oxidative stress from smoking, it significantly amplifies the cardiovascular risks in individuals who carry the ε4 gene compared to others (Breitling L. P., 2013).

3.5 Association of Smoking with Genetic Polymorphism Leads to Stroke

The association between tobacco and the likelihood of stroke with ischemic attack has been recognized for a considerable period. Traditionally, research have been limited to exploring correlations rather than causality because of the constraints of observational analysis. Recent epidemiological studies have shown that current smokers are at a greater risk of ischemic stroke compared to individuals who have never smoked (Isordia-Salas I. S., 2023) .Yet, there is limited information regarding the connection between smoking and certain forms of ischemic stroke. A recent case control research suggested that, smoking could heighten the vulnerability to major artery atherosclerotic stroke. Tobacco smoke consists of numerous detrimental

substances that are transmitted from the lungs to the bloodstream. These substances alter and harm cells, so impacting the functioning of your body (Orhan G. E., 2016). These alterations impact the circulatory system in your body and elevate your susceptibility to stroke. Smoking has an impact on the cholesterol levels in your body. It decreases the amounts of beneficial HDL cholesterol and increases the levels of harmful LDL cholesterol. Elevated levels of LDL cholesterol heighten the likelihood of experiencing a stroke. Cigarette smoke involves carbon monoxide and nicotine. Carbon monoxide decreases the oxygenation of your blood, while nicotine accelerates your heart rate, leading to an increase in blood pressure. 50% of all fatal strokes are associated with high blood pressure. Tobacco smoke contains compounds that increase the likelihood of blood clotting. Collectively, these smoking-induced effects elevate your susceptibility to developing atherosclerosis, sometimes referred to as arterial stiffening. Individuals with atherosclerosis experience arterial narrowing and decreased arterial flexibility, resulting in reduced blood flow, elevated blood pressure, and an increased risk of blood clot formation. Cerebral embolisms obstruct blood flow and result in the demise of brain cells (Munafò, 2004).

These AGTR1 A1166C, AGT M235T, as well as AGT T174M polymorphism were linked to a higher likelihood of ischemic stroke in young individuals from Mexico. In young patients with ischemic stroke (IS), these genetic variations could potentially contribute to the early onset of endothelial dysfunction, elevated vascular tone and blood pressure, migration of smooth muscle cells, and accelerated cell division, hence increasing the susceptibility to this kind of cerebrovascular disease. The presence of polymorphisms linked with thrombophilic illnesses fibrinolytic activity and as well as increased platelet aggregability did not show any correlation with stroke caused by ischemia in the same group of individuals (Orhan G. E., 2016).

3.6 Association of Smoking with Genetic Polymorphism Leads to Fertility Issue

Climate and lifestyle factors, such as nutrition, alcohol use, physical activity, and exposure to tobacco smoke, contribute significantly to the worsening of infertility issues in idiopathic male infertility cases. Topical exposure to toxicants causes distinct changes at different stages of spermatogenesis, including mitotic, meiotic, and post-meiotic phases. Indeed, it has been verified that there is a rising trend in male fertility impairment, which could perhaps be linked to environmental variables and lifestyles (Amor H. A., 2023). This study specifically examines the impact of tobacco smoke on the structure of spermatozoa, the genetic variation in nuclear protein genes, and the ability of sperm to fertilize an egg. We analyze semen samples from both heavy-smoker and nonsmoker patients who are undergoing intracytoplasmic sperm injection (ICSI) counseling. The quality of human sperm is often determined by the basic parameters of semen analysis established by the World Health Organization (WHO): sperm counts, motility, and morphology. A recent study has revealed a correlation between the integrity of DNA and traditional semen characteristics. A higher proportion of damage to DNA is linked to an increase in abnormalities of semen (Ji, 2012).

Research indicates that smoking can lead to genetic and epigenetic abnormalities in sperm, such as oxidative damage to DNA, chromatin packing issues, chromosomal changes, mutations, polymorphisms, DNA methylation changes, mRNA expression dysregulation, all of which can impact sperm function and male fertility (West, 2017) .Recent research suggests that epigenetic and genetic modifications in sperm cells produced by harmful substances in tobacco can be passed on to the next generation. Smoking can impact sperm DNA integrity through chemical compounds found in cigarette smoke like lead, mercury, arsenic, carbon monoxide, nicotine, and cotinine. These substances are absorbed into the bloodstream and

accumulate in seminal plasma, leading to oxidative stress and significant changes in sperm quality, including DNA fragmentation. Oxidative injury is the primary reason for sperm DNA breakdown, which can hinder sperm functions and result in reduced male fertility (Amor H. A., 2023).

Smoking leads to the creation of molecules known as free radicals, which in turn result in oxidative stress within the body. Sperm DNA can be damaged by oxidative stress, resulting in decreased fertility. PGAM5 has demonstrated its involvement in cellular defense against oxidative stress. Therefore, a decrease in the expression of this gene could render sperm more vulnerable to harm caused by oxidative stress induced by smoking. Furthermore, research has demonstrated that smoking negatively affects the mitochondrial activity in different organs, including sperm (Ji, 2012). PGAM5 is involved in the control of mitochondrial function, hence a decrease in the expression of this gene may result in more mitochondrial malfunction during response to smoking. Smoking induces inflammatory in the body, and persistent inflammation has been associated with reduced fertility. PTPRN2 has been demonstrated to have a function in the regulation of inflammation. Consequently, a decrease in the activity of this gene could render sperm more susceptible to the harmful effects of inflammation generated by smoking (Amor H. A., 2023).

Chapter 4

Conclusion

Tobacco consumption has long been recognized as one of the most serious global health problems. During the 20th century, this phenomenon caused the death of around 100 million individuals, with the majority of fatalities occurring in the more prosperous nations of the developed world. Wealthy nations currently bear a greater proportion of the healthcare costs related to tobacco in lower to middle-income countries. Projections indicate that by 2150, tobacco usage could pose a significant hazard to the survival of one billion individuals. Upon inhalation, nicotine is rapidly absorbed by the body, penetrating the skin's outermost layer and mucosa linings of the mouth, nose, and lungs. It then enters the bloodstream and efficiently travels to the brain. It stimulates the adrenal glands to release epinephrine, a type of neurotransmitter and hormone commonly referred to as adrenaline. This leads to a boost in pulse and circulation, as well as the narrowing of blood vessels. Moreover, it stimulates the secretion of a neurotransmitter known as dopamine, which controls the pleasure region of the brain. Smoking sends harmful compounds into our lungs, which has a detrimental effect on the entire body. These contaminants have a detrimental effect on our DNA, specifically targeting portions that play a crucial role in safeguarding against cancer. The chemicals present in cigarette smoke impede the process of repairing cellular DNA damage. This suggests that damage to the genome may occur. Cancer caused by the progressive buildup of damage to DNA within an individual cell. Furthermore, the correlation between tobacco uses and the probability of experiencing an ischemic stroke has been acknowledged for a significant duration of time. Traditionally, research has been restricted to investigating associations rather than causality due to the limitations of observational analysis. Recent epidemiological researches have demonstrated that persons that now smoke are more susceptible to

experiencing ischemic stroke in comparison to those who have never smoked. Smoking increases the likelihood of dying from any cause and has a substantial impact on the development of arterial heart disease (ASCVD). Both actively smoking and being exposed to secondhand smoke are responsible for over 30% of deaths caused by cardiovascular heart disease (CHD). Furthermore, the act of smoking can have a detrimental effect on the integrity of sperm DNA due to the presence of several chemical components in cigarette smoke, such as lead, arsenic monoxide, nicotine, and cotinine. These toxins enter the bloodstream and build up in the fluid that surrounds sperm, causing oxidative stress and notable alterations in sperm quality, such as DNA fragmentation. Sperm DNA degradation is mostly caused by oxidative damage, leading to impaired sperm activity and decreased male fertility. Recent years have seen the emergence of large-scale genome-wide association studies (GWAS) that consistently demonstrate the predominant genetic influence on smoking-related characteristics arising from variations in the gene responsible for the nicotinic receptor subunit.

In conclusion, extensive research has established that cigarette smoking is a potent catalyst for DNA methylation and the modification of gene expression, both of which have been linked to adverse health effects.

References

Amor, H. A. (2023). The Impact of Heavy Smoking on Male Infertility and Its Correlation with the Expression Levels of the PTPRN2 and PGAM5 Genes.

Ariyoshi, N. M.-A. (2002). Genetic polymorphism of CYP2A6 gene and tobacco-induced lung cancer risk in male smokers.

Bazo, A. P. (2011). DNA repair gene polymorphism is associated with the genetic basis of atherosclerotic coronary artery disease.

Bhandari, I., Colet, E., Parker, J., Pines, Z., Pratap, R., & Ramanujam, K. (1997, March). Advanced Scout: Data Mining and Knowledge Discovery in NBA Data. *Data Mining and Knowledge Discovery*, 121-125.

Breitling, L. P. (2013). Current genetics and epigenetics of smoking/tobacco-related cardiovascular disease.

Brian, S. (2012, January 25). The Problem of Shot Selection in Basketball. *PLoS One*. Retrieved from https://doi.org/10.1371/journal.pone.0030776

Chiarella, P. C. (2023). Contribution of Genetic Polymorphisms in Human Health.

Chiarella, P. C. (n.d.). Contribution of Genetic Polymorphisms in Human Health. *2023*.

Choudhury, R. D., & Bhargava, P. (2007). Use of Artificial Neural Networks for Predicting the Outcome. *International Journal of Sports Science and Engineering, 1*(2), pp. 87-96.

Doll, R. H. (1964). Mortality in Relation to Smoking: Ten Years' Observations of British Doctors.

Duckworth, F., & Lewis, T. (1999). *Your Comprehensive Guide to the Duckworth/Lewis Method for Resetting Targets in One-day Cricket.* University of the West of England.

Dunning, A. M. (1999). A systematic review of genetic polymorphisms and breast cancer risk.

Goeckenjan, G. (2015). Smoking and lung cancer.

Guo, Q. (2016). EliScholar – A Digital Platform for Scholarly Publishing at Yale Smoking , Genetic Polymorphisms In Dna Repair Genes And Risk Of Thyroid Cancer.

-Gutaj, N. G.-O. (2014). Influence of cigarette smoking on thyroid gland - An update.

Helmut Nair, U. R. (2002). Genetic polymorphism of CYP genes, alone or in combination, as a risk modifier of tobacco-related cancers.

Hoffmann, H. I. (n.d.). Genetic polymorphisms and the effect of cigarette smoking in the comet assay. *2005*.

Ismail, S. E. (2012). Genetic polymorphism studies in humans.

Isordia-Salas, I. S. (2023). Genetic Variants Associated with High Susceptibility of Premature Ischemic Stroke.

Ji, G. G. (2012). Genetic variants in antioxidant genes are associated with sperm DNA damage and risk of male infertility in a Chinese population.

Kasajova, P. H.-B. (2016). Active cigarette smoking and the risk of breast cancer at the level of N-acetyltransferase 2 (NAT2) gene polymorphisms.

Maha, R. K. (2009). Association of polymorphisms in estrogen and thyroid hormone receptors with thyroid cancer risk.

Mishra, A. C. (2015). Harmful effects of nicotine.

Munafò, M. R. (2004). The genetic basis for smoking behavior: A systematic review and meta-analysis.

Organization, W. S. (2017). Understanding Smoking and Stroke.

Orhan, G. E. (2016). The impact of detoxifying and repair gene polymorphisms on oxidative stress in ischemic stroke.

RICHARD DOLL. (n.d.). Mortality in Relation to Smoking: Ten Years' Observations of British Doctors. *2024*.

Sankaranarayanan, V. V., Sattar, J., & Lakshmanan, L. S. (2014). Auto-play: A data mining approach to ODI cricket simulation and prediction. *SIAM International Conference on Data Mining*, (p. 1064).

Tulabandhula, T., & Rudin, C. (2014). Tire Changes, Fresh Air, and Yellow Flags: Challenges in Predictive Analytics for Professional Racing. *Big data*. Retrieved from http://doi.org/10.1089/big.2014.

Verde, Z. S. (2016). Effect of genetic polymorphisms and long-term tobacco exposure on the risk of breast cancer.

Ware, J. J. (2012). From men to mice: CHRNA5/CHRNA3, smoking behavior and disease.

West, R. (2017). Tobacco smoking: Health impact, prevalence, correlates and interventions.

Yongtang Xu, J. Z. (2010). Combined effects of cigarette smoking, gene polymorphisms and methylations of tumor suppressor genes on non small cell lung cancer: A hospital-based case-control study in China.

Zhou, W. L. (2003). Polymorphisms in the DNA repair genes XRCC1 and ERCC2, smoking, and lung cancer risk.