A REVIEW ON SINGLE NUCLEOTIDE POLYMORPHISM (SNPs) AND THEIR EFFECT ON CANCER RISK IN SOUTH ASIAN POPULATION

By

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Declaration

It is hereby declared that

1. The thesis submitted is my 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 have acknowledged all main sources of help.

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Approval

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Ethics Statement

The study did not involve any type of animal trial or human trial.

Abstract

Cancer is one of the leading causes of death and currently 1 in 6 death is known to occur due to cancer. Each type of cancer is linked to variations occurring in the gene. Any form of genetic variation which disrupts the biological function usually causes cancer. Single nucleotide polymorphism (SNP) is the most common form of genetic variation. SNPs are when one nucleotide is replaced by another by another nucleotide. SNPs mainly occur in the promoter, exon, intron and untranslated region (UTR) of a gene. So the function of a gene if affected by the position where a SNP occurs. The study of SNP can be utilized to find out the disease causing genes and develop more precise medicine. SNPs are mainly employed as genetic markers and can help us predict cancer. Currently the population of South Asian is above 1 billion according to World Bank. Identifying the most commonly occurring SNPs in the South Asian population will give us a better understanding on cancer and to recognize the molecular mechanisms involved in a disease which can serve as predictive markers and possible drug target-sites for pharmacological action.

Keywords: SNP, gene, cancer, polymorphism, susceptibility, variation

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List of Acronyms

SNP	Single Nucleotide Polymorphism
TCC	Transitional cell carcinoma
ALL	Acute Lymphocytic Leukemia
CLL	Chronic Lymphocytic Leukemia
AML	Acute Myeloid Leukemia
CML	Chronic Myeloid Leukemia
CHL	Classic Hodgkin Lymphoma
NHL	Non Hodgkin Lymphoma
EBV	Epstein-Barr virus
ADHD	Attention Deficit Hyperactivity Disorder
GWAS	Genome Wide Association Studies
DNMT	DNA methyltransferase
MS	Methionine Synthase
MTHFR	Methylene TetrahydrofolateReductase
TKD	Tyrosine Kinase Domain
EGFR	Epidermal Growth Factor Gene
COMT	Catechol-O-Methyltransferase

IncRNAs	Long Non-Coding RNA
UTR	Untranslated Regions
SNV	Single Nucleotide Variation
NPC	Nasopharyngeal Carcinoma
BRCA	Breast Cancer Gene
XRCC	X-ray-complementing Chinese Hamster Gene
TP53	Tumor Protein
GSTM1	Glutathione S-transferase Mu 1

Chapter 1

Introduction

1.1 What is Cancer and how does SNPs raise the risk of cancer?

The terminology "cancer" is used to refer to a large group of diseases which can occur in any part of the body, other terms used to define cancer are neoplasm and malignant tumors. The development of cancer may occur in any part of the body and has different sub types, respectively (Lynch, 1976). One characteristic feature of cancer is the abnormal growth of cells beyond their boundaries and which may then spread to adjacent body part and even affect other organs. These phenomenon is known as metastasizing and is main cause of demise from cancer (McGough, 2006). It has been estimated that around 70% of death from cancer occur in low and middle-income countries. The major types of cancers resulting in mortality are lung, colorectal, stomach, breast and liver cancer (American Cancer Society, 2019).

Cancer is a genetic disease. It is the second highest reason for death affecting globally. 1 in 6 death is known to occur due to cancer. The type of genes which affect the cellular growth and cause uncontrollable growth are known as oncogenes (Lodishet al. 2000). One of the most frequent type of genetic changes causing cancer is Single Nucleotide Polymorphism (SNP). SNP refers to a region in the nucleotide where a high substitution rate has been observed in individuals in a population giving rise to cancer and mutations (Vignal et al. 2008).

This paper focuses on the SNP variants occurring in South Asian population. According to WHO most of the South Asian countries fall under the lower and middle-income countries, where cancer is an arising threat. The aim of this paper was also to provide a brief review on SNPs, how they

affect and cause cancer, types of different SNPs and how the effect of SNPs on cancer polymorphism highly depend on the region of the gene where they occur (promoter, exonal, intronal and untranslated region or UTR region of a gene).

1.2 Global scenario of Cancer

Globally, cancer is one of the leading causes of death (Dikshit et al. 2012). Moreover, the mortality rate due to cancer is expected to increase, irrelevant of how developed a country is due to the escalating growth and aging of population (Bray et al. 2012). In addition to that, there were about 14.1 million cancer cases in 2012 with the magnitude of cancer reports being expected to rise over 20 million by 2025 (Fidler et al. 2016).

It has been reported that lung and breast cancers were the most common cancers worldwide in both men and women, while in developed countries prostate cancer was reported to be the most diagnosed cancer in men, whilst in women lung cancer reports were the highest (Fidler et al. 2016). Other recurring report of cancers globally in men were liver, stomach and colon cancers (American Cancer Society, 2019). While in the case of women cervix uteri, stomach and colorectal cancers were the most common. On the other hand, in developed countries, bladder cancer in men and uterine cancer in female were reported to be the highest. In the case of less developed countries liver and stomach cancers were frequent (Siegel et al. 2017). Less developed countries account for 57% and developed countries account for 65% of cancer related deaths worldwide (Bray et al. 2012). This may be due to lower consumption of tobacco, more youth and the other health related issues rather than cancer. However it is expected that cancer will be more prevalent in less developed countries due to more aging and increase in their population (Torre et al. 2015).

It has also been found that cancer is sometimes sex dependent and females in general are 20% less likely to be affected by any type of cancer as opposed to males (Siegel et al. 2017). According to Han et al. (2014) cancer development and death occurs due to five main reasons, smoking/chewing of tobacco, less consumption of green leafy vegetables, increased body max index (BMI), lack of exercise and high alcohol consumption (Han et al. 2014).

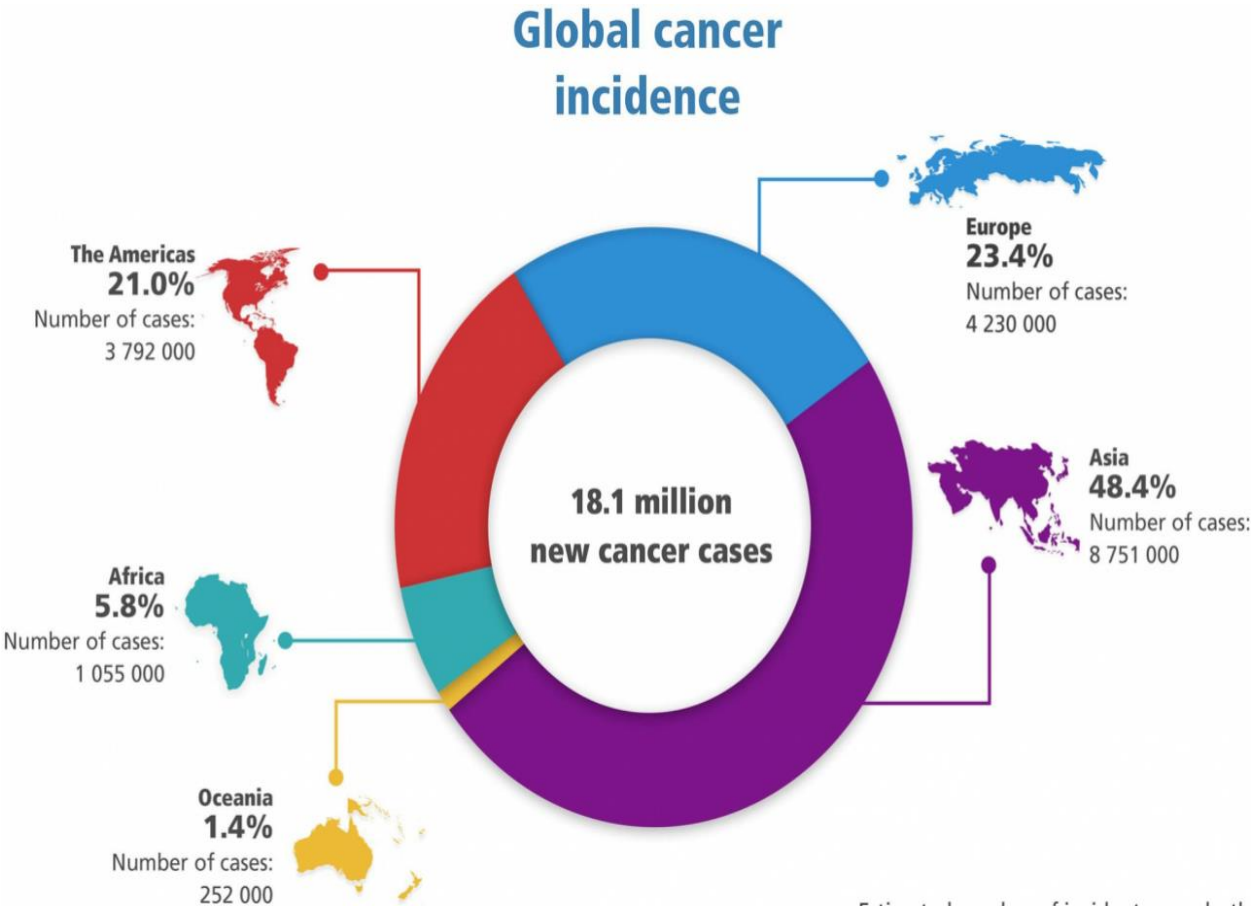

Figure 1: Global cancer incidence (retrieved from GLOBOCAN 2018) (Bray et al. 2018)

1.3 Literature Review

Cancer is the second leading reason of demise globally, affecting all, in spite of their demography or ethnicity. Currently 1 in 6 death is reported to occur globally due to cancer with breast and prostate cancer as the leading cause of deaths (American Cancer Society, 2019). In 2018, there were about 9.6 million cancer related deaths. Around 70% of these cancer related deaths has been reported to occur in middle and lower income countries (World Health Organization, 2018). This is reported to occur due to poor economic resources and knowledge (Moore et al. 2010). In this review, information is provided on SNP (single nucleotide polymorphism), how SNP causes cancer and types of SNPs variants observed in different types of cancer in the South Asian population.

The current population of Southern Asia (Bangladesh, India, Pakistan, Iran, Afghanistan, Nepal, Sri Lanka, Bhutan and Maldives) is above 1 billion according to the World Bank. People in these region share similar cultural activities (World Bank, 2020). The level of economic development in these regions are very limited and is further proved in their response against cancer control. It has been already reported that cancer pose a huge threat in these regions and is already prevalent. Breast, cervical and oral cancers are very common in South Asian Population (Ali et al. 2008). Oral cancer was most observed in Nepali population, Breast cancer in Bangladeshi population, esophageal cancer in Indian and Pakistan (Baluchistan) populations, Breast cancer in Sri Lankan while colorectal, liver, renal cancer were rare in these regions (Moore et al. 2010).

Cancer is a genetic disease. Genes carry out instructions to make proteins. Any types of changes upon these genes can cause them to synthesize proteins which do not function or have abnormal function. Cancer occurs if such changes affect the normal cellular growth (Bray et al. 2012). These

type of genes whose genetic change affects the cellular growth are called oncogenes causing uncontrollable cell growth. Genes are inherited from parents (National Cancer Institute, 2017). Additionally changes in gene can occur due to environmental factors. I.e. substances which damage the DNA such as radiations and carcinogens (Barnes et al. 2018). There are many types of genetic changes which can occur to a DNA. One such change that occurs in DNA is Single Nucleotide Polymorphism (SNP).

Single Nucleotide Polymorphism is one of the most frequent types of genetic mutations and is a common reason behind cancer. The human DNA is composed of 4 types of nucleotides, which are adenine, guanine, cytosine and thymine (Alberts et al. 2002). In brief, a SNP can occur when one nucleotide is replaced by another, for e.g. Cytosine (C) with Thymine (T). SNPs are reported to occur in everyone and are found after each 1000 nucleotides, which roughly corresponds to 4-5 million SNPs in a single person's genome (Vignal et al. 2008). SNPs always do not pose a problem but there are many types of SNPs which can affect the function of gene. When the function of gene is affected, this can result in cancer (Robert and Pelletier, 2018). For example the BRCA1 gene is responsible for the synthesis of proteins which works as tumor suppressor. I.e. tumor suppressor proteins regulate cell division (Genetics Home Reference, 2020). The SNP of BRCA1 gene, BRCA1 rs1799950 has an odds ratio over 1.5 for causing breast cancer (SNPedia, 2019).

Studying of SNPs and haplotypes have significant implications in the field of cancer. SNPs are mainly employed as genetic markers. SNPs can also help us to give a better understanding in drug response, susceptibility to toxins and the possibility of developing diseases (Fridley and Biernacka, 2011). Additionally, the polymorphic site of a gene greatly influences the structure and function of a protein. This give us a great chance to recognize the molecular mechanisms involved in a disease which can serve as predictive markers and possible drug target-sites for pharmacological

action (Mcvicker et al. 2014). In this study, the type of SNPs (Single Nucleotide Polymorphism) observed in various oncogenes seen in South Asian population studies were collected and organized. These will help us give a better understanding to detect the subtle genetic effects. So the main objective of this project is to gather the different cancer causing SNPs in South Asian population. Moreover, there is very limited study on SNP and their effects on cancer in the South Asian population. A major limitation of this study would be lack of resources on South Asian population.

1.4 Types of Cancer

Cells are the basic unit of life, they grow and divide to from new cells. Once a cell becomes too old and damaged, they self-destruct in a process known as apoptosis and then new cells take their place (Carella, 2003).

Cancer occurs due to genetic changes which causes interferences with these sequential processes mentioned above. The cell division and growth in cancer becomes uncontrollable and may form a mass of cells which is known as "tumor". There are two types of tumor, "benign" and "malignant". A benign tumor stays immobile, doesn't spread and affect adjacent tissues, while the malignant tumor is lethal and spreads to nearby tissues and invade them (Lodish et al. 2000). In some types of cancer, there is not tumor formation such as lymphoma, myeloma and leukemia. There are over one hundred fifty types of cancer (Sinha et al. 2018). Cancers are classified based on the origin of where it began. Based on that they are classified into four main types: carcinoma, sarcoma, leukemia and lymphoma (McGough, 2006).

1.4.1 Carcinoma

Carcinomas are the most frequent type of cancer. It starts on the surface of the skin or tissues which

covers the internal organ or gland. I.e. they occurs on the epithelial layer. They mostly cause solid tumor (Du & Wang, 2011). Carcinoma are further categorized based on where the cancer occurs, as follows:

(a) Cancers that occurs on the mucus and fluid producing cells are known adenocarcinoma. Examples of adenocarcinoma include breast cancer, prostate cancer, lung cancer etc. (Kuhn et al. 2018).

(b) Cancers that occur on the bottom layer of the epidermis is known as basal cell carcinoma. It mostly appears as a transparent bump on the surface of the skin. It especially occurs on the head and neck (American Cancer Society, 2019).

(c) Squamous cell carcinoma occurs on the squamous cells (the epidermis). Squamous cells are flat cells which are located near the skin and shed continuously (American Cancer Society, 2019). They cover the external surface of our skin. They appear as red scaly skin with raise growth. It is the second most common cancer (Combalia & Carrera, 2020).

(d) Transitional cell carcinoma affects the transitional cells. The transitional cells include the cells of the urinary system. TCC affect the renal pelvis, bladder and upper part of the ureter (Al-Husseini et al. 2019). Transitional cell carcinoma of the kidney is rare but transitional cell carcinoma of the bladder is common (Garnick, 2006).

1.4.2 Sarcoma

A sarcoma occurs on bones and connecting (soft) tissues. Tendons, muscles, fat, joint blood vessels, cartilage etc. are parts where sarcoma develops (Vodanovich & Choong, 2018).There are seventy types of carcinoma, amongst which osteosarcoma is the most common cancer of the bone.

The soft tissue sarcoma is hard to spot and develops initially as a painless lump (Potter et al. 2018). As it gets bigger it causes difficulty in breathing and discomfort. The most commonly occurring soft tissue sarcoma are Kaposi sarcoma, liposarcoma, histiocytoma and leiomyocasrcoma (National Cancer Institute, 2020).

1.4.3 Leukemia

Leukemia originates in cells in the bone marrow. Leukemia occurs when the white blood cells grow and divide in an uncontrollable manner. As the marrow cells undergo leukemic change, they survive better, tend to cluster and stop the development of normal cells (Garnick, 2006). Cancer of the blood is known as leukemia. Rather they do not form tumors and cluster in the blood and bone marrow. As a result, the function of normal blood cells get disrupted, it gets hard for the body to respond for blood coagulation, supply tissues with enough oxygen, etc. (Cooper, 2000).
Leukemia is divided into four categories.

(a) Acute Lymphocytic Leukemia: It occurs due to clustering of leukemia in the bone marrow. Acute Lymphocytic Leukemia (ALL) is also known as acute lymphoblastic leukemia and acute lymphoid leukemia. The abnormal white blood cells progress rapidly and are carried by the blood stream to the brain, liver, testes etc. (Terwilliger & Abdul-Hay, 2017). They have no immune function. Here the leukemia cells undergo rapid growth and division. In acute lymphocytic leukemia (ALL), there is more B cells than T cells (Tomizawa & Kiyokawa, 2017).

(b) Chronic Lymphocytic Leukemia: it is it the most common type of leukemia in adults (Mayo Clinic, 2019). In chronic lymphocytic leukemia (CLL), the white blood cells mature partially and cannot fight against pathogens as well as normal white blood cells. Moreover, they tend survive longer and tend to accumulate and disrupt normal cell functions (Hallek, 2019).

(c) Acute Myeloid Leukemia, involves the overproduction of blood cells. They grow abnormally and tend to cluster. In Acute Myeloid Leukemia (AML). It starts in the bone marrow and then spreads to other parts of the body such as the spleen, lymph nodes, liver etc. (Villela & Bolaños-Meade, 2011). It occurs in other cells other than lymphocytes, it affects the myeloid cells which include the red blood cell, platelets and white blood cells other than lymphocytes (Saultz & Garzon, 2016).

(d) Chronic Myeloid Leukemia (CML) is also called chronic myelogenous leukemia takes place in certain blood cells in the bone marrow. The myeloid cells such as red blood cell, platelets and white blood cells other than lymphocytes mature partially (National Cancer Institute, 2020). They function but not as well as normal cells. They grow abnormally, survive longer and cluster in the blood, lymph node etc. Chronic Myeloid Leukemia takes longer to develop, however it is less likely to cure (Cancer.org, 2016).

1.4.4 Lymphoma

Cancer that occurs in the lymphatic system is known as lymphoma. The lymphatic system helps us fight against infections. The lymphocytes help us fight against infection and travel around the body in the lymphatic system (Storck et al. 2019). They consist of a fluid known as lymph which is secreted by the lymph node. In lymphoma, there is an uncontrollable growth of lymphocytes (T cells and B cells), which cluster in the lymph nodes (Walter, 2013). There are two main categories of lymphoma:

(a) Hodgkin Lymphoma, is known to occur in any part of the body as the lymphatic system present throughout the system. However, it is usually known to start in the upper part of the body, in the lymph nodes (Ansell, 2015). The cancer cells in the Classic Hodgkin Lymphoma (CHL) are known

as Reed Sternberg cells which an abnormal variant of B lymphocyte (Shanbhag & Ambinder, 2019). Patients suffering from Hodgkin Lymphoma has an enlarged lymph node with a few number of the cancer cell but high number of normal immunity cells. These cause the enlargement of the lymph node (Yung & Linch, 2003).

(b) Non Hodgkin Lymphoma, depends on whether the B cell or T cell has been affected. The treatment depend on how mature these cells have become prior to becoming cancerous (National Cancer Institute, 2019). Non Hodgkin Lymphoma (NHL) can occur in any part of the body where there is the presence of lymph tissues (Armitage et al. 2017). The type of Non-Hodgkin Lymphoma is also based on the rate of spread. They are aggressive lymphoma and aggressive lymphoma (Ansell & Armitage, 2005).

1.5 Factors Causing Cancer

Cancer is stated to be a genetic disease, however there are many other factors which can influence and increase the risk of cancer in an individual. They are as follows:

1.5.1 Environmental Factors

The environment in which a person works is an important factor leading to the development of cancer. Occupations where the employees are prone to carcinogenic chemical exposure such as in chemical factory are more likely to develop cancer (Weinberg, 1988). Additionally, the demographic region where one lives can contribute to cancer development. Such as men in Japan are 5-6 times more likely to have stomach cancer due to consumption of fermented food (Naylor et al. 2006), while American women are 20 times more likely to develop breast cancers due to the intake of high fat diet (Breastcancer.org, 2020), on the other hand the population in Africa is 10

times more likely to suffer from lung cancer attributed to high Hepatitis B infection, etc. (Alberts et al. 2002).

1.5.2 Infection

Cancer is most commonly attributed to environment or lifestyle of a person. However, certain infections have proved to cause cancer.

(a) Parasites: There are many different types of trematodes which have been reported to cause cancer. The main two types are *Schistosomahaematobium* which causes bladder cancer (Fried et al. 2011) and *Clonorchissinensis*which is reported to cause cholangiocarcinoma andhepatocarcinoma (Benamrouz et al. 2012).

(b) Bacteria: *Helicobacter pylori*, is reported to cause stomach cancer. The bacteria is found in the mucosa of the gastric epithelium. The bacterium is known to survive for a long time (Abadi, 2017). Also *H.pylori*is the main known factor causing gastric cancer. They are linked with causing stomach cancer and lymphoma as well (Selgrad et al. 2008).

(c) Virus: Viral infections promote cancer. Each type of virus have their own different mechanism. Some types of viruses have been reported to initiate and promote tumor growth, while some influence the host cell growth and promote tumor growth, these is caused by the human papilloma virus (HPV) (McLaughlin-Drubin et al. 2012). HPV have reported to be associated with head, neck and urogenital cancer (Gallo, 2011). On the other hand the human T-cell leukemia virus type 1 (HTLV-1) is known to cause T-cell leukemia (Brady et al. 2008). The Epstein-Barr virus (EBV) causes gastric lymphoma, Burkitt's lymphoma and nasopharyngeal carcinoma. The EBV virus is reported to prevent cell apoptosis as well (Ayee et al. 2019).

1.5.3 Obesity

Obesity has been reported to be directly linked to cancer. Cancers linked to obesity include colon, uterus, breast, liver, esophagus, kidney, gallbladder, thyroid, pancreas and ovaries (Wang et al. 2015). Additionally there are also risk for blood cancers such as non-Hodgkin's lymphoma, myeloma and leukemia (Larsson and Wolk, 2007). The main link between obesity and cancer is due to increased aromatase activity. The aromatase enzyme converts androgens to estrogens (Serdar et al. 2012). The fat cells release molecules called adipokines which increases the aromatase activity. The increased levels of estrogen bind to estrogen receptors on cells and promote cellular division, hence increasing the risk of cancer (Wang and Dubois, 2006).

1.5.4 Chronic Inflammation

It has been reported that chronic inflammation is linked to cancer, on both experimental and epidemiological basis. Chronic inflammation can occur due bacterial or viral infections, autoimmune disorder and other unknown origins of inflammatory conditions (Multhoff et al. 2012). Chronic Inflammation causes cancer due to activity and production of leukocytes, also due to the production of proteins which disrupt the function of target cells and cause angiogenesis (Coussens and Werb, 2002). Several types of cancer has been reported to occur due to chronic inflammation such as colon cancer, liver cancer etc. (Allavena et al. 2008).

1.5.5 Tobacco

Life time tobacco usage causes about one in two deaths according to WHO reports, moreover from 2005-2009, around 42,000 deaths occurred annually amongst nonsmokers due to passive smoking. It has been attributed that, around 30% cancer related deaths are linked to smoking (World Health Organization, 2018). The exposure of tobacco affects all, whether it be firsthand (direct exposure

to tobacco), secondhand (passive exposure of tobacco smoke to non-tobacco smokers) or third-hand (absorption of tobacco smoke residues through the skin or mouth found on the surface or dust; prevalent in babies and young children) (Sikorska-Jaroszyńska et al. 2012). Along with other health issues, firsthand smoking causes nose, throat, mouth, larynx, pancreas, stomach, kidney, lung, liver, blood, intestine and colon cancer. While secondhand and third-hand exposure can suffer from lung and breast cancer along with other health problems (Winickoff et al. 2009)

1.5.6 Radiation

Radiation are of two types, ionizing and non-ionizing radiation. Ionizing radiation include X-ray radiation, gamma rays, radon in soil etc. while non-ionizing radiation involves the UV radiation from the sun (Kwan-Hoong, 2003). Ionizing radiations possess sufficient energy to penetrate the cells and damage the DNA structure and cause cancer. While non-ionizing radiation possess lower energy but constant exposure can cause cancer, commonly causing basal cell carcinoma, squamous cell carcinoma and melanoma (National Toxicology Program, 2011).

1.5.7 Drugs

There are reports that some drug may potentially cause cancer. They include certain antineoplastic drugs, hormonal drugs and drugs which cause immune deficiency. Most of them occur due to long term abuse of illicit drugs (Gong et al. 2014). There were also reports that Ritalin (Methylphenidate) used for attention deficit hyperactivity disorder (ADHD) in children causes chromosomal abnormalities which may cause cancer (Wagner and Colombo, 2020).While recently FDA has reported that ranitidine and zantac causes cancer. In addition to that, the misuse of anabolic steroids are also linked to cancer (National Cancer Institute, 2019).

1.5.8 Carcinogens

Carcinogens refer to any chemical substance which induces and promote carcinogenesis, i.e. the formation of cancer. This may be due to damage they inflict upon the genome or disrupt a metabolic process (Loomis et al. 2018). The list of carcinogen and the cancer they are responsible for are given below:

Table 1: List of Carcinogens and Cancers They Cause (National Toxicology Program, 2016

Carcinogen	**Type of Cancer**
Benzo [a]-pyrene (Tobacco)	Lung Cancer
Alcohol	Esophagus, Larynx, Pharynx and Mouth Cancer
Dietary Fat	Breast Cancer
Fermented Food	Stomach Cancer
Estrogen	Ovarian, Endometrial and Breast Cancer
UV Light	Skin Cancer
X-ray and Gamma Radiation	Lung, Brest, Mouth, Thyroid, Leukemia, Colon, Stomach, Skin, Ovarian and Lung Cancer
Tamoxifen	Endometrial Cancer

Aflatoxin	Liver Cancer
Nickel	Nasal and Lung Cancer
Mustard Gas	Lung Cancer
2-napthylamine	Bladder Cancer
Cr (VI)	Lung Cancer

Chapter 2

Methodology

Paper related to SNP and their effect on cancer along with the variants found in South Asian population (Bangladesh, India, Pakistan, Iran, Afghanistan, Nepal, Sri Lanka, Bhutan and Maldives) were collected from three major sites (i) PubMed, (ii) Google Scholar and (iii) Scopus. There were no SNP related (cancer) study in some of the regions (Iran, Afghanistan, Bhutan and Maldives). Initially the papers were searched using keywords such as SNP cancer risk, genetic cancer risk South Asia, SNP cancer risk Bangladesh etc. Any forms of duplication was avoided by cross checking. Available books, publications, research studies, journals, articles, and websites were also be used to collect information.

Studying of SNPs and haplotypes have significant implications in the field of cancer. SNPs are mainly employed as genetic markers. SNPs can also help us to give a better understanding in drug response, susceptibility to toxins and the possibility of developing diseases (Fridley and Biernacka, 2011). Additionally, the polymorphic site of a gene greatly influences the structure and function of a protein. This give us a great chance to recognize the molecular mechanisms involved in a disease which can serve as predictive markers and possible drug target-sites for pharmacological action (Mcvicker et al. 2014). In this study, the type of SNPs (Single Nucleotide Polymorphism) observed in various oncogenes seen in South Asian population studies were collected and organized. These will help us give a better understanding to detect the subtle genetic effects. So the main objective of this project is to gather the different cancer causing SNP variants in South Asian population.

Chapter 3

Review on SNPs and their association to cancer

3.1 What are SNP?

SNP stands for single nucleotide polymorphism and refers to a region in the nucleotide where a high substitution rate has been observed in individuals in a population giving rise to cancer and mutations to that individual. It is one of the most common form of genetic variations (Vignal et al. 2008). According to Brookes, "SNPs are single base pair positions in genomic DNA, at which different sequence alternatives (alleles) exist in normal individuals in some population(s), herein the least frequent allele has an abundance of 1% or greater" (Brookes, 1999). SNPs affect various important functions of our life such as cellular metabolism, our body immunity system, repairing DNA mismatches, cellular cycle regulation and can hence easily induce cancer (Khlestkina and Salina, 2006).

SNPs are reported to occur once in every one thousandth (1in 1000) nucleotide at average. This means there are about 4 to 5 million SNPs occurring in an individual on average. SNPs occurring in the non-coding regions tend to manifest cancer (Ramírez-Bello and Jiménez-Morales, 2017). SNPs are of mainly two types, (i) Linked SNPs and (ii) Causative SNPs. The causative SNPs affects the way a protein will function in a person (Biernacka and Cordell, 2007). The Causative SNP is further categorized into two types, the coding and the non-coding region SNPs. The non-coding is the segment of the DNA that consist of gene but doesn't code for a protein while the coding region is the segment of DNA or RNA that codes for protein (Elkhattabi et al. 2019). The coding region is further divided to synonymous and non-synonymous SNPs (NCBI, 2005). The synonymous SNP doesn't affect the amino acid sequence while the non-synonymous SNP affects

the amino acid sequence (Chu and Wei, 2019). The non-synonymous SNP is usually further divided to missense and non-sense. In the missense SNP, different codon occurs so the amino acid sequence is altered. While in the non-sense mutation, the codon is changed to a premature stop codon, this results in the truncation of the forming protein (Vignal et al. 2008).

SNPs are positioned and located in different regions of the genome such as the exon, promoter, intron and untranslated regions (UTRs). Hence the genetic expression and the type of cancer that occurs will vary depending on the location and position of the SNP (Deng et al. 2017). To briefly explain, the SNPs in the promoter region affects the genetic expression by changing the DNA methylation, histone binding activity and transcription factor binding (Wunsch et al. 2005). While the genetic transcription and translation is suppressed by SNPs in the exonal region (Deng et al. 2017). On the other hand it has been observed that SNP in the intron region affects and disrupts the functions of the long non-coding RNA (IncRNA) (Chiang et al. 2017). SNPs in the 3 prime UTR region disrupts the microRNA (mi-RNA) binding while SNP in the 5 prime UTR region disrupts translation (Steri et al. 2018). On the other hand it has been seen that SNPs occurring far away from the actual genes will either decrease or increase gene transcription through long range cis effects (Ramírez-Bello and Jiménez-Morales, 2017).

In theory four types of alleles are possible at the specific nucleotide position as there are four exiting nucleotide types in the genome. The SNP markers are biallelic and transversions. A biallelic site is a specific locus in a genome that contains two observed alleles. Transversion refers to the exchange of purine rings instead of pyrimidine rings (Deng et al. 2017).

On the other hand from a clinical perspective, SNPs are used as biomarkers for many types of cancers. They are classified according to three types, (i) Hybridization based DNA marker, (ii)

PCR based DNA markers and lastly (iii) Sequencing based DNA marker (Khlestkina and Salina, 2006).

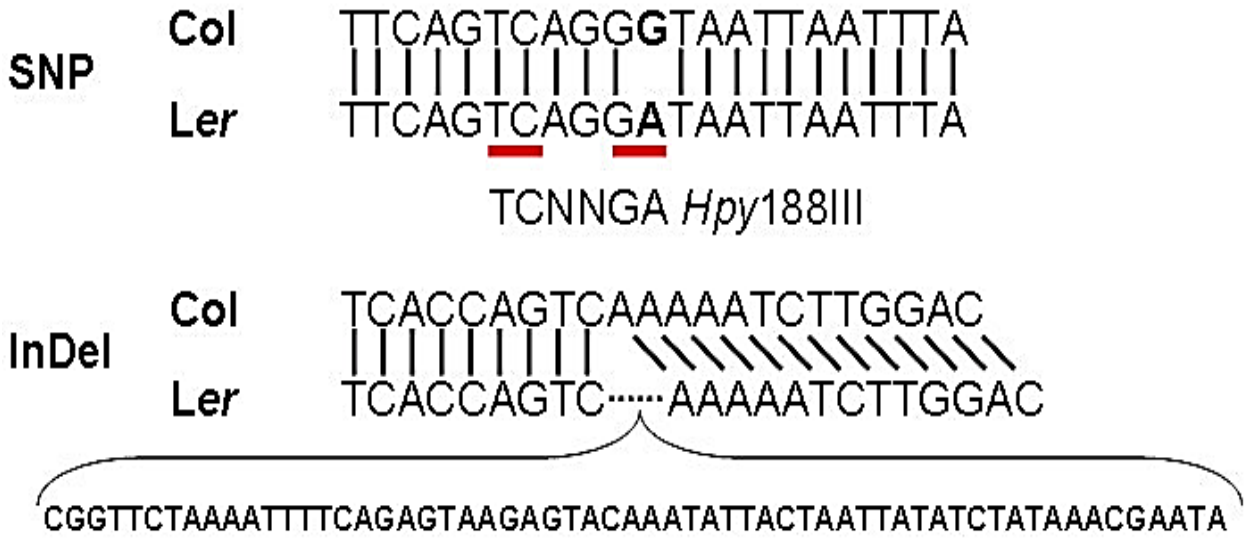

Figure 2: Figure illustrating an example of SNP occurring, insertion and deletion polymorphism (InDel). [It shows the insertion and deletion polymorphism (InDel) exhibited in Col-0 and Ler. SNP (Col: G to Ler:A) and insertion and deletion (InDel) polymorphism (of 60 nucleotides) is seen here in the promoter region of At5g48100.] (Retrieved from: Ishihara, 2007)

3.2 Effect of promoter region SNPs on cancer susceptibility

The promoter region of a gene controls the initiation and transcription via cis acting elements, Any type of promoter related SNP affects the transcription binding, translation, changes the promoter activity and translation. Moreover, this impacts the protein level and type in individuals which makes that individual more prone to certain diseases including cancer (Wunsch et al. 2005). Additionally, polymorphism on the promoter regions make an individual more susceptible to cancer due to effects on the epigenetic mechanisms such as DNA methylation and histone modifications (Deng et al. 2017).

3.2.1 Impact on TATA box function due to promoter region SNP

The TATA box is a sequence of genes exhibited in the core promoter region. It has been observed that SNP polymorphism in the TATA box disrupts the promoter activity and transcription as it a part of the core promoter region (Peltoketo et al. 1994).

3.2.2 Impact on transcription factor binding due to promoter region SNP

The promoter region of a gene contains a lot of various binding sites needed for transcription factors that control gene transcription. It has been observed that SNP polymorphism in the promoter region reduces the rate of transcription by preventing the binding of the transcription factors to the promoter (Deng et al. 2017). Such as in the SNP polymorphisms in rs16260 (-160C > A) and rs5030625 (-347G-> GA) in the CDH1 promoter decreases the transcriptional activity to certain degrees (Kang et al. 2007).

3.2.3 Impact on epigenetic mechanisms due to promoter region SNP

It has been observed that DNA methylation takes place mainly in the CpG islands region of the promoter. Hence, SNPs in the promoter region can hamper DNA methylation and as a result can effect gene expression (Fan et al. 2010). The SNPs affecting the DNA methylation of CpG loci are known as methylation, they change the number of CpG dinucleotide which leads to alterations in the DNA methylation as well as histone acetylation and gene slicing (Ishihara, 2007).

The promoter region SNPs had been seen to alter the amount of methylation loci hence affecting the gene expression and raising cancer susceptibility (Vohra et al. 2020). According to GWAS (Genome Wide Association Studies) some SNPs change the methylation by an allele-specific manner. They also demonstrated that there are 38 SNPs in the 12 CpG loci which affects expression and methylation in 10 genes (IRF6, TSPYL5, CRIM1, CHL1, DDT, PIGC, TMOD1,

ZNF266, BDKRB2 and GSTT1) (Zhang et al. 2010).

SNPs in the promoter region also has impacts on the transcription factor binding which guards the CpG island such as the SP1 transcription factor affects methylation in the CpG islands.It has also been observed that SNPs in the promoter region disrupt DNA methylation by releasing methylation related enzymes. Such as polymorphism in the DNMT (DNA methyltransferase), MS (methionine synthase) and MTHFR (methylene tetrahydrofolatereductase) promoter region disrupt DNA synyhesis and causes irregular DNA methylation (Boumber et al. 2008). Additionally it has also been seen that polymorphism in the non-coding sequences impacts the histone modification such as glycosylation, ubiquitination, methylation and phosphorylation (Mcvicker et al. 2014). These all hamper the transcriptional rate. Histone modifications also occur due to promoter SNPs found in the transcription factor binding sites. Such as increased levels of IL-10 production is linked to rs1800896 (A-1082G) GG genotype (Deng et al. 2017).

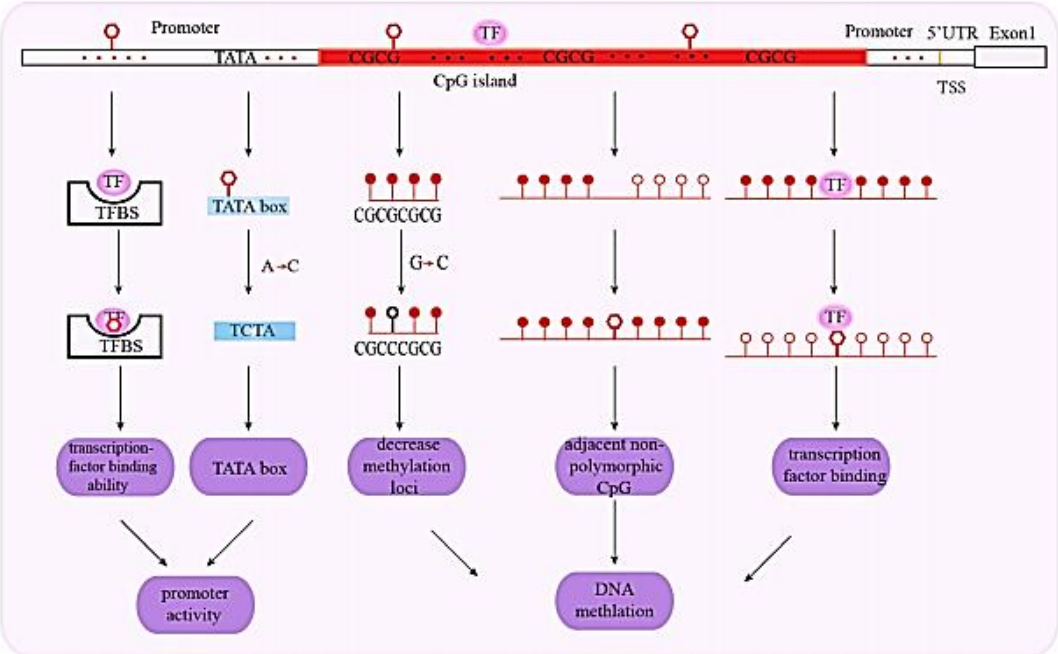

Figure 3: Mechanisms linked with cancer susceptibility due to promoter SNPs. [SNPs occurring in the transcription factor binding site disrupts the binding between the transcription factors with the gene promoter. SNPs taking place

in the TATA box hamper the promoter activity with the A to C substitutions. DNA methylation is lowered by SNPs in the CpG islands.] (Deng et al. 2017)

3.3 Effects of exonal SNPs on cancer susceptibility

SNPs on the exon are divided to synonymous and non-synonymous coding SNPs (cSNPs) depending on their potentiality to remove the encoded amino acid. Exonal SNPs tend to promote cancer susceptibility by genetic mechanisms (Chu and Wei, 2019).

It has been observed that non-synonymous (cSNPs) disrupt protein function. These occurs due amino acid substitutions. In most cases changes in the first two bases of the codon results in amino acid substitution (Du et al. 2016). Alterations in the amino acid sequences affect the secondary structure of the protein due to changes in hydrogen bonding and phosphorylation (Berg et al. 2002). These structural and chemical changes affects the interactions and functions of the protein (Robert and Pelletier, 2018). As a result, such alterations impact the cell signaling pathways as well as the amounts of tumor suppression and oncogene proteins (Schaefer and Rost, 2012). There are over thirteen thousand known SNPs occurring in the exonal region of which 42% are synonymous cSNPs and the rest are non-synonymous cSNP. In the case of non-synonymous cSNP the structural and functional response of the encoded protein is hampered, hence raising the cancer susceptibility (Tennessen et al. 2012). Such as in the EGFR (epidermal growth factor gene), a non-synonymous SNP will raise the cancer susceptibility due to elimination of TKD (tyrosine kinase domain). The TKD (tyrosine kinase domain) is targeted by small molecules such as erlotinib. Met 769 forms a single hydrogen bond with erlotinib in the EGFR (epidermal growth factor gene) (Raghav et al. 2013). While another such molecule geftinib forms two hydrogen bonds with Gly 772 and exhibits higher affinity with five EGFR (epidermal growth factor gene) proteins than the wild type. The EGFR-TKD polymorphism causes structural changes and this raise the protein activity and

sensitivity to TK1 (Deng et al. 2017).

A non-synonymous SNP can hamper the stability, post-translation changes and protein interaction. For example it has been seen that the Leu858Arg mutation raises the chances of EGFR (epidermal growth factor gene) to form dimers and this is linked to cell proliferation (Shan et al. 2012). On the other hand, synonymous SNP do not affect the amino acid sequence on an encoded protein and instead causes base substitution in the third base of the codon (Yates & Sternberg, 2013). Moreover, recent studies have exhibited that synonymous SNPs impacts the genetic function and expression of a gene by altering the expressions of adjacent genes. Furthermore, many studies have also proved that synonymous SNPs are associated with changes in structure, function and expression of proteins (Deng et al. 2017).

Synonymous cSNPs has also been observed to from different type of haplotypes which regulate the solidity of mRNA secondary structure which affects and decreases enzyme function (Lubelski et al. 2007). Such as in the case of COMT (Catechol-O-Methyltransferase) gene, one non-synonymous SNP and two synonymous cSNP form different haplotype SNPs. Changes in structure of the messenger RNA are seen due to such haplotypes. The mRNAs with higher stable secondary structures account for low COMT (Catechol-O-Methyltransferase) activity and expression (Nackley et al. 2006).

Synonymous SNPs also has impacts upon the messenger RNA structure, stability, splicing and hence the protein folding. Such alterations have serious affects upon the protein function and this causes alterations in cellular response to therapeutic medications, hence explaining why the response of medication varies from individual to individual (Hunt et al. 2009).

Synonymous SNPs can also increase or decrease the rate at which ribosomes move along the

mRNA, hence this affects the dynamics of translation. As a consequence, the protein structure and function is also affected. This may also result in variations in the mRNA secondary structures and protein secondary structures (Shen et al. 1999).

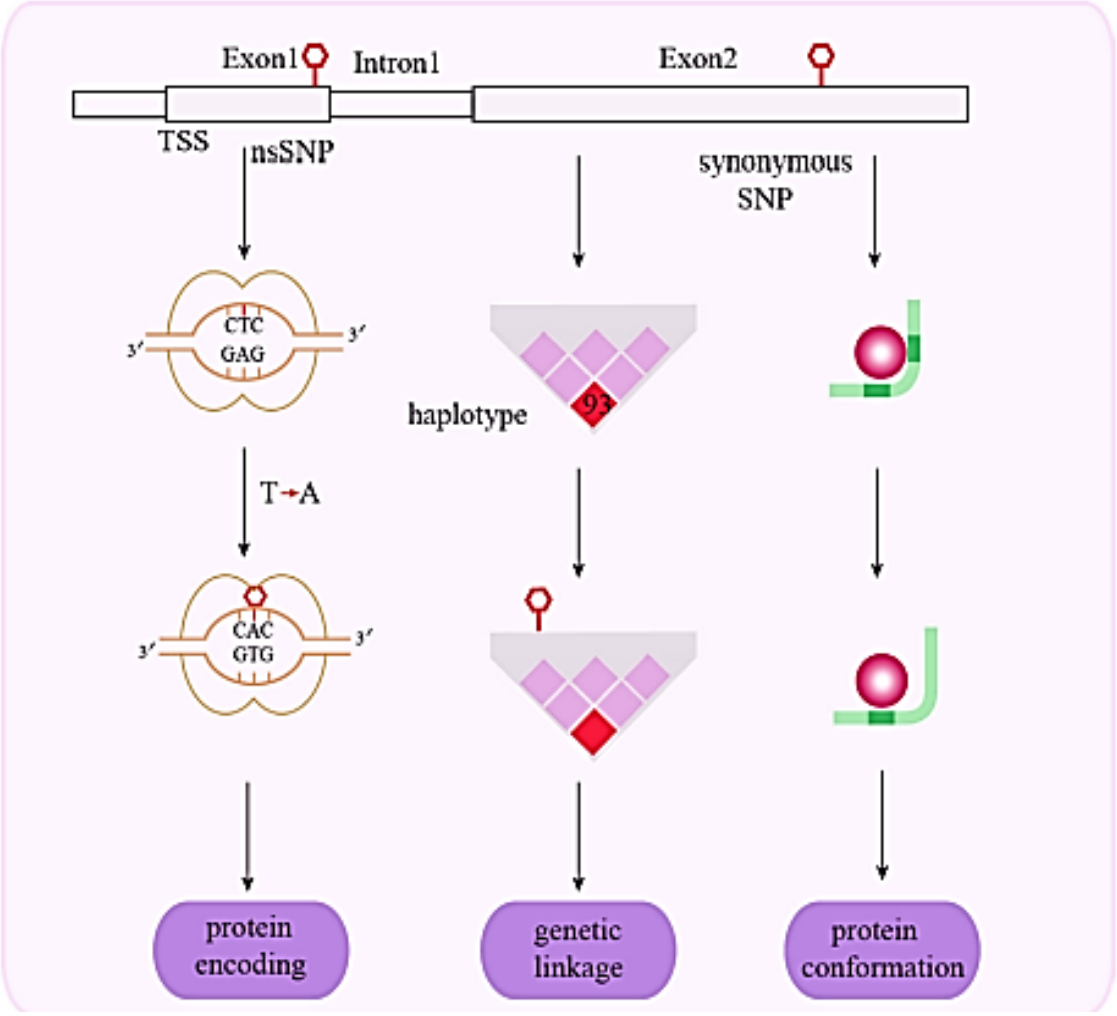

Figure 4: Mechanisms linked with cancer susceptibility due to exonal SNPS. [The amino acid sequence is altered due to non-synonymous exonal SNPs. Alterations in function and protein confirmation occur due to synonymous exonal SNPs] (Deng et al. 2017).

3.4 Effects of Intronal SNPs on cancer susceptibility

Introns consist of enhancers or other cis-elements, they are involved in modulating transcription,

translation and gene expression. The splicing of introns raise the stability of mRNA. The introns also function in genome imprinting and alternative splicing (Zhang et al. 2014). It has also been observed that the functional SNPs are associated with the SNPs of adjacent genes. They affect their mRNA splicing and binding. These affects the sequence and function of proteins. Hence, based on the above observations, it is stated that intronal SNPs cause cancer susceptibility by both epigenetic and genetic processes (Campbell at al. 2016).

3.4.1 Impact on gene expression by cis acting elements

Theintronal region consists of numerous cis regulatory elements such as insulator, silencers, enhancers etc. which regulate the gene expression. These are known as the "hot spots" where genetic variations occur the most. The current studies and researches ongoing, involve grasping the functions of these loci's (Zhang et al. 2014). Such as GWAS (genome-wide association study) recognized rs2981578 variant in breast cancer, as one of the highest occurring risk alleles (Robbez-Masson et al. 2013). On another instance, it has also been observed that the variant of the enhancers, ESR1 and FoxA1 is responsible for causing breast cancer (Cowper-Sa et al. 2012). Also three different SNPs, rs2981578, rs35054928 and rs45631563 in FGFR2 gene lowers the genetic expression of FGFR2 due to silent elements and augment silencer activity. These raises breast cancer risk (Campbell et al. 2016).

3.4.2 Impact on protein synthesis by mRNA spilcing due to intronal SNPs

It has been observed that sequential alterations as result of synonymous or non-synonymous SNPs hampers the splicing activity of mRNA. As a consequence, splice variants are formed. Splice donor, exon splicing enhancers, acceptor sites etc. are some of the elements involved in mRNA splicing (Tran et al. 2005). For instance, a SNP has been seen that changes from G to A in DMD

intron 32 shuts down splice donor sites. Then in IRF4, an intronal polymorphism is linked with elevated male acute lymphoblastic leukemia due to substitution from C to T bases (Robbez-Masson et al. 2013). Another example consists of the gene ZNF419. It has been seen that polymorphism occurring on the splice donor of the ZNF419 gene produces a variant of ZAPHIR antigen which is not compatible and causes renal cancer (Broen et al. 2011).

3.4.3 Impact on genomic imprinting due to intronal SNPs

Genomic variation in genetics refers to the variation in genetic expressions due to genes obtained from both paternal and maternal alleles which is caused by differences in histone acetylation and DNA methylation (Verhaegh et al. 2008). It has been observed that polymorphisms occurring in the imprinted regions hamper the genetic expression (Gong et al. 2016). For instance, H19 is an imprinted gene and is known to function as coding for oncofetal RNA. However heterozygotes for the H19 gene, known as H19 rs2839698 TC raise the chances of bladder cancer (Raghav et al. 2013).

3.4.4 Impact on genetic expression regulation by intronal SNP

Intronal sequences consist of various RNA motif which do not encode for any protein but modulate the expression of proteins by transcriptional and epigenetic mechanisms. The IncRNAs (long non-coding RNA), are part of the non-coding RNAs (Huang et al. 2018). They are involved in modifications of histone and chromatin, transcriptional activation, activation or repression of tumor suppressor gene etc. The IncRNAs are jointly associated with the formation of malignant tumors as well (Deng et al. 2017). It has also been observed that they hamper the normal biological functions as well due to competitive micro RNA. Hence raising the susceptibility to cancer (Li et al. 2015). For example, the binding of miR-128-3p is influenced by the rs2147578 polymorphism

in lncLAMC2-1:1, which increases the risk for colorectal cancer (CRC) (Chu et al. 2015). On another instance, it has been seen SNPs occurring in the lncRNAs H19, HOTAIR (HOX transcript antisense RNA) and PRNCR1 raises the risk of gastrointestinal cancer. On the other hand, in EGLN2 gene, rs10680577 insertion/deletion polymorphism raises the levels of EGLN2and RERT-lncRNA, which elevates the risk of liver cancer (Broen et al. 2011).

3.4.5 Impact on chromatin looping due to intronal SNP

It has been observed in males that the intronal SNP rs12203592, which is located in intron 4 of IRF4 gene, intensifies the physical interaction between the enhancer and IRF4 promoter by an allele dependent chromatin looping mechanism. This raises the IRF4 transcriptional rate (Wright et al. 2010).

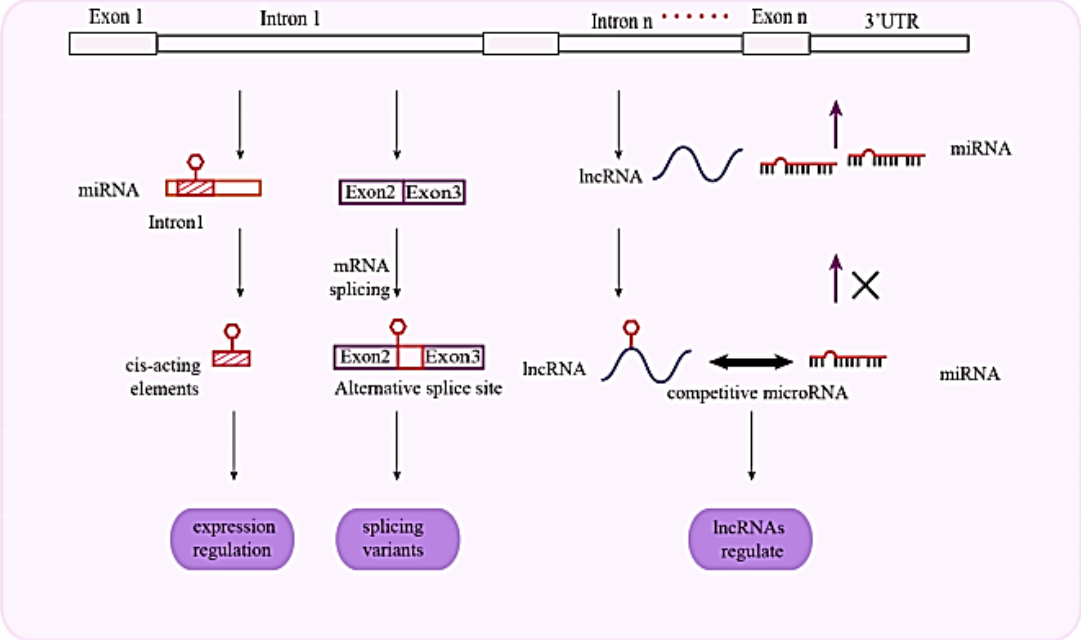

Figure 5: Mechanisms linked with cancer susceptibility due to intronal SNPs. [The genetic expression of a gene is modulated by cis acting elements. Regulation of protein synthesis is also modulated by intronal SNPs by controlling

of IncRNA and splicing action of mRNA.] (Deng et al. 2017)

3.5 Effects of UTR related SNPs on cancer susceptibility

The UTR refers to the untranslated regions found on either one of the sides of the coding sequence in the mRNA strand. In the mRNA, the 5′ and 3′ UTRs are the most important as they regulate translation. The mRNA stability is influenced by the 3′-UTR while the initiation of translation is modulated by the 5′-UTR (Wilkie et al. 2003).

It has been observed that single nucleotide variations (SNVs) are very troublesome as they hamper the secondary structure as well as the miRNA target sites in the untranslated regions. Such alterations has shown to effect the expression the known cancer genes as well as their signaling pathways (Sabarinathan et al. 2014). The mRNA folding, transcription stability, control of translation and/or mRNA processing is hampered by such sequential alterations in the untranslated regions. Hence SNPs occurring in the UTR regions have proved to have functional disruption upon the mRNA expression as well as stability (Wilkie et al. 2003).

3.5.1 Impact on transcription and protein translation \

The 5′-UTRs consist of genetic elements which modulate the genetic expression, it has been observed that polymorphism occurring on this region is associated with various genetic diseases as they control the mRNA translation, stability, processing and transport (Sabarinathan et al. 2014). There are a number of factors which affect the overall translational rate. These include the start of the translational site, the overall extent of the 5′-UTR, the secondary structure and the binding sites of the ribosome. Hence translation efficiency is disrupted by mutations or polymorphisms occurring in the 5′-UTRs region (Aouacheria et al. 2007). For instance it has been observed in multiple myeloma cases that in the 5′-UTR region, a +2756 C to T mutations in the the c-Myc

gene raises the activity of IRES, as a result increasing the levels of c-Myc expression and therefore tumor genesis (Chappell et al. 2000). Another example include a -34 G to T substitution, taking place in the 5′UTR of CDKN2A gene. Such alterations causes' addition of ORF (open reading frame) which restrains translation and this causes losing of allele function, which raises melanoma susceptibility (Cazzola and Skoda, 2000).

The 5 prime untranslated region also plays a part in transcription. In the 5′-UTR of CR2 gene, a +24 T/C polymorphism is shown to be linked with nasopharyngeal carcinoma activity (Mendell and Dietz, 2001). It has been observed that individuals having the C allele are more like to suffer from NPC (nasopharyngeal carcinoma) than individual's possessing the T allele (Deng et al. 2017).

3.5.2 Impact on mRNA degradation and translation modulation

Genetic expression is modulated by the 3′-UTRs via mRNA degradation and translation mechanisms. The 3′-UTRs are responsible for translation efficiency, polyadenylation, mRNA degradation as well as subcellular localization. Hence due to the above reasons, mutations occurring in the 3′-UTRs is linked to a number of diseases (Fan et al. 2013). The 3′-UTRs is essential for normal genetic function. Hence the mi-RNA binding sites is changed which as a consequence adversely affect the mRNA degradation and protein translation due to polymorphisms taking place in the 3′-UTRs (Aouacheria et al. 2007).

3.5.3 Impact on mi-RNA mediated translational repression

MicroRNAs (mi-RNAs) function by stopping translation and by destabilizing their target mRNAs. They do this by binding to the 3′-UTRs of the targeted transcript. Now it has been observed that SNPs occurring in the 3′-UTRs changes the target recognition of mi-RNAs. The SNPs do these by disturbing the sequence complementary to it (Barnes et al. 2007). Other types of polymorphisms

are known to hamper the functional activities of mi-RNAs and also affect the expression of their targets (Hu et al. 2009). For instance it has been seen that in the estrogen receptor-α (ER-α) gene, the polymorphism rs93410170 C > T SNP in the 3′-UTR, causes the mediation of mi-R 206 which is associated with high breast cancer risk (Brendle et al. 2008).

It has also been seen that polymorphisms or mutations occurring in the 3′ target hamper protein translation even without the presence of any changes in the mRNA expression (Kertesz et al. 2007). For example, in the IL23R gene, the C allele in rs10889677A > C polymorphism occurring in the 3′-UTR is linked to lung, breast and nasopharyngeal cancer. The IL23R gene transcription is elevated as the greater A allele decreases miR-let-7f binding sites (Zheng et al. 2012).

SNPs occurring in the mi-RNA are also known to affect the processing and targeting of the mi-RNA itself. A mature mi-RNA consists of two regions, a 3′ mismatch tolerant region and a 5′ seed region. The seed region is known to consist of 2-7 nucleotides, found at the 5′ of mi-RNA. It functions as specifying the identification for mi-RNA targets. Hence SNPs occurring in the seed region disrupt the binding between the mi-RNA to its target mRNA (Kertesz et al. 2007). For instance, the rs11614913 T > C SNP in miR-196a2 is associated with breast cancer. In brief, SNPs occurring in mi-RNA can be devastating as they change the binding sites. As a consequence, protein synthesis and gene expression is disrupted, even without the presence of any alterations in the encoding mRNA (Hu et al. 2009).

3.5.4 Impact in mi-RNAs due to SNPs

Synthesis of mi-RNAs is affected by polymorphisms or mutations occurring outside the pre mi-RNA structure and the seed sequence. For instance, the conversion of pri-miR-125 to pre-miR-125a is stopped due to SNPs taking place in the seed region of miR-125a. As a consequence, the

miR125a modulated translational repression is decreased (Xu et al. 2011). Another example include, miR-15a/miR-16a. Where a polymorphism (C > T) takes place in the primary transcript, as a result the expression of miR-15 and miR16 is decreased. Such polymorphism causes chronic lymphocytic leukemia in individuals (Duan et al. 2007).

The seed region is a region which is known to have two to seven nucleotides which is found at the 5′ seed of the mi-RNA. The seed region functions in identifying the specific targets of mi-RNA. So as a result, SNPs which occur at the seed region hampers the binding between mRNA and the mi-RNA.

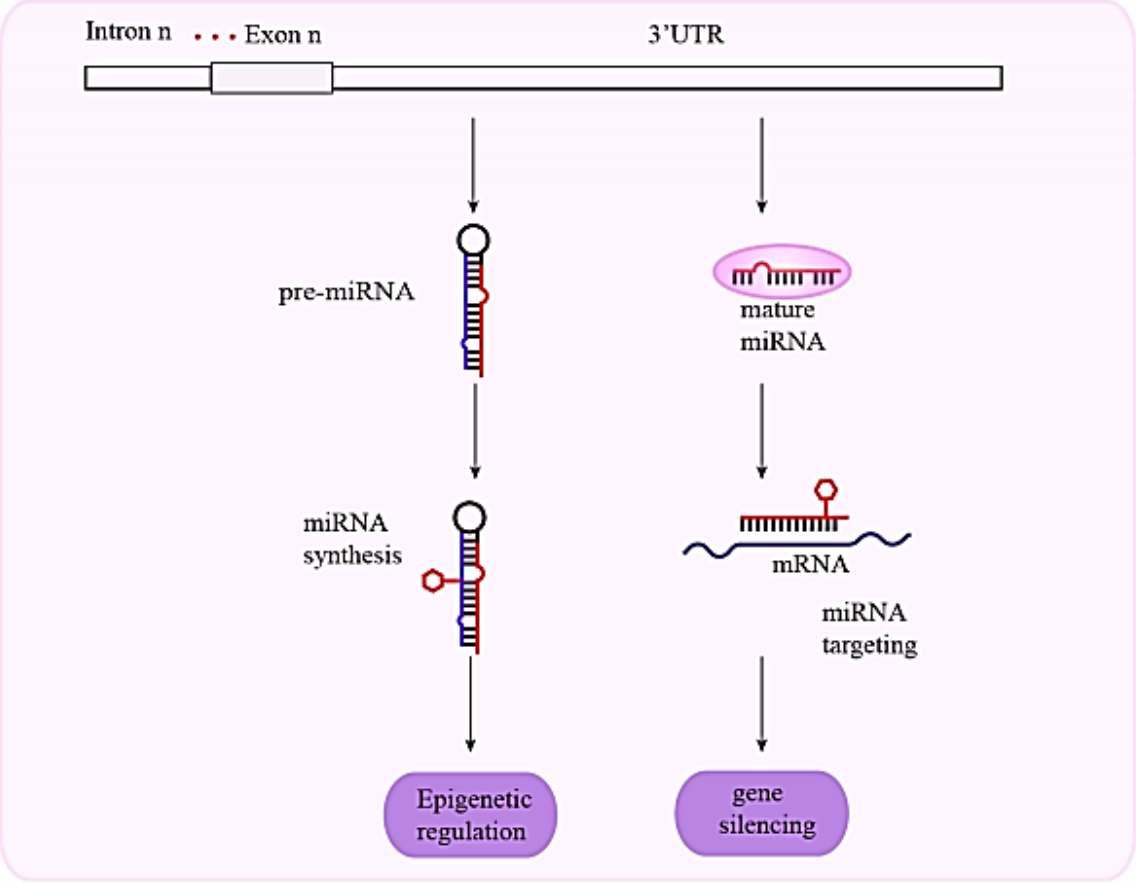

Figure 6: Mechanisms linked with cancer susceptibility due to 3'-UTR SNPs. [SNPs in the 3'-UTR regions disrupt the gene silencing and mi-RNA synthesis processes.] (Deng et al. 2017).

3.6 Effects on transcription due to SNPs occurring in the undefined regions

Through the utilization of long range cis effects the gene transcription is affected by SNPs occurring in the undefined regions. These SNPs are found in the non-coding regions. They modulate the function via long range interaction using chromatin. Such interactions are vitally found in regions where histone modification and transcription binding sites occur (Hu et al. 2009). There are many genes and their variants seen in prostate cancer which showed the involvement of long range chromatin interactions. For instance, RFX6, CAPG, MYC, C2orf43, NFASC and AGAP7P. Their variants include rs10993994, rs1446669, rs1078004, rs4631830, rs13394027 and rs699664 (Du et al. 2016). Another example consists of SNP rs965513 which affects the function of the genes PTCSC2 and FOXE1. This causes thyroid cancer (He et al. 2015). On the other hand variations in 11q13 is linked to breast cancer, the variant rs554219 is responsible for such (French et al. 2013).

3.7 Effects on tRNAs and rRNAs due to SNPs

It has been seen that SNPs occurring on the tRNA and rRNA results in defects in translation and transcription. In many instances such changes in the tRNA and rRNA are associated with cancer (Cao et al. 2014). The secondary and tertiary structure of the tRNA is changed due to mutations in the mitochondrial tRNA genes. Such alterations causes defection in the respiratory chain. For instance, colorectal cancer risk is raised by the polymorphic variant A12308G of tRNA Leu (Mohammed et al. 2015). Additionally, polymorphic variants of the tRNA genes are linked to mitochondrial dysfunction in breast cancer. Lung cancer is also known to occur due to changes in the secondary structure of cis non-coding rRNA (Shiao et al. 2009).

Chapter 4

Most frequent SNPs in South Asian Population and their Effects

(i) BRCA1 gene

The BRCA1 gene is found on the 17q21 position of the chromosome, it is known to act as a tumor suppressor gene. Breast cancer and ovarian cancer are strongly associated due to SNPs taking place in the BRCA1 gene. The BRCA1 gene has numerous roles such as cell cycle regulation, repairing DNA damage, oncogenes, tumor suppression and repression (Xu et al. 2018). It has been reported that defects in the BRCA1 gene causes problems in the S phase, G2 phase and M phase in cell division. Deficiency in the BRCA1 gene also causes instable spindle fiber formation. Such effects causes DNA damages in the cells formed (Nishat et al. 2019).

According to the collected articles, the following SNPs in BRCA1 gene were observed:

Table 2: SNPs linked to BRCA1 Gene Related Cancer

Authors	Year	Cancer	SNP	Control	Case	Population
(Parvin et al. 2016)	2016	Breast Cancer	BRCA1rs80357713, BRCA1rs80357906	250	310	Bangladeshi
(Nishat et al. 2019)	2019	Breast Cancer	exon11 of BRCA1	130	130	Bangladeshi
(Hansa, Kannan, and Ghosh, 2012)	2007	Breast Cancer	185DelAG, 1014DelGT	32	32	Indian

			3889DelAG			
(Singh et al. 2018)	2018	Breast Cancer	c.68_69delAG, c.5074+1G>A,	1010	1010	Indian
(Bhatta et al. 2016)	2016	Breast Cancer	185delAG, 1294del40	50	50	Nepalese
(Ahmad et al. 2019)	2019	Breast Cancer	rs8176318	300	300	Pakistani
(Abbas et al. 2019)	2019	Breast Cancer	BRCA1 rs80356932	100	100	Pakistani

(ii) BRCA2 gene

The BRCA2 gene also known as breast cancer susceptibility gene 2 is found on the chromosome 13q. The BRCA2 gene mainly acts in DNA repairing. Hence just like the BRCA1 gene, any forms of mutations hampers the normal cellular activities. These results in the formation of tumors (Cavanagh and Rogers, 2015).

According to the collected articles, the following SNPs in BRCA2 gene were observed:

Table 3: SNPs linked to BRCA2 Gene Related Cancer

Authors	Year	Cancer	SNP	Control	Case	Population
(Parvin et al. 2016)	2016	Breast Cancer	BRCA2rs11571653	250	310	Bangladeshi

(Joseph et al. 2011)	2011	Breast Cancer	BRCA2 exon 8	36	107	Indian
(Liede et al. 2002)	2002	Breast Cancer	BRCA2 (3337CrT)	200	461	Pakistani
(Liede et al. 2002)	2018	Breast Cancer	BRCA2 rs80359182	100	100	Pakistani
(De Silva et al. 2017)	2016	Breast Cancer	exon 11 of BRCA2	25	48	Sri Lankan

(iii) XRCC1 gene

XRCC1 stands for X-ray Repair Cross Complementing group 1 and is located on the 19q13.31 position in the chromosome. It is reported that the XRCC1 gene is involved in the repairing of DNA strands due to the subjection of extreme ionizing radiations (Wang et al. 2010). The XRCC1 gene codes for protein which is known to interact with SSBR (DNA single strand break repair) components such as DNA polymerase, DNA ligase, DNA phosphatase etc. In this way, the XRCC1 gene helps to repair breaks in the DNA. Recent studies have also shown that the XRCC1 gene interacts with PARP1 gene to stop neurodegenerative diseases (Caldecott, 2020).

According to the collected articles, the following SNPs in XRCC1 gene were observed:

Table 4: SNPs linked to XRCC1 Gene Related Cancer

Authors	Year	Cancer	SNP	Control	Case	Population

(Tasnim et al. 2017)	2017	Lung Cancer	XRCC1 rs25487	242	202	Bangladeshi
(Pachouri et al. 2007)	2007	Lung Cancer	XRCC1 Arg399Gln XRCC1 Arg194Trp	122	103	Indian
(Sreeja et al. 2008)	2008	Lung Cancer	XRCC1 Arg399Gln	211	211	Indian
(Wang et al. 2010)	2010	Colorectal Cancer	XRCC1 Arg399Gln	291	302	Indian
(Nissar et al. 2015)	2015	Colorectal Cancer	XRCC1 Arg194Trp	100	100	Indian
(Berhane et al. 2012)	2012	Prostate Cancer	XRCC1 Arg309Gln	150	150	Indian
(Kumar et al. 2012)	2012	Head and Neck Cancer	XRCC1 Arg194Trp XRCC1 Arg280His XRCC1 Arg399Gln	278	278	Indian
(Mahjabeen et al. 2013)	2013	Head and Neck Cancer	XRCC1 Arg399Gln (rs25487)	150	300	Pakistani
(Bashir et al. 2018)	2018	Thyroid	XRCC1 Arg280His	400	456	Pakistani

		Carcinoma	XRCC1 Arg194Trp			

(iv) XRCC2 gene

The XRCC2 gene is located on the 7q36.1 position and is a part of the RecA/Rad51 protein family. The X-ray repair cross complementing gene 2. They function in repairing DNA damage and maintain the stability of chromosome. It has also been reported that the XRCC2 in correct segregation of the chromosomes. The XRCC2 gene also plays an important part in the HR (homologous recombination) pathway (Andreassen and Hanenberg, 2019).

According to the collected articles, the following SNPs in XRCC3 gene were observed:

Table 5: SNPs linked to XRCC2 Gene Related Cancer

Authors	Year	Cancer	SNP	Control	Case	Population
(Sirisena et al. 2018)	2018	Breast Cancer	XRCC2 rs3218550	350	350	Sri Lankan

(v) XRCC3 gene

The XRCC3 gene also known as X-ray repair complementing defective repair in Chinese hamster cells 3 is needed for repairing double strand breaks in the DNA (NCBI, 2020). The XRCC3 also plays a role in maintaining the stability of chromosomes. It is known to be a part of the RecA/Rad51 related proteins. They are known to form a complex with the RecA/Rad51 and take part in the HRR (homologous recombination repair genetics) (Ali et al. 2016).

According to the collected articles, the following SNPs in XRCC3 gene were observed:

Table 6: SNPs linked to XRCC3 Gene Related Cancer

Authors	Year	Cancer	SNP	Control	Case	Population
(Wang et al. 2010)	2010	Colorectal Cancer	XRCC3 Thr241Met	291	302	Indian
(Mandal et al. 2010)	2010	Prostate Cancer	XRCC3 (C18067T, rs861539),	224	192	Indian

(vi) XRCC7 gene

The XRCC7 gene is involved in the DSBR (double strand break repair) process and undertakes the NHEJ (non-homologous end joining) pathway to achieve this. The XRCC7 gene is known to code for DNA-PKcs (catalytic subunit of DNA activated protein kinase) (Gangwar et al. 2009). The DNA-PKcs is then reported to be taken to the site of the DSB (DNA double strand breaks) where it forms a complex known as DNA-PK which is essential for this pathway (Saadat and Rabizadeh-Hafshenjani, 2016).

According to the collected articles, the following SNPs in XRCC7 gene were observed:

Table 7: SNPs linked to XRCC7 Gene Related Cancer

Authors	Year	Cancer	SNP	Control	Case	Population
(Gangwar et al. 2009)	2009	Bladder Cancer	XRCC7 (G6721T, rs7003908)	250	212	Indian
(Mandal et al.	2010	Prostate	XRCC7 (G6721T,	224	192	Indian

2010)		Cancer	rs7003908)			
(Gangwar et al. 2009)	2009	Bladder Cancer	XRCC7 (G6721T, rs7003908)	250	212	Indian

(vii) CYP1A1 gene

The CYP1A1 gene is located on the 15q24.1 position of the chromosome in exon 7. The gene is part of the cytochrome P450 enzymes. The enzymes in the cytochrome P450 family are involved in processes in metabolism of drug and synthesis of lipids such as steroids and cholesterol (NCBI, 2020). CYP1A1 gene is also reported to have a part in the metabolism of polycyclic hydrocarbons found in tobacco. In brief. CYP1A1 gene play a vital part in the phase I part of xenobiotic metabolism (i.e. detoxification process of poisons/carcinogens), where a polar group is introduced to the unwanted substance (Peddireddy et al. 2016).

According to the collected articles, the following SNPs in CYP1A1 in gene were observed:

Table 8: SNPs linked to CYP1A1 Gene Related Cancer

Authors	Year	Cancer	SNP	Control	Case	Population
(Islam et al. 2013)	2013	Lung Cancer	CYP1A1 rs4646903 CYP1A1 rs1048943 CYP1A1 rs1799814	116	106	Bangladeshi
(Peddireddy et al. 2016)	2016	Lung Cancer	CYP1A1 m1 CC	250	246	Indian
(Girdhar et al.	2016	Lung	CYP1A1 Ile462Val	320	320	Indian

2016)		Cancer	CYP1A1 MSPI (T6235C)			
(Sobti et al. 2003)	2003	Lung Cancer	CYP1A1 Msp1 (CYP1A1*1/2A or CYP1A1*2A/*2A)	76	100	Indian
(Sheikh et al. 2009)	2009	Lung Cancer	CYP1A1m1 CYP1A1m2	163	103	Indian
(Sobti et al. 2004)	2004	Lung Cancer	CYP1A1*1/2A, CYP1A1*2C CYP1A1 Msp1	76	100	Indian
(Sreeja et al. 2005)	2005	Lung Cancer	CYP1A1 Msp1	146	146	Indian
(Kiruthiga et al. 2011)	2011	Breast Cancer	CYP1A1*1/M1 CYP1A1*2/M2	146	146	Indian
(Jain et al. 2017)	2017	Cervical Cancer	CYP1A1 rs4646903 CYP1A1 rs1048943	100	100	Indian
(Singh et al. 2015)	2015	Head and Neck Cancer	CYP1A1 T3801C	230	170	Indian

(Singh et al. 2009)	2009	Head and Neck Cancer	CYP1A1∗2A CYP1A1∗2C	200	200	Indian
(Masood et al. 2011)	2011	Oral Cancer	CYP1A1 (A2842 to C and Frameshift)	150	228	Pakistani
(Zakiullah et al. 2015)	2015	Oral Cancer	CYP1A1 rs4646903	151	200	Pakistani

(viii) CYP2A6

The cytochrome P450 2A6 enzyme is known to be part of sub family of three other genes which are CYP2A6, CYP2A7 and CYP2A13. The CYP2A6 gene is reported to have around 40 polymorphic variants. The gene is mostly found in the liver and expressed there. Lower levels have been reported to be found in other tissues as well such as the nasal mucosa. The CYP2A6 is known to m etabolize nicotine, coumarin, valproic acid, pilocarpine, SM-12502, caffeine, letrozole and tyrosol (Raunio and Rahnasto-Rilla, 2012).

According to the collected articles, the following SNPs in CYP2A6 gene were observed:

Table 9: SNPs linked to CYP2A6 Gene Related Cancer

Authors	Year	Cancer	SNP	Control	Case	Population
(Islam et al. 2013)	2013	Lung Cancer	CYP2A6*1B1 CYP2A6*4	116	106	Bangladshi

(Ruwali et al. 2009)	2009	Head and Neck Cancer	CYP2A6*1B CYP2A6*4C	350	350	Sri Lankan

(ix) CYP3A4

The CYP3A4 gene also known as cytochrome P450 Family 3 Subfamily A Member 4 is responsible for encoding enzymes which are part of the cytochrome P450 enzymes. These enzymes are mainly monooxygenases. They are also reported to synthesize cholesterols and lipids. The enzyme is also one the most important enzymes in adults and is widely found in the liver and the gut (Klein and Zanger, 2013).

According to the collected articles, the following SNPs in CYP3A4 gene were observed:

Table 10: SNPs linked to CYP3A4 Gene Related Cancer

Authors	Year	Cancer	SNP	Control	Case	Population
(Islam et al. 2014)	2014	Lung Cancer	CYP3A4*1B	116	106	Bangladeshi
(Abdullah et al. 2016)	2016	Cervical Cancer	CYP3A4*1B	30	30	Bangladeshi

(x) CYP3A5

Cytochrome P450 Family 3 Subfamily A Member 5 are monooxygenases. They are known to syntheiselipds, steroids and cholesterol as well as drug metabolism such as testosterone and

progesterone (Gene Cards, 2020). The CYP3A5 is located on the 7q21.1. They are also reports to metabolize steroid hormones and vitamins (Vyhlidal et al. 2015).

According to the collected articles, the following SNPs in CYP3A5 gene were observed:

Table 11: SNPs linked to CYP3A5 Gene Related Cancer

Authors	Year	Cancer	SNP	Control	Case	Population
(Bellah et al. 2015)	2015	Prostate Cancer	CYP3A5 rs776746 (CYP3A5*3)	100	100	Bangladeshi
(Islam et al. 2014)	2014	Lung Cancer	CYP3A5*3	116	106	Bangladeshi

(xi) CYP17

CYP17 gene is located on the position 10q24.3. The protein produced is known as CYP17 or Cytochrome P450 17α Hydroxylase/17, 20 Lyase. The CYP17 has two distinct functions and they are 17α hydroxylase and 17, 20-lyase activity. These are important for the synthesis of gonadal and adrenal steroids (NCBI, 2020). The CYP17 is reported to be found in nonsteroidogenic tissues and liver. CYP17 is also involved in steroid metabolism as well. Polymorphisms which affect the expression of CYP17 gene can also affect the production of steroids hence raising the susceptibility of prostate cancer (Bellah et al. 2015).

According to the collected articles, the following SNPs in CYP17 gene were observed:

Table 12: SNPs linked to CYP17 Gene Related Cancer

Authors	Year	Cancer	SNP	Control	Case	Population

(Ranbir Chander Sobti et al. 2009)	2009	Prostate Cancer	A2/A2 CYP17	170	157	Indian
(Sobti et al. 2006)	2006	Prostate Cancer	A2/A2 CYP17	100	100	Indian
(Rai et al. 2014)	2014	Gallbladder Cancer	CYP17 (rs743572)	230	414	Indian

(xii) TP53

TP53 gene is found on the position 17p13.1 and the protein itself is known to be composed of 393 amino acids and is a phosphoprotein. The TP53 also known P53 protein is involved in roles to fix DNA damage. It is also involved in many other cellular processes regulation of cell cycle, stability of the genome and endogenous cellular processes (NCBI, 2020). The TP53 protein is called to be a "tumor suppressor" as it ensures cells grow and divide at a stable rate. Recent researches are being done in to understand the biochemical pathways by which TP53 protein acts which will be a great aid in treating cancer (Harris, 1996).

According to the collected articles, the following SNPs in TP53 gene were observed:

Table 13: SNPs linked to TP53 Gene Related Cancer

Authors	Year	Cancer	SNP	Control	Case	Population
(Chowdhury et al. 2015)	2015	Lung Cancer	TP53 codon 72 (Pro/Pro)	50	50	Bangladeshi

(Mostaid et al. 2014)	2014	Lung Cancer	P53 Pro47Ser P53 Arg72Pro	116	106	Bangladeshi
(Ranbir C Sobti et al. 2009)	2009	Lung Cancer	P53 Arg/Pro P53 Pro/Pro	151	151	Indian
(Tilak et al. 2013)	2013	Lung Cancer	P53 (Arg72Pro)	202	175	Indian
(Saikia et al. 2015)	2015	Lung Cancer	p53 codon 72 (Pro/Pro)	544	272	Indian
(Shabnaz et al. 2016)	2016	Breast Cancer	TP53 rs1042522	250	310	Bangladeshi
(Hossain et al. 2017)	2017	Breast Cancer	TP53 codon (Arg/Arg, Arg/Pro, and Pro/Pro)	125	125	Bangladeshi
(Sharma et al. 2014)	2014	Breast Cancer	TP53 (p.P47S, p.R72P)	200	200	Indian
(Hosen et al. 2015)	2015	Bladder Cancer	TP53 codon 72 (Pro/Pro)	140	102	Bangladeshi
(Jaiswal et al. 2011)	2011	Bladder Cancer	TP53 codon 248 (Arg/Trp-Arg/Gln)	200	200	Indian

(Pandith et al. 2010)	2010	Bladder Cancer	TP53 (Arg/Trp, Arg/Gln)	138	108	Indian
(Rivu et al. 2017)	2017	Colorectal Cancer	TP53 gene codon 72 (Arg72Pro)	295	288	Bangladeshi
(Singamsetty et al. 2014)	2014	Colorectal Cancer	TP53 (Pro72Pro, Ser47/Pro72)	107	103	Indian
(Mittal et al. 2011)	2011	Prostate Cancer	TP53 (intron 6 G>A and R72P G>C)	265	177	Indian
(Khan et al. 2014)	2014	Prostate Cancer	TP53 (rs1042522, Pro72Arg)	107	146	Pakistani
(Apu et al. 2020)	2020	Cervical Cancer	TP53 codon 72 (Arg/Pro, Pro/Pro) and codon 47 (Arg/Pro,Pro/Pro)	102	134	Bangladeshi
(Apu et al. 2020)	2020	Esophageal Cancer	TP53 codon 72 (Pro/Pro, Arg/Pro)	100	100	Indian
(Manoharan et al. 2019)	2019	Head and Neck Cancer	TP53 (c.422G>T, c.455C>T, c.524G>A,	20	44	Sri Lankan

			c.578A>G, c.747G>T)			
(Patel et al. 2013)	2013	Oral Cancer	TP53 (Arg72Pro)	110	79	Indian
(Saleem et al. 2013)	2013	Oral Cancer	TP53 (Pro72Arg)	260	260	Pakistani

(xiii) GSTM1

GSTM1 stands for glutathione S-transferase Mu 1. The GSTM1 gene encodes this protein. The glutathione S-transferase M1 is a member of the GST family of enzymes. The GST enzymes are mainly involved in detoxification of drugs, carcinogens and other toxins. They are found as a cluster in the position 1p13.3 (NCBI, 2020).

It has been reported that the frequency of SNPs seen in GSTM1 is low. The main type of polymorphism occurring is the null allele. This is the phenomenon where individuals lacks copy of one or both GSTM1 genes (Uddin et al. 2014). Individuals who lack the gene are more susceptible to asthmas, allergy and certain types of cancer, especially if they are also lacking the other GST genes as well (Singh et al. 2008).

According to the collected articles, the following SNPs in GSTM1 gene were observed:

Table 14: SNPs linked to GSTM1 Gene Related Cancer

Authors	Year	Cancer	SNP	Control	Case	Population
(Nasir Uddin et al.	2014	Lung	Null polymorphism	116	110	Bangladeshi

2014)		Cancer				
(Kimi et al. 2016)	2016	Breast Cancer	Null polymorphism	10	22	Indian
(Vijayalakshmi et al. 2005)	2005	Prostate Cancer	Null polymorphism	144	127	Indian
(Srivastava et al. 2005)	2005	Prostate Cancer	Null polymorphism	100	75	Indian
(Singh et al. 2008)	2008	Cervical Cancer	Null polymorphism	168	150	Indian
(Sharma et al. 2013)	2013	Esophageal Cancer	Null polymorphism	436	315	Indian
(Ghatak et al. 2016)	2016	Gastric Cancer	Null polymorphism	80	80	Indian
(Nosheen et al. 2010)	2010	Head and Neck Cancer	Null polymorphism	150	388	Pakistani
(Zakiullah et al. 2015)	2015	Oral Cancer	Null polymorphism	151	200	Pakistani

(Masood et al. 2011)	2011	Oral Cancer	Null polymorphism	150	228	Pakistani

(xiv) GSTT1

Glutathione S-transferase (GST) theta 1 is a gene which is reported to be a part of a superfamily of proteins, these proteins are involved in the conjugation of reduced glutathione many types of compounds. These compounds are mostly hydrophobic and electrophilic in nature (Sharma et al. 2015). The gene is located on 22q11.23 on exon 6 (NCBI, 2020).

According to the collected articles, the following SNPs in GSTT1 gene were observed:

Table 15: SNPs linked to GSTT1 Gene Related Cancer

Authors	Year	Cancer	SNP	Control	Case	Population
(Sharma et al. 2015)	2015	Lung Cancer	Null polymorphism	270	270	Indian
(Sreeja et al. 2005)	2005	Lung Cancer	Null polymorphism	146	146	Indian
(Kimi et al. 2016)	2016	Breast Cancer	Null polymorphism	10	22	Indian
(Singh et al. 2008)	2008	Cervical Cancer	Null polymorphism	168	150	Indian

(Sharma et al. 2013)	2013	Esophageal Cancer	Null polymorphism	436	315	Indian
(Ghatak et al. 2016)	2016	Gastric Cancer	Null polymorphism	80	80	Indian
(Nosheen et al. 2010)	2010	Head and Neck	Null polymorphism	150	388	Pakistani
(Zakiullah et al. 2015)	2015	Oral Cancer	Null polymorphism	151	200	Pakistani

Chapter 5

Conclusion

Overall, it may be said the purpose of this study is to focus on the variant of SNPs occurring in cancer patients in the South Asian population. The main objective of this review is to find out the different variations in SNP and how they affect the South Asian population in terms of cancer regardless of age and gender.

Cancer is a genetic disease. It is the second highest reason for death affecting globally. 1 in 6 death is known to occur due to cancer. Currently breast and prostate cancer are one of the most commonly occurring cancer (WHO, 2018). Chromosome contain genes which are known to synthesize proteins. Proteins have various function in our system such as building tissues, repairing cells, metabolic reaction etc. However, if there are any changes or presence of abnormality in the cell, these may result in proteins which have abnormal function (National Cancer Institute, 2017). The type of genes which affect the cellular growth and cause uncontrollable growth are known as oncogenes. Genes are inheritable, they are inherited from parents. Hence an abnormal gene may be passed on to the child by his/her parents (Barnes et al. 2018). Additionally, genetic changes may also occur as a result of the environment. E.g. due to radiation and carcinogens.

One of the most frequent type of genetic changes causing cancer is Single Nucleotide Polymorphism (SNP). SNP refers to a region in the nucleotide where a high substitution rate has been observed in individuals in a population giving rise to cancer and mutations (Vignal et al. 2008). In short adenine, guanine, cytosine and thymine are the four types of nucleotides which makes up the human DNA. Replacement of the position of a nucleotide with another nucleotide

results in SNP for e.g. Cytosine (C) is replaced with Thymine (T) (Alberts et al. 2002).

There are two types of SNPs linked SNPs and causative SNPs. The causative SNP is responsible for the way a protein works inside the human body. SNPs are found in different regions in the genome for example the exon, promoter, intron and untranslated regions (UTRs). Based on where the SNP is located and positioned the type of cancer occurs (Deng et al. 2017). In short, promoter region SNPs disrupt the genetic function by altering the DNA methylation, histone binding activity and transcription factor binding (Ishihara, 2007).. While the genetic transcription and translation is suppressed by SNPs in the exonal region (Chu and Wei, 2019). Moreover also it has been observed that SNP in the intron region affects and disrupts the functions of the long non-coding RNA (IncRNA) (Zhang et al. 2014). Lastly, SNPs occurring in the 3 prime UTR region stop and affect the microRNA (mi-RNA) binding, while SNP in the 5 prime UTR region disrupts translation (Fan et al. 2013). From observations it had been noted that SNPs that occur far from the actual gene will increase or decrease the gene transcription through long range cis effects (Ramírez-Bello and Jiménez-Morales, 2017).

Paper regarding SNP and effect on cancer patients in the South Asian population (Bangladesh, India, Pakistan, Iran, Afghanistan, Nepal, Sri Lanka, Bhutan and Maldives) were collected and gathered from PubMed, Google Scholar and Scopus. Keywords such as SNP cancer risk, genetic cancer risk South Asian population, SNP cancer risk Bangladesh, SNP cancer risk India etc. were used to search for the paper. Any forms of duplication was avoided by cross checking. Available books, publications, research studies, journals, articles, and websites were also be used to collect information.

Results of this review reveal lung cancer and breast cancer were most common. SNPs in TP53,

BRCA, XRCC1, CYP1A1 and GSTM1 were most common. In TP53 the Arg72Pro type mutation was most common while in GSTM1 and GSTT1 the null polymorphism was commonly observed. From this review it has been noticed that medications for cancer treatment should be more gene specific. If we can control the gene responsible for faulty protein, then the impact of cancer could be reduced. Understanding SNP can help us develop better medical techniques, as it will help us to be more specific.

In spite of vast researches the mechanisms of SNPs causing cancer yet remain a complicated issue. For instance, the effects of promoter region SNPs on histone modification and DNA is evident, however association between epigenetic and genetic mechanisms due to SNPs is still obscure (Deng et al. 2017). Additionally, the effects of non-synonymous SNPs on the chemical and biochemical processes are still unspecified. Lastly, the effect of SNP in the 5′- and 3′UTRs causing cancer has been proved but the mechanisms require more detailed study (Duan et al. 2007).

To conclude, clinicians, geneticists as well as patients will be benefited greatly by the identification of SNPs in genes which causes diseases such as cancer. It will also help us understand adverse drug reactions much better (Fridley and Biernacka, 2011). This also gives us a great chance to recognize the molecular mechanisms involved in a disease which can serve as predictive markers and possible drug target-sites for pharmacological action. As more functional polymorphisms are identified, it will be possible to make more genetic markers and develop personalized medicines as well (Mcvicker et al. 2014).

References

Abadi, Amin Talebi Bezmin. 2017. "Strategies Used by Helicobacter Pylori to Establish Persistent Infection." *World Journal of Gastroenterology* 23(16):2870–82.

Abbas, Saba, Ayesha Siddique, Naeem Shahid, Rabbia Tariq Khan, and Warda Fatima. 2019. "Breast Cancer Risk Associated with BRCA1/2 Variants in the Pakistani Population." *Breast Cancer* 26(3):365–72.

Abdullah, Shamim, Hossain Shafayat, Sazib Saifuzzaman, Shahariar Fahim, and Hossain Golam. 2016. "Genetic Polymorphisms of CYP3A4 1B of Cervical Cancer Patients in Bangladeshi Population, Bangladesh." *International Journal of Advances in Medicine* (May):455–59.

Ahmad, Mushtaq, Fazal Jalil, Mutiul Haq, and Aftab Ali Shah. 2019. "Effect of Variation in Mirna-Binding Site (Rs8176318) of the Brca1 Gene in Breast Cancer Patients." *Turkish Journal of Medical Sciences* 49(5):1433–38.

Al-Husseini, Muneer J., Ahmad Kunbaz, Anas M. Saad, João Vasco Santos, Sami Salahia, Marium Iqbal, and Fares Alahdab. 2019. "Trends in the Incidence and Mortality of Transitional Cell Carcinoma of the Bladder for the Last Four Decades in the USA: A SEER-Based Analysis." *BMC Cancer* 19(1):1–12.

Ali, Alaa Mohammed, Huda Abdulkareem, Mohammad Al Anazi, Narasimha Reddy Parine, Jilani Purusottapatnam Shaik, Abdullah Alamri, Akbar Ali Khan Pathan, and Arjumand Warsy. 2016. "Polymorphisms in DNA Repair Gene XRCC3 and Susceptibility to Breast Cancer in Saudi Females." *BioMed Research International* 2016.

Ali, Rabia, Aleyamma Mathew, and B. Rajan. 2008. "Effects of Socio-Economic and

Demographic Factors in Delayed Reporting and Late-Stage Presentation among Patients with Breast Cancer in a Major Cancer Hospital in South India." *Asian Pacific Journal of Cancer Prevention* 9(4):703–7.

Allavena, Paola, Cecilia Garlanda, Maria Grazia Borrello, Antonio Sica, and Alberto Mantovani. 2008. "Pathways Connecting Inflammation and Cancer." *Current Opinion in Genetics and Development* 18(1):3–10.

American Cancer Society. 2019a. "About Basal and Squamous Cell Skin Cancer What Are Basal and Squamous Cell Skin Cancers?" 13.

American Cancer Society. 2019. *American Cancer Society. Facts & Figures 2019*.

Andreassen, PR, and H. Hanenberg. 2019. "XRCC2 (X-Ray Repair Cross Complementing 2)." *HHS Public Access* 23(1):1–7.

Apu, Mohd Nazmul Hasan, A. Z. M. Rashed, Tafsir Bashar, Md Morshadur Rahman, and Md Shaki Mostaid. 2020. "TP53 Genetic Polymorphisms and Susceptibility to Cervical Cancer in Bangladeshi Women: A Case–Control Study." *Molecular Biology Reports* 47(6):4357–64.

Ayee, Richmond, Maame Ekua Oforiwaa Ofori, Edward Wright, and Osbourne Quaye. 2019. "Epstein Barr Virus Associated Lymphomas and Epithelia Cancers in Humans." *Journal of Cancer* 11(7):1737–50.

Barnes, Jessica L., Maria Zubair, Kaarthik John, Miriam C. Poirier, and Francis L. Martin. 2018. "Carcinogens and DNA Damage." *Biochemical Society Transactions* 46(5):1213–24.

Bashir, Kashif, Romana Sarwar, Shazia Fatima, Soma Saeed, Ishrat Mahjabeen, and Mahmood Akhtar Kayani. 2018. "Haplotype Analysis of XRCC1 Gene Polymorphisms and the Risk of

Thyroid Carcinoma." *Journal of B.U.ON*. 23(1):234–43.

Bellah, Sm Faysal, Maizbha Uddin Ahmed, Sikder Nahidul Islam Rabbi, Mohd Nazmul Hasan Apu, Md Siddiqul Islam, Mir Muhammad Nasir Uddin, Mohammad Safiqul Islam, and Abul Hasnat. 2015. "Prostate Cancer Risk in Relation to CYP3A4 and CYP3A5 Genotypes in the Bangladeshi Population." *Dhaka University Journal of Pharmaceutical Sciences* 14(2):179–85.

Benamrouz, S., V. Conseil, C. Creusy, E. Calderon, E. Dei-Cas, and G. Certad. 2012. "Parasites and Malignancies, a Review, with Emphasis on Digestive Cancer Induced by Cryptosporidium Parvum (Alveolata: Apicomplexa)." *Parasite* 19(2):101–15.

Berhane, Nega, Rabinder Chandera Sobti, and Salih Abdul Mahdi. 2012. "DNA Repair Genes Polymorphism (XPG and XRCC1) and Association of Prostate Cancer in a North Indian Population." *Molecular Biology Reports* 39(3):2471–79.

Bhatta, Bibek, Roshina Thapa, Sanjay Shahi, Yogesh Bhatta, Dipendra Raj Pandeya, and Bal Hari Poudel. 2016. "A Pilot Study on Screening of BRCA1 Mutations (185delAG, 1294del40) in Nepalese Breast Cancer Patients." *Asian Pacific Journal of Cancer Prevention* 17(4):1829–32.

Biernacka, Joanna M., and Heather J. Cordell. 2007. "Exploring Causality via Identification of SNPs or Haplotypes Responsible for a Linkage Signal." *Genetic Epidemiology* 31(7):727–40.

Boumber, Yanis A., Yutaka Kondo, Xuqi Chen, Lanlan Shen, Yi Guo, Carmen Tellez, Marcos R. H. Estécio, Saira Ahmed, and Jean Pierre J. Issa. 2008. "An Sp1/Sp3 Binding Polymorphism Confers Methylation Protection." *PLoS Genetics* 4(8).

Brady, G., G. J. MacArthur, and P. J. Farrell. 2008. "Epstein-Barr Virus and Burkitt Lymphoma." *Postgraduate Medical Journal* 84(993):372–77.

Bray, Freddie, Jacques Ferlay, Isabelle Soerjomataram, Rebecca L. Siegel, Lindsey A. Torre, and Ahmedin Jemal. 2018. "Global Cancer Statistics 2018: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries." *CA: A Cancer Journal for Clinicians* 68(6):394–424.

Bray, Freddie, Ahmedin Jemal, Nathan Grey, Jacques Ferlay, and David Forman. 2012. "Global Cancer Transitions According to the Human Development Index (2008-2030): A Population-Based Study." *The Lancet Oncology* 13(8):790–801.

Brendle, Annika, Haixin Lei, Andreas Brandt, Robert Johansson, Kerstin Enquist, Roger Henriksson, Kari Hemminki, Per Lenner, and Asta Försti. 2008. "Polymorphisms in Predicted MicroRNA-Binding Sites in Integrin Genes and Breast Cancer: ITGB4 as Prognostic Marker." *Carcinogenesis* 29(7):1394–99.

Buch, Shama C., Perin N. Notani, and Rajani A. Bhisey. 2002. "Polymorphism at GSTM1 , GSTM3 and GSTT1 Gene Loci and Susceptibility to Oral Cancer in an Indian Population at GSTM1 , GSTM3 and GSTT1 Gene Loci on Oral Cancer Tobacco , Bidi or Cigarette . DNA Extracted from White Blood Cells of 297 Cancer Patients and 4." *Carcinogenesis* 23(5):803–7.

Caldecott, Keith W. 2020. "XRCC1 Protein; Form and Function XRCC1 Protein; Form and Function." *DNA Repair* (February):102664.

Campbel, Thomas M., Mauro A. A. Castro, Ines De Santiago, Michael N. C. Fletcher, Silvia Halim, Radhika Prathalingam, Bruce A. J. Ponder, and Kerstin B. Meyer. 2016. "FGFR2 Risk

SNPs Confer Breast Cancer Risk by Augmenting Oestrogen Responsiveness." *Carcinogenesis* 37(8):741–50.

Cancer.org. 2016. "What Is Chronic Myeloid Leukemia?" *American Cancer Society* (Cml):1–10.

Carella, G. 2003. "Introduction to Apoptosis in Ophthalmology." *European Journal of Ophthalmology* 13 Suppl 3:1–26.

Cavanagh, Helen, and Katherine M. A. Rogers. 2015. "The Role of BRCA1 and BRCA2 Mutations in Prostate, Pancreatic and Stomach Cancers." *Hereditary Cancer in Clinical Practice* 13(1):1–7.

Chowdhury, Miraj Kobad, Md Moniruzzaman, Abdullah Al Emran, Mohammad Golam Mostafa, Ruhul H. Kuddus, and M. Aftab Uddin. 2015. "TP53 Codon 72 Polymorphisms and Lung Cancer Risk in the Bangladeshi Population." *Asian Pacific Journal of Cancer Prevention* 16(8):3493–98.

Chu, Duan, and Lai Wei. 2019. "Nonsynonymous, Synonymous and Nonsense Mutations in Human Cancer-Related Genes Undergo Stronger Purifying Selections than Expectation." *BMC Cancer* 19(1):1–12.

Combalia, Andrea, and Cristina Carrera. 2020. "Squamous Cell Carcinoma: An Update on Diagnosis and Treatment." *Dermatology Practical & Conceptual* 10(3):e2020066.

Coussens, LM, and Zena Werb. 2002. "Inflammation and Cancer." *NIH Public Access* 420(6917):860–67.

Deng, Na., Heng. Zhou, Hua. Fan, and Yuan. Yuan. 2017. "Single Nucleotide Polymorphisms and Cancer Susceptibility." *Single Nucleotide Polymorphisms and Cancer Susceptibility*

8(66):110635–49.

Dikshit, Rajesh, Prakash C. Gupta, Chinthanie Ramasundarahettige, Vendhan Gajalakshmi, Lukasz Aleksandrowicz, Rajendra Badwe, Rajesh Kumar, Sandip Roy, Wilson Suraweera, Freddie Bray, Mohandas Mallath, Poonam K. Singh, Dhirendra N. Sinha, Arun S. Shet, Hellen Gelband, and Prabhat Jha. 2012. "Cancer Mortality in India: A Nationally Representative Survey." *The Lancet* 379(9828):1807–16.

Du, Caigan, and Yuzhuo Wang. 2011. "The Immunoregulatory Mechanisms of Carcinoma for Its Survival and Development." *Journal of Experimental and Clinical Cancer Research* 30(1):12.

Du, Meijun, Lori Tillmans, Jianzhong Gao, Ping Gao, Tiezheng Yuan, Rachel L. Dittmar, Wei Song, Yuehong Yang, Natasha Sahr, Tao Wang, Gong Hong Wei, Stephen N. Thibodeau, and Liang Wang. 2016. "Chromatin Interactions and Candidate Genes at Ten Prostate Cancer Risk Loci." *Scientific Reports* 6:1–13.

Duan, Ranhui, Chang Hui Pak, and Peng Jin. 2007. "Single Nucleotide Polymorphism Associated with Mature MiR-125a Alters the Processing of Pri-MiRNA." *Human Molecular Genetics* 16(9):1124–31.

Elkhattabi, Lamiae, Imane Morjane, Hicham Charoute, Soumaya Amghar, Hind Bouafi, Zouhair Elkarhat, Rachid Saile, Hassan Rouba, and Abdelhamid Barakat. 2019. "In Silico Analysis of Coding/Noncoding SNPs of Human RETN Gene and Characterization of Their Impact on Resistin Stability and Structure." *Journal of Diabetes Research* 2019.

Fan, Hong, Dongsheng Liu, Xuemei Qiu, Fengchang Qiao, Qingxiang Wu, Xianwei Su, Feng Zhang, Yunwei Song, Zhujiang Zhao, and Wei Xie. 2010. "A Functional Polymorphism in

the DNA Methyltransferase-3A Promoter Modifies the Susceptibility in Gastric Cancer but Not in Esophageal Carcinoma." *BMC Medicine* 8:1–9.

Fidler, Miranda M., Isabelle Soerjomataram, and Freddie Bray. 2016. "A Global View on Cancer Incidence and National Levels of the Human Development Index." *International Journal of Cancer* 139(11):2436–46.

Fridley, Brooke L., and Joanna M. Biernacka. 2011. "Gene Set Analysis of SNP Data: Benefits, Challenges, and Future Directions." *European Journal of Human Genetics* 19(8):837–43.

Fried, Bernard, Aditya Reddy, and David Mayer. 2011. "Helminths in Human Carcinogenesis." *Cancer Letters* 305(2):239–49.

Gangwar, Ruchika, Dinesh Ahirwar, Anil Mandhani, and Rama Devi Mittal. 2009. "Do DNA Repair Genes OGG1, XRCC3 and XRCC7 Have an Impact on Susceptibility to Bladder Cancer in the North Indian Population?" *Mutation Research - Genetic Toxicology and Environmental Mutagenesis* 680(1–2):56–63.

Garnick, MB. 2006. "An Introduction to Cancer Care An Introduction to Cancer Care." *Nursing Standard* 20(49):31–31.

Geneva: World health Organization. 2018. *Who Global Report on Trends in Prevalence of Tobacco Smoking 2000-2025, Second Edition*.

Ghatak, Souvik, Ravi Prakash Yadav, Freda Lalrohlui, Payel Chakraborty, Soumee Ghosh, Sudakshina Ghosh, Madhusudan Das, Jeremy L. Pautu, John Zohmingthanga, and Nachimuthu Senthil Kumar. 2016. "Xenobiotic Pathway Gene Polymorphisms Associated with Gastric Cancer in High Risk Mizo-Mongoloid Population, Northeast India."

Helicobacter 21(6):523–35.

Girdhar, Yashila, Navneet Singh, Digambar Behera, and Siddharth Sharma. 2016. "Combinations of the Variant Genotypes of CYP1A1, GSTM1 and GSTT1 Are Associated with an Increased Lung Cancer Risk in North Indian Population: A Case-Control Study." *Pathology and Oncology Research* 22(3):647–52.

Gong, Shun, Ping Sheng, Hai Jin, Hua He, Enbo Qi, Wen Chen, Yan Dong, and Lijun Hou. 2014. "Effect of Methylphenidate in Patients with Cancer-Related Fatigue: A Systematic Review and Meta-Analysis." *PLoS ONE* 9(1):1–8.

Hallek, Michael. 2019. "Chronic Lymphocytic Leukemia: 2020 Update on Diagnosis, Risk Stratification and Treatment." *American Journal of Hematology* 94(11):1266–87.

Han, Xuesong, June Stevens, Kimberly P. Truesdale, Patrick T. Bradshaw, Anna Kucharska-Newton, Anna E. Prizment, Elizabeth A. Platz, and Corinne E. Joshu. 2014. "Body Mass Index at Early Adulthood, Subsequent Weight Change and Cancer Incidence and Mortality." *International Journal of Cancer* 135(12):2900–2909.

Hansa, Jagadish, Ravi Kannan, and Sankar Kumar Ghosh. 2012. "Screening of 185DelAG, 1014DelGT and 3889DelAG BRCA1 Mutations in Breast Cancer Patients from North-East India." *Asian Pacific Journal of Cancer Prevention* 13(11):5871–74.

Harris, Curtis C. 1996. "Structure and Function of the P53 Tumor Suppressor Gene: Clues for Rational Cancer Therapeutic Strategies." *Journal of the National Cancer Institute* 88(20):1442–55.

Hosen, Md Bayejid, Md Abdus Salam, Md Fakhrul Islam, Ashfaque Hossain, M. Zakir Hossain

Hawlader, and Yearul Kabir. 2015. "Association of TP53 Gene Polymorphisms with Susceptibility of Bladder Cancer in Bangladeshi Population." *Tumor Biology* 36(8):6369–74.

Hossain, Amir, Gazi Md Monjur Murshid, Md Nazmul Hasan Zilani, Fahrima Islam, Razia Sultana, Tamanna Sultana, Md Golam Hossain, and Md Mustafizur Rahman. 2017. "TP53 Codon 72 Polymorphism and Breast Cancer Risk in Bangladeshi Population." *Breast Cancer* 24(4):571–78.

Hu, Zhibin, Jie Liang, Zhanwei Wang, Tian Tian, Xiaoyi Zhou, Jiaping Chen, Ruifen Miao, Yan Wang, Xinru Wang, and Hongbing Shen. 2009. "Common Genetic Variants in Pre-MicroRNAs Were Associated with Increased Risk of Breast Cancer in Chinese Women." *Human Mutation* 30(1):79–84.

Huang, Xin, Weiyue Zhang, and Zengwu Shao. 2018. "Association between Long Non-Coding RNA Polymorphisms and Cancer Risk: A Meta-Analysis." *Bioscience Reports* 38(4).

Institute, National Cancer. 2020. "Cancer Facts & Figures 2020." *CA: A Cancer Journal for Clinicians* 1–76.

Ishihara, Hirofumi. 2007. "Analysis of Two Single Trait Loci Affecting Flavonol Glycoside Accumulations in Arabidopsis Thaliana Natural Variations." (January 2007).

Islam, Mohammad Safiqul, Maizbha Uddin Ahmed, Muhammad Shahdaat Bin Sayeed, Abdullah Al Maruf, A. G. M. Mostofa, Syed Md Akram Hussain, Yearul Kabir, Ann K. Daly, and Abul Hasnat. 2013. "Lung Cancer Risk in Relation to Nicotinic Acetylcholine Receptor, CYP2A6 and CYP1A1 Genotypes in the Bangladeshi Population." *Clinica Chimica Acta*416:11–19.

Islam, Mohammad Safiqul, A. G. M. Mostofa, Maizbha Uddin Ahmed, Muhammad Shahdaat Bin

Sayeed, Md Rajib Hassan, and Abul Hasnat. 2014. "Association of CYP3A4, CYP3A5 Polymorphisms with Lung Cancer Risk in Bangladeshi Population." *Tumor Biology* 35(2):1671–78.

Jain, Vijaylakshmi, Yashwant K. Ratre, Dnyanesh Amle, Pankaj K. Mishra, and Pradeep K. Patra. 2017. "Polymorphism of CYP1A1 Gene Variants Rs4646903 and Rs1048943 Relation to the Incidence of Cervical Cancer in Chhattisgarh." *Environmental Toxicology and Pharmacology* 52(November 2016):188–92.

Jaiswal, Praveen K., Apul Goel, and Rama D. Mittal. 2011. "Association of P53 Codon 248 (Exon7) with Urinary Bladder Cancer Risk in the North Indian Population." *BioScience Trends* 5(5):205–10.

Joseph, Shyn, Sudha Sellappa, Shibily Prathyumnan, and Kripa S. Keyan. 2011. "A Novel Polymorphism in BRCA2 Exon 8 and Breast Cancer Risk in South India." *Asian Pacific Journal of Cancer Prevention* 12(1):309–11.

Kang, Shan, Xiao Wei Ma, Wang Na, Xiu Feng Zhang, Deng Gui Wen, Wei Guo, Zheng Mao Zhang, and Yan Li. 2007. "Association of Three Single Nucleotide Polymorphisms of the E-Cadherin Gene with Endometriosis in a Chinese Population." *Reproduction* 134(2):373–78.

Khan, Mohammad Haroon, Hamid Rashid, Qaiser Mansoor, Abdul Hameed, and Muhammad Ismail. 2014. "Association of Rs1042522 Polymorphism with Increased Risk of Prostate Adenocarcinoma in the Pakistani Population and Its HuGE Review." *Asian Pacific Journal of Cancer Prevention* 15(9):3973–80.

Khlestkina, E. K., and E. A. Salina. 2006. "SNP Markers: Methods of Analysis, Ways of Development, and Comparison on an Example of Common Wheat." *Russian Journal of*

Genetics 42(6):585–94.

Kimi, Lalro, Souvik Ghatak, Ravi Prakash Yadav, Lalhma Chhuani, Doris Lallawmzuali, Jeremy L. Pautu, and Nachimuthu Senthil Kumar. 2016. "Relevance of GSTM1, GSTT1 and GSTP1 Gene Polymorphism to Breast Cancer Susceptibility in Mizoram Population, Northeast India." *Biochemical Genetics* 54(1):41–49.

Kiruthiga, P. V., M. Rajesh Kannan, C. Saraswathi, S. Karutha Pandian, and K. Pandima Devi. 2011. "CYP1A1 Gene Polymorphisms: Lack of Association with Breast Cancer Susceptibility in the Southern Region (Madurai) of India." *Asian Pacific Journal of Cancer Prevention* 12(8):2133–38.

Klein, Kathrin, and Ulrich M. Zanger. 2013. "Pharmacogenomics of Cytochrome P450 3A4: Recent Progress toward the 'Missing Heritability' Problem." *Frontiers in Genetics* 4(FEB):1–15.

Kuhn, E., P. Morbini, A. Cancellieri, S. Damiani, A. Cavazza, and C. E. Comin. 2018. "Adenocarcinoma Classification: Patterns and Prognosis." *Pathologica* 110(1):5–11.

Kumar, Anil, Mohan Chand Pant, Hirdya Shanker Singh, and Shashi Khandelwal. 2012. "Associated Risk of XRCC1 and XPD Cross Talk and Life Style Factors in Progression of Head and Neck Cancer in North Indian Population." *Mutation Research - Fundamental and Molecular Mechanisms of Mutagenesis* 729(1–2):24–34.

Kwan-Hoong, NG. 2003. "Non-Ionizing Radiations - Sources, Biological Effects, Emissions and Exposures." *Proceedings of the International Conference on Non-Ionizing Radiation at UNITEN* (October):1–16.

Larsson, Susanna C., and Alicja Wolk. 2007. "Obesity and Risk of Non-Hodgkin's Lymphoma: A Meta-Analysis." *International Journal of Cancer* 121(7):1564–70.

Liede, Alexander, A. Imtiaz Malik, Zeba Aziz, Patricia Rios, Elaine Kwan, and Steven Narod. 2002. "Contribution of BRCA1 and BRCA2 Mutations to Breast and Ovarian Cancer in Pakistan." *Human Mutation* 71(3):595–606.

Loomis, Dana, Neela Guha, Amy L. Hall, and Kurt Straif. 2018. "Identifying Occupational Carcinogens: An Update from the IARC Monographs." *Occupational and Environmental Medicine* 75(8):593–603.

Lubelski, Jacek, Wil N. Konings, and Arnold J. M. Driessen. 2007. "Distribution and Physiology of ABC-Type Transporters Contributing to Multidrug Resistance in Bacteria." *Microbiology and Molecular Biology Reviews* 71(3):463–76.

Lynch, H. T. 1976. "Introduction to Cancer Genetics." *Cancer Genetics* 3–31.

Mahjabeen, Ishrat, Ruqia Mehmood Baig, Nosheen Masood, Maimoona Sabir, Uzma Inayat, Faraz Arshad Malik, and Mahmood Akhtar Kayani. 2013. "Genetic Variations in XRCC1 Gene in Sporadic Head and Neck Cancer (HNC) Patients." *Pathology and Oncology Research* 19(2):183–88.

Mandal, Raju K., Rakesh Kapoor, and Rama Devi Mittal. 2010. "Polymorphic Variants of DNA Repair Gene XRCC3 and XRCC7 and Risk of Prostate Cancer: A Study from North Indian Population." *DNA and Cell Biology* 29(11):669–74.

Manoharan, Vahinipriya, Eric Hamilton Karunanayake, Kamani Hemamala Tennekoon, Sumadee D. E. Silva, Kanishka D. E. Silva, Preethika Angunawela, and John Lunec. 2019. "Nucleotide

Variants and Protein Expression of TP53 in a Sri Lankan Cohort of Patients with Head and Neck Cancer." *Molecular Medicine Reports* 19(4):2781–91.

Masood, Nosheen, Mahmood Akhtar Kayani, Fraz Arshad Malik, Ishrat Mahjabeen, Ruqia Mehmood Baig, and Rani Faryal. 2011. "Genetic Variations in Carcinogen Metabolizing Genes Associated with Oral Cancer in Pakistani Population." *Asian Pacific Journal of Cancer Prevention* 12(2):491–95.

McLaughlin-Drubin, Margaret E., Jordan Meyers, and Karl Munger. 2012. "Cancer Associated Human Papillomaviruses." *Current Opinion in Virology* 2(4):459–66.

Mcvicker, Graham, Bryce Van De Geijn, Jacob F. Degner, Carolyn E. Cain, Nicholas E. Banovich, Anil Raj, Noah Lewellen, Marsha Myrthil, Yoav Gilad, and Jonathan K. Pritchard. 2014. "NIH Public Access." 342(6159):747–49.

Mendell, Joshua T., and Harry C. Dietz. 2001. "When the Message Goes Awry: Disease-Producing Mutations That Influence MRNA Content and Performance." *Cell* 107(4):411–14.

Mittal, Rama Devi, Ginu P. George, Jyotsna Mishra, Tulika Mittal, and Rakesh Kapoor. 2011. "Role of Functional Polymorphisms of P53 and P73 Genes with the Risk of Prostate Cancer in a Case-Control Study from Northern India." *Archives of Medical Research* 42(2):122–27.

Mohammed, Fawziah M. A., Ali Reza Rezaee khorasany, Elaheh Mosaieby, and Massoud Houshmand. 2015. "Mitochondrial A12308G Alteration in $TRNA^{Leu(CUN)}$ in Colorectal Cancer Samples." *Diagnostic Pathology* 10(1):4–7.

Mostaid, Md Shaki, Maizbha Uddin Ahmed, Mohammad Safiqul Islam, Muhammad Shahdaat Bin Sayeed, and Abul Hasnat. 2014. "Lung Cancer Risk in Relation to TP53 Codon 47 and Codon

72 Polymorphism in Bangladeshi Population." *Tumor Biology* 35(10):10309–17.

Multhoff, Gabriele, Michael Molls, and Jürgen Radons. 2012. "Chronic Inflammation in Cancer Development." *Frontiers in Immunology* 2(JAN):1–17.

Nasir Uddin, Mir Muhammad, Maizbha Uddin Ahmed, Mohammad Safiqul Islam, Mohammad Siddiqul Islam, Muhammad Shahdaat Bin Sayeed, Yearul Kabir, and Abul Hasnat. 2014. "Genetic Polymorphisms of GSTM1, GSTP1 and GSTT1 Genes and Lung Cancer Susceptibility in the Bangladeshi Population." *Asian Pacific Journal of Tropical Biomedicine* 4(12):982–89.

National Toxicology Program. 2011. "Ionizing Radiation: X-Radiation and Gamma Radiation." *Report on Carcinogens : Carcinogen Profiles / U.S. Dept. of Health and Human Services, Public Health Service, National Toxicology Program* 12(Iarc 2000):237–40.

Naylor, G. M., T. Gotoda, M. Dixon, T. Shimoda, L. Gatta, R. Owen, D. Tompkins, and A. Axon. 2006. "Why Does Japan Have a High Incidence of Gastric Cancer? Comparison of Gastritis between UK and Japanese Patients." *Gut* 55(11):1545–52.

Nishat, Latifa, Zinnat Ara Yesmin, Farida Arjuman, Sufi Hannan Zulfiqar Rahman, and Laila Anjuman Banu. 2019. "Identification of Mutation in Exon11 of BRCA1 Gene in Bangladeshi Patients with Breast Cancer." *Asian Pacific Journal of Cancer Prevention* 20(11):3515–19.

Nissar, Saniya, Aga Syed Sameer, Roohi Rasool, Nissar A. Chowdri, and Fouzia Rashid. 2015. "Polymorphism of the DNA Repair Gene XRCC1 (Arg194Trp) and Its Role in Colorectal Cancer in Kashmiri Population: A Case Control Study." *Asian Pacific Journal of Cancer Prevention* 16(15):6385–90.

Nosheen, M., M. Ishrat, F. A. Malik, R. M. Baig, and M. A. Kayani. 2010. "Association of GSTM1 and GSTT1 Gene Deletions with Risk of Head and Neck Cancer in Pakistan: A Case Control Study." *Asian Pacific Journal of Cancer Prevention* 11(4):881–85.

Pachouri, Suparna S., Ranbir Chander Sobti, Pushpinder Kaur, and Jagmohan Singh. 2007. "Contrasting Impact of DNA Repair Gene XRCC1 Polymorphisms Arg399Gln and Arg194Trp on the Risk of Lung Cancer in North-Indian Population." *DNA and Cell Biology* 26(3):186–91.

Pandith, Arshad A., Zafar A. Shah, Nighat P. Khan, Roohi Rasool, Dil Afroze, Adfar Yousuf, Saleem Wani, and Mushtaq Siddiqi. 2010. "Role of TP53 Arg72Pro Polymorphism in Urinary Bladder Cancer Predisposition and Predictive Impact of Proline Related Genotype in Advanced Tumors in an Ethnic Kashmiri Population." *Cancer Genetics and Cytogenetics* 203(2):263–68.

Parvin, Salma, Md Siddiqul Islam, Mir Md Abdullah Al-Mamun, Mohammad Safiqul Islam, Maizbha Uddin Ahmed, Eva Rahman Kabir, and Abul Hasnat. 2016. "Association of BRCA1, BRCA2, RAD51, and HER2 Gene Polymorphisms with the Breast Cancer Risk in the Bangladeshi Population." *Breast Cancer* 24(2):229–37.

Patel, Kinjal R., Bhairavi N. Vajaria, Rasheedunnisa Begum, Franky D. Shah, Jayendra B. Patel, Shilin N. Shukla, and Prabhudas S. Patel. 2013. "Association between P53 Gene Variants and Oral Cancer Susceptibility in Population from Gujarat , West India." 14:1093–1100.

Peddireddy, Vidyullatha, Siva Prasad Badabagni, Sandhya Devi Gundimeda, Vasudha Mamidipudi, Pardhanandana Reddy Penagaluru, and Hema Prasad Mundluru. 2016. "Association of CYP1A1, GSTM1 and GSTT1 Gene Polymorphisms with Risk of Non-Small

Cell Lung Cancer in Andhra Pradesh Region of South India." *European Journal of Medical Research* 21(1):1–14.

Potter, Jared W., Kevin B. Jones, and Jared J. Barrott. 2018. "Sarcoma–The Standard-Bearer in Cancer Discovery." *Critical Reviews in Oncology/Hematology* 126(February):1–5.

Raghav, Dhwani, Vinay Sharma, and Subhash Mohan Agarwal. 2013. "Structural Investigation of Deleterious Non-Synonymous SNPs of EGFR Gene." *Interdisciplinary Sciences: Computational Life Sciences* 5(1):60–68.

Rai, Rajani, Kiran L. Sharma, Sanjeev Misra, Ashok Kumar, and Balraj Mittal. 2014. "CYP17 Polymorphism (Rs743572) Is Associated with Increased Risk of Gallbladder Cancer in Tobacco Users." *Tumor Biology* 35(7):6531–37.

Ramírez-Bello, Julián, and Mayra Jiménez-Morales. 2017. "[Functional Implications of Single Nucleotide Polymorphisms (SNPs) in Protein-Coding and Non-Coding RNA Genes in Multifactorial Diseases]." *Gaceta Medica de Mexico* 153(2):238–50.

Raunio, Hannu, and Minna Rahnasto-Rilla. 2012. "CYP2A6: Genetics, Structure, Regulation, and Function." *Drug Metabolism and Drug Interactions* 27(2):73–88.

Rivu, Sanzana Fareen, Mohd Nazmul Hasan Apu, Samia Shabnaz, Noor Ahmed Nahid, Md Reazul Islam, Mir Md Abdullah Al-Mamun, Zabun Nahar, Sikder Nahidul Islam Rabbi, Maizbha Uddin Ahmed, Mohammad Safiqul Islam, and Abul Hasnat. 2017. "Association of TP53 Codon 72 and CDH1 Genetic Polymorphisms with Colorectal Cancer Risk in Bangladeshi Population." *Cancer Epidemiology* 49:46–52.

Robert, Francis, and Jerry Pelletier. 2018. "Exploring the Impact of Single-Nucleotide

Polymorphisms on Translation." *Frontiers in Genetics* 9(October):1–11.

Ruwali, Munindra, Mohan C. Pant, Parag P. Shah, Bhartendu N. Mishra, and Devendra Parmar. 2009. "Polymorphism in Cytochrome P450 2A6 and Glutathione S-Transferase P1 Modifies Head and Neck Cancer Risk and Treatment Outcome." *Mutation Research - Fundamental and Molecular Mechanisms of Mutagenesis* 669(1–2):36–41.

Saadat, Mostafa, and Akram Rabizadeh-Hafshenjani. 2016. "DNA Repair Gene XRCC7 G6721T Variant and Susceptibility to Colorectal Cancer." *Egyptian Journal of Medical Human Genetics* 17(4):373–76.

Saikia, Bhaskar Jyoti, Mandakini Das, Santanu Kumar Sharma, Gaganpreet Singh Sekhon, Eric Zomawia, Yanglem Mohen Singh, Jagadish Mahanta, and Rup Kumar Phukan. 2015. "Association of a P53 Codon 72 Gene Polymorphism with Environmental Factors and Risk of Lung Cancer: A Case Control Study in Mizoram and Manipur, a High Incidence Region in North East India." *Asian Pacific Journal of Cancer Prevention* 15(24):10653–658.

Saleem, Saima, Abid Azhar, Abdul Hameed, Mansoor Ahmed Khan, Zubair Ahmed Abbasi, Navid Rashid Qureshi, and Muhammad Ajmal. 2013. "P53 (Pro72Arg) Polymorphism Associated with the Risk of Oral Squamous Cell Carcinoma in Gutka, Niswar and Manpuri Addicted Patients of Pakistan." *Oral Oncology* 49(8):818–23.

Saultz, Jennifer, and Ramiro Garzon. 2016. "Acute Myeloid Leukemia: A Concise Review." *Journal of Clinical Medicine* 5(3):33.

Schaefer, Christian, and Burkhard Rost. 2012. "Predict Impact of Single Amino Acid Change upon Protein Structure." *BMC Genomics* 13 Suppl 4(Suppl 4):S4.

Selgrad, Michael, Peter Malfertheiner, Lucia Fini, Ajay Goel, C. Richard Boland, and Luigi Ricciardiello. 2008. "The Role of Viral and Bacterial Pathogens in Gastrointestinal Cancer." *Journal of Cellular Physiology* 216(2):378–88.

Serdar, E. Bulun, Chen Dong, Moy Irene, C. Brook. David, and Zhao Hong. 2012. "Aromatase, Breast Cancer and Obesity: A Complex Interaction." *Bone* 23(2):83–89.

Shabnaz, Samia, Maizbha Uddin Ahmed, Md Siddiqul Islam, Md Reazul Islam, Mir Md Abdullah Al-Mamun, Mohammad Safiqul Islam, and Abul Hasnat. 2016. "Breast Cancer Risk in Relation to TP53 Codon 72 and CDH1 Gene Polymorphisms in the Bangladeshi Women." *Tumor Biology* 37(6):7229–37.

Shan, Yibing, Michael P. Eastwood, Xuewu Zhang, Eric T. Kim, Anton Arkhipov, Ron O. Dror, John Jumper, John Kuriyan, and David E. Shaw. 2012. "Oncogenic Mutations Counteract Intrinsic Disorder in the EGFR Kinase and Promote Receptor Dimerization." *Cell* 149(4):860–70.

Shanbhag, Satish, and Richard Ambinder. 2019. "Nihms908823.Pdf." 68(2):116–32.

Sharma, Anita, Bhudev Chander Das, Ashok Sehgal, Ravi Mehrotra, Premashish Kar, Sarita Sardana, Rup Phukan, Jagdish Mahanta, Joydeep Purkayastha, Sunita Saxena, Sujala Kapur, Indranil Chatterjee, and Joginder Kumar Sharma. 2013. "GSTM1 and GSTT1 Polymorphism and Susceptibility to Esophageal Cancer in High- and Low-Risk Regions of India." *Tumor Biology* 34(5):3249–57.

Sharma, Neha, Amrita Singh, Navneet Singh, Digamber Behera, and Siddharth Sharma. 2015. "Genetic Polymorphisms in GSTM1, GSTT1 and GSTP1 Genes and Risk of Lung Cancer in a North Indian Population." *Cancer Epidemiology* 39(6):947–55.

Sharma, Sarika, Vasudha Sambyal, Kamlesh Guleria, Mridu Manjari, Gupta Sudan, Manjit Singh Uppal, Neeti Rajan Singh, Darpan Bansal, and Arun Gupta. 2014. "Analysis of TP53 Polymorphisms in North Indian Sporadic Esophageal Cancer Patients." *Asian Pacific Journal of Cancer Prevention* 15(16):6871–78.

Sheikh, Shaffi M., Mohd Amin Shah, Imtiyaz Ahmad Bhat, Parvaiz Koul, Syed Nisar Ahmad, and Mushtaq A. Siddiqi. 2009. "CYP1A1 Polymorphisms and Risk of Lung Cancer in the Ethnic Kashmiri Population." *Asian Pacific Journal of Cancer Prevention* 10(4):651–56.

Shen, L. X., J. P. Basilion, and Jr Stanton. 1999. "Single-Nucleotide Polymorphisms Can Cause Different Structural Folds of MRNA." *Proceedings of the National Academy of Sciences of the United States of America* 96(14):7871–76.

Siegel, Rebecca L., Kimberly D. Miller, and Ahmedin Jemal. 2017. "Cancer Statistics, 2017." *CA: A Cancer Journal for Clinicians* 67(1):7–30.

Sikorska-Jaroszyńska, Małgorzata H. J., Maria Mielnik-Błaszczak, Dorota Krawczyk, Alicja Nasiłowska-Barud, and Jerzy Błaszczak. 2012. "Passive Smoking as an Environmental Health Risk Factor." *Annals of Agricultural and Environmental Medicine* 19(3):547–50.

De Silva, Sumadee, Kamani Hemamala Tennekoon, Aravinda Dissanayake, Kanishka De Silva, and Lakshika Jayasekara. 2017. "Novel and Reported Pathogenic Variants in Exon 11 of BRCA2 Gene in a Cohort of Sri Lankan Young Breast Cancer Patients." *Familial Cancer* 16(3):329–38.

Singamsetty, Gopi Krishna, Sravanthi Malempati, Srichandana Bhogadhi, Ravinder Kondreddy, Suresh Govatati, Naveen Kumar Tangudu, Sowdamani Govatati, Anil Kumar Kuraganti, Manjula Bhanoori, and Kondaiah Kassetty. 2014. "TP53 Alterations and Colorectal Cancer

Predisposition in South Indian Population: A Case-Control Study." *Tumor Biology* 35(3):2303–11.

Singh, Arvind P., Parag P. Shah, Munindra Ruwali, Neeraj Mathur, Mohan C. Pant, and Devendra Parmar. 2009. "Polymorphism in Cytochrome P4501A1 Is Significantly Associated with Head and Neck Cancer Risk." *Cancer Investigation* 27(8):869–76.

Singh, Hariom, Rekha Sachan, S. Devi, Sachchida N. Pandey, and B. Mittal. 2008. "Association of GSTM1, GSTT1, and GSTM3 Gene Polymorphisms and Susceptibility to Cervical Cancer in a North Indian Population." *American Journal of Obstetrics and Gynecology* 198(3):303.e1-303.e6.

Singh, Jaya, Nishita Thota, Suhasini Singh, Shila Padhi, Puja Mohan, Shivani Deshwal, Soumit Sur, Mithua Ghosh, Amit Agarwal, Ramesh Sarin, Rosina Ahmed, Sachin Almel, Basumita Chakraborti, Vinod Raina, Praveen K. DadiReddy, B. K. Smruti, Senthil Rajappa, Chandragouda Dodagoudar, Shyam Aggarwal, Manish Singhal, Ashish Joshi, Rajeev Kumar, Ajai Kumar, Deepak K. Mishra, Neeraj Arora, Aarati Karaba, Satish Sankaran, Shanmukh Katragadda, Arunabha Ghosh, Vamsi Veeramachaneni, Ramesh Hariharan, and Ashraf U. Mannan. 2018. "Screening of over 1000 Indian Patients with Breast and/or Ovarian Cancer with a Multi-Gene Panel: Prevalence of BRCA1/2 and Non-BRCA Mutations." *Breast Cancer Research and Treatment* 170(1):189–96.

Singh, Seram Anil, Javed Hussain Choudhury, Wetetsho Kapfo, Sharbadeb Kundu, Bishal Dhar, Shaheen Laskar, Raima Das, Manish Kumar, and Sankar Kumar Ghosh. 2015. "Influence of the CYP1A1 T3801C Polymorphism on Tobacco and Alcohol-Associated Head and Neck Cancer Susceptibility in Northeast India." *Asian Pacific Journal of Cancer Prevention*

16(16):6953–61.

Sinha, Tarini. 2018. "Tumors: Benign and Malignant." *Cancer Therapy & Oncology International Journal* 10(3):1–3.

Sirisena, Nirmala Dushyanthi, Adebowale Adeyemo, Anchala Ishani Kuruppu, Nilakshi Samaranayake, and Vajira Harshadeva Weerabaddana Dissanayake. 2018. "Genetic Variants Associated with Clinicopathological Profiles in Sporadic Breast Cancer in Sri Lankan Women." *Journal of Breast Cancer* 21(2):165–72.

Sobti, R. C., Khadijeh Onsory, Adnan Issa Al-Badran, Pushpinder Kaur, Masatoshi Watanabe, A. Krishan, and Harsh Mohan. 2006. "CYP17, SRD5A2, CYP1B1, and CYP2D6 Gene Polymorphisms with Prostate Cancer Risk in North Indian Population." *DNA and Cell Biology* 25(5):287–94.

Sobti, R. C., S. Sharma, A. Joshi, S. K. Jindal, and A. Janmeja. 2003. "CYPIAI and CYP2D6 Polymorphism and Risk of Lung Cancer in a North Indian Population." *Biomarkers* 8(5):415–28.

Sobti, R. C., S. Sharma, A. Joshi, S. K. Jindal, and A. Janmeja. 2004. "Genetic Polymorphism of the CYP1A1, CYP2E1, GSTM1 and GSTT1 Genes and Lung Cancer Susceptibility in a North Indian Population." *Molecular and Cellular Biochemistry* 266(1–2):1–9.

Sobti, Ranbir C, Pushpinder Kaur, Satinder Kaur, Ashok K. Janmeja, Surinder K. Jindal, Jai Kishan, and Sara Raimondi. 2009. "Impact of Interaction of Polymorphic Forms." 28(9):443–49.

Sobti, Ranbir Chander, Lipsy Gupta, Hitender Thakur, Amlesh Seth, Sharwan K. Singh, and

Pushpinder Kaur. 2009. "CYP17 Gene Polymorphism and Its Association in North Indian Prostate Cancer Patients." *Anticancer Research* 29(5):1659–63.

Sreeja, Leelakumari, Vani Syamala, Sreedharan Hariharan, Jayaprakash Madhavan, Sivanandan Choondal Devan, and Ravindran Ankathil. 2005. "Possible Risk Modification by CYP1A1, GSTM1 and GSTT1 Gene Polymorphisms in Lung Cancer Susceptibility in a South Indian Population." *Journal of Human Genetics* 50(12):618–27.

Sreeja, Leelakumari, Volga S. Syamala, Vani Syamala, Sreedharan Hariharan, Praveenkumar B. Raveendran, R. V. Vijayalekshmi, Jayaprakash Madhavan, and Ravindran Ankathil. 2008. "Prognostic Importance of DNA Repair Gene Polymorphisms of XRCC1 Arg399Gln and XPD Lys751Gln in Lung Cancer Patients from India." *Journal of Cancer Research and Clinical Oncology* 134(6):645–52.

Srivastava, Daya Shankar Lal, Anil Mandhani, Balraj Mittal, and Rama Devi Mittal. 2005. "Genetic Polymorphism of Glutathione S-Transferase Genes (GSTM1, GSTT1 and GSTP1) and Susceptibility to Prostate Cancer in Northern India." *BJU International* 95(1):170–73.

Steri, M., M. L. Idda, Whalen, M.B., and V. Orru. 2018. "HHS Public Access." *Physiology & Behavior* 9(4):139–48.

Storck, Katharina, Markus Brandstetter, Ulrich Keller, and Andreas Knopf. 2019. "Clinical Presentation and Characteristics of Lymphoma in the Head and Neck Region." *Head and Face Medicine* 15(1):4–11.

Tasnim, Tasnova, Mir Md Abdullah Al-Mamun, Noor Ahmed Nahid, Md Reazul Islam, Mohd Nazmul Hasan Apu, Most Umme Bushra, Sikder Nahidul Islam Rabbi, Zabun Nahar, Jakir Ahmed Chowdhury, Maizbha Uddin Ahmed, Mohammad Safiqul Islam, and Abul Hasnat.

2017. "Genetic Variants of SULT1A1 and XRCC1 Genes and Risk of Lung Cancer in Bangladeshi Population." *Tumor Biology* 39(11).

Tennessen, Jacob A., Abigail W. Bigham, Timothy D. O 'connor, Wenqing Fu, Eimear E. Kenny, Simon Gravel, Sean Mcgee, Ron Do, Xiaoming Liu, Goo Jun, Hyun Min Kang, Daniel Jordan, Suzanne M. Leal, Stacey Gabriel, Mark J. Rieder, Goncalo Abecasis, David Altshuler, Deborah A. Nickerson, Eric Boerwinkle, Shamil Sunyaev, Carlos D. Bustamante, Michael J. Bamshad, and Joshua M. Akey. 2012. "Evolution and Functional Impact of Rare Coding Variation from Deep Sequencing of Human Exomes Broad GO, Seattle GO, on Behalf of the NHLBI Exome Sequencing Project." *Science* 337(6090):64–69.

Terwilliger, T., and M. Abdul-Hay. 2017. "Acute Lymphoblastic Leukemia: A Comprehensive Review and 2017 Update." *Blood Cancer Journal* 7(6):e577.

Tilak, Anup R., Sachin Kumar, Mohan C. Pant, Neeraj Mathur, and Ashwani Kumar. 2013. "Polymorphism Arg72Pro of P53 Confers Susceptibility to Squamous Cell Carcinoma of Lungs in a North Indian Population." *DNA and Cell Biology* 32(2):66–72.

Tomizawa, Daisuke, and Nobutaka Kiyokawa. 2017. "Acute Lymphoblastic Leukemia." *Hematological Disorders in Children: Pathogenesis and Treatment* (December):33–60.

Torre, Lindsey A., Freddie Bray, Rebecca L. Siegel, Jacques Ferlay, Joannie Lortet-Tieulent, and Ahmedin Jemal. 2015. "Global Cancer Statistics, 2012." *CA: A Cancer Journal for Clinicians* 65(2):87–108.

Tran, Hoai Thu Thi, Yasuhiro Takeshima, Agus Surono, Mariko Yagi, Hiroko Wada, and Masafumi Matsuo. 2005. "A G-to-A Transition at the Fifth Position of Intron-32 of the Dystrophin Gene Inactivates a Splice-Donor Site Both in Vivo and in Vitro." *Molecular*

Genetics and Metabolism 85(3):213–19.

Verhaegh, Gerald W., Linda Verkleij, Sita H. H. M. Vermeulen, Martin den Heijer, J. Alfred Witjes, and Lambertus A. Kiemeney. 2008. "Polymorphisms in the H19 Gene and the Risk of Bladder Cancer." *European Urology* 54(5):1118–26.

Vignal, A., D. Milan, M. SanCristobal, and A. Eggen. 2008. "A Review on SNPs and Other Types of Molecular Markers." *Genetics, Selection, Evolution : GSE* 40:241–64.

Vijayalakshmi, K., V. Vettriselvi, M. Krishnan, Sunil Shroff, K. N. Vishwanathan, Vikram R. Jayanth, and Solomon F. D. Paul. 2005. "Polymorphisms at GSTM1 and GSTP1 Gene Loci and Risk of Prostate Cancer in a South Indian Population." *Asian Pacific Journal of Cancer Prevention* 6(3):309–14.

Villela, Luis, and Javier Bolaños-Meade. 2011. "Acute Myeloid Leukaemia: Optimal Management and Recent Developments." *Drugs* 71(12):1537–50.

Vyhlidal, Carrie A., Robin E. Pearce, Roger Gaedigk, Justina C. Calamia, Diana L. Shuster, Kenneth E. Thummel, and J. Steven Leeder. 2015. "Variability in Expression of CYP3A5 in Human Fetal Liver." *Drug Metabolism and Disposition* 43(8):1286–93.

Wagner, Jennifer A., and Jennifer M. Colombo. 2020. "Medicine and Media: The Ranitidine Debate." *Clinical and Translational Science* 1–3.

Walter, John. 2013. "The Lymphoma Guide." *The Leukemia & Lymphoma Society* 1–48.

Wang, D., and R. N. Dubois. 2006. "Prostaglandins and Cancer." *Gut* 55(1):115–22.

Wang, Jingwen, Yang Zhao, Jing Jiang, Vendhan Gajalakshmi, Kiyonori Kuriki, Seiichi Nakamura, Susumu Akasaka, Hideki Ishikawa, Sadao Suzuki, Teruo Nagaya, and Shinkan

Tokudome. 2010. "Polymorphisms in DNA Repair Genes XRCC1, XRCC3 and XPD, and Colorectal Cancer Risk: A Case-Control Study in an Indian Population." *Journal of Cancer Research and Clinical Oncology* 136(10):1517–25.

Wang, Xuyi, Evan R. Simpson, and Kristy A. Brown. 2015. "Aromatase Overexpression in Dysfunctional Adipose Tissue Links Obesity to Postmenopausal Breast Cancer." *Journal of Steroid Biochemistry and Molecular Biology* 153:35–44.

Weinberg, RA. 1988. "The Roots of Human Cancer." *American Academy of Arts & Sciences* 41(8):28–36.

Wilkie, Gavin S., Kirsten S. Dickson, and Nicola K. Gray. 2003. "Regulation of MRNA Translation by 5′- and 3′-UTR-Binding Factors." *Trends in Biochemical Sciences* 28(4):182–88.

Winickoff, Jonathan P., Joan Friebely, Susanne E.tanski, Cheryl Sherrod, Georg E.matt, Melbourne F. Hovell, and Robert C. McMillen. 2009. "Beliefs about the Health Effects of 'Thirdhand' Smoke and Home Smoking Bans." *Pediatrics* 123(1).

Xu, Gui Ping, Qing Zhao, Ding Wang, Wen Yue Xie, Li Jun Zhang, Hua Zhou, Shi Zhi Chen, and Li Fang Wu. 2018. "The Association between BRCA1 Gene Polymorphism and Cancer Risk: A Meta-Analysis." *Oncotarget* 9(9):8681–94.

Zakiullah, Ahmadullah, Muhammad Khisroon, Muhammad Saeed, Ajmal Khan, Fazli Khuda, Sajid Ali, Nabila Javed, Muhammad Ovais, Nosheen Masood, Nasir Khan Khalil, and Mohammad Ismail. 2015. "Genetic Susceptibility to Oral Cancer Due to Combined Effects of GSTT1, GSTM1 and CYP1A1 Gene Variants in Tobacco Addicted Patients of Pashtun Ethnicity of Khyber Pakhtunkhwa Province of Pakistan." *Asian Pacific Journal of Cancer*

Prevention 16(3):1145–50.

Zhang, Dandan, Lijun Cheng, Judith A. Badner, Chao Chen, Qi Chen, Wei Luo, David W. Craig, Margot Redman, Elliot S. Gershon, and Chunyu Liu. 2010. "Genetic Control of Individual Differences in Gene-Specific Methylation in Human Brain." *American Journal of Human Genetics* 86(3):411–19.