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EXPLORING THE IMPACT OF THE MICRO-RNA GENETIC VARIANT RS20541 ON GLIOBLASTOMA AND ITS IMPLICATIONS ACROSS MULTIPLE CANCER TYPES: A META-ANALYSIS

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Abstract

Through a thorough Meta-analysis, this work explores the relationship between the microRNA gene variant rs20541 and Glioblastoma, as well as its possible consequences for other cancer types. One type of cancer reported to be susceptible to single nucleotide polymorphisms (SNPs) is glioblastoma. It's interesting to note that a frequently occurring SNP in microRNA has been linked to carcinogenesis in a variety of cancer types. The purpose of this study is to investigate the unique effects of rs20541 on glioblastoma as well as any possible wider implications for this gene in relation to other malignancies. The research also emphasizes how this immunoregulatory cytokine interleukin-13 (IL13) affects tumor immunosurveillance. It is known that IL13 has a major impact on carcinogenesis, indicating that it plays a role in the intricate processes that underlie the onset and spread of cancer. Through clarifying the connection with the IL13 microRNA genetic variation and cancer, this work aims to improve our knowledge of the molecular processes underlying the advancement of cancer and offer insights into possible medical treatment pathways. Inconclusive results have been found in several research examining the impact of IL13 rs20541 polymorphisms affecting cancer risk. Given this, the current work aims to elucidate this relationship using a thorough meta-analysis. For the purpose of both quantitative and qualitative information synthesis, a total of twenty studies have been included, following the PRISMA standards for data retrieval. A meta-analysis presents a useful chance to synthesize and evaluate data from various studies, offering a more thorough knowledge of the association among IL13 rs20541 polymorphism and cancer risk, especially in light of the conflicting results from earlier research. This study attempts to overcome the constraints associated with individual investigations and provide strong insights into the possible influence of this gene polymorphism on cancer susceptibility by using a rigorous technique and following established principles. The goal of this work is to add to the pool of knowledge already accessible about the involvement of IL13 rs20541 polymorphisms towards the development of cancer through a systematic examination and synthesis of relevant evidence. In the end, the results of this meta-analysis might affect risk evaluation and screening, as well as possibly guide individualized preventive and curative plans. Meta-analysis was performed on the SNP rs20541 in different ethnicities of Asian and European populations by using SPSS and STATA. According to our meta-analysis, the IL13 rs20541 polymorphism increases a person's risk of developing cancer, particularly gliomas. Our meta-analysis suggests that the variant allele present(A) in IL13 rs20541 polymorphism is highly significant in Asian population and European population as depicted by the P-values. It is also significantly associated or present in Gliomas as compared with other cancer. Further validation of our findings would need larger, future investigations using well-matched groups and standardized, impartial, heterogeneous patients.

Keywords: *Polymorphism, Asian, European, Gliomas, IL13, Immunosurveillance.*

CHAPTER 1:

INTRODUCTION

Introduction

An illness known as cancer occurs when some body cells proliferate out of control and invade other bodily regions. With trillions of cells making up an individual's body, cancer can begin practically anywhere. Human cells typically divide to create new cells as needed by the body by growing and multiplying. New cells replace old ones when they die as a result of aging or injury. This controlled mechanism can occasionally malfunction, causing damaged or aberrant cells to proliferate and expand when they ought not to. Tumors are clumps of tissue that can be formed by these cells. Cancerous or benign growths can both occur. Malignant tumors have the ability to metastasize, or expand into, neighboring tissues and organs. This process allows the tumors to grow into new locations inside the body. Malignant tumors is another term for cancerous tumors. Blood malignancies, including leukemia's, typically do not develop into solid tumors, although many cancers do (Faghih et al., 2011). Benign tumors do not penetrate or spread to neighboring tissues. Benign tumors seldom grow back after removal, while malignant tumors occasionally do. Nevertheless, benign tumors can occasionally grow to be rather enormous. Some, like benign brain lesions, are potentially fatal or cause severe symptoms.

Cancer is a genetic illness, meaning that alterations to the genes that regulate our cells' growth and division are what cause it. Cancer-causing genetic alterations may occur because: Of mistakes made during cell division.

Of environmental contaminants, like soot from tobacco products and UV radiation from the sun, damaging DNA.

We acquired those from our grandparents.

Typically, the human body gets rid of cells that have DNA that has been damaged before they become malignant. However, as we grow older, the body's capacity to do so decreases. This contributes to the increased risk for developing cancer in adolescence.

Cancer is caused by various combinations of genetic alterations. There will be more alterations as the malignancy spreads. Multiple cells within a single tumor may exhibit distinct genetic alterations.

1.1 Gene types implicated with cancer:

Proto-oncogenes, tumor-suppressing genes, and DNA-repairing genes are among the three primary gene categories that are typically impacted by the genetic alterations that lead to cancer. These alterations are occasionally referred to as cancer "drivers." Proto-oncogenes play a role in the proper division and development of cells. On the other hand, these types of genes can evolve into genes that cause cancer (also known as oncogenes), enabling cells to proliferate and thrive when they shouldn't, by changing in specific ways or becoming more active than usual. Additionally, genes known as tumor suppressors regulate the division and development of cells. Certain tumor suppression gene mutations can cause uncontrollably dividing cells. Genes that repair defective DNA are known as DNA repair genes. When these genes are mutated, cells are more likely to experience other genetic changes as well as chromosomal abnormalities such chromosomal duplicate work and deletion. When combined, these alterations have the potential to make the cells malignant. Scientists have discovered that specific mutations are frequently present in a variety of cancer forms, as they continue to learn further concerning the genetic changes that cause cancer. These days, a wide range of cancer therapies are available that focus on the gene abnormalities that cause cancer. Anybody with cancer that carries the particular mutation may utilize some of these medications, regardless of the cancer's initial growth location.

1.2 Relationship between cancer risk and polymorphisms in the IL13 gene:

Complex interplay between hereditary and environmental variables lead to the multifactorial disease known as cancer (Pharoah et al., 2004). There are significant differences in the incidence of many cancers across various ethnic and racial communities, which may be partially explained by lifestyle choices and genetic makeup. It has been demonstrated that inflammation and the innate immune system are key players in the development of cancer (Iscovich and Howe., 1998). It is being demonstrated that inflammation and the innate immune system are key players in the development of cancer (Lin and Karin., 2007). Thus far, the vulnerability to cancer has been associated with genetic mutations in numerous genes connected with inflammation (Amirian et al., 2011; Chen et al., 2011; Reid-Lombardo et al., 2011). The primary secretors of interleukin-13 (IL13), a critical immune regulatory cytokine, are natural-killing T cells, or T cells, and Th2-like lymphocytes (Hershey., 2003). Because it stimulates the manufacture of IgE, IL13 is a key factor in allergic responses at the responder level (Van et al., 1998). According to recent reports, tumor resistant recurrence may result from a reduction in IL13 secretion (Terabe et al., 2004). Furthermore, IL13 functions as a malignant cell proliferation stimulant and can decrease tumor immunity monitoring in B chronic lymphocytic carcinoma and Hodgkin's disease by deviating the response of the immune system from Th1 to Th2 (Chaouchi et al., 1996; Skinnider et al., 2002). It has been demonstrated that IL13 can stop poor-quality glioma from growing in human cell lines (Liu et al., 2000). The IL13 gene spans 2938 bps and is found on chromosome 5q31 (Palmer et al., 1998). Many epidemiological investigations proposed that a person's susceptibility to cancer was determined by single-nucleotide polymorphisms (SNPs) in the IL13 gene (Chen et al., 2001).

1.3 Glioblastoma:

The most common type of malignant cancer of the brain is glioblastoma (Figure 1). In older patients, 90% of cancers develop quickly from scratch without any clinical or pathologic indication of a less aggressive antecedent lesion (both primary glioblastomas). Anaplastic syndrome or undesirable diffuse astrocytomas develop into secondary glioblastomas. They have a far better prognosis, are more commonly seen in the frontal lobe, generally appear in younger individuals, and have less necrosis (Peiffer and Kleihues., 1999). Although primary as well as secondary glioblastomas are nearly identical by histology, their inherited and methylation profiles are different. IDH1 genetic changes, which are not present in initial glioblastomas and are linked to a hypermethylation phenotype, are pivotal genetic markers of secondary glioblastoma (Fujisawa et al., 2000). In progenitor undesirable diffuse astrocytomas or oligodendrogliomas, IDH1 mutations are the first genetic abnormality that can be detected, suggesting that the neurological precursor cell types of these tumors are different from those of main glioblastomas. We come to the conclusion that this genetic change, rather than medical criteria, is a more accurate and dependable clinical molecular indicator of subsequent glioblastomas. Primary and secondary glioblastomas are discrete tumor types that arise from numerous precursor cells and might call for alternative therapeutic methods, while having a similar histopathological expression (Ohgaki et al., 2013).

The first person to distinguish between both primary and secondary glioblastoma was Hans-Joachim Scherer, a German neuropathologist (Scherer et al., 1940).

He noted, "From anatomical and medical viewpoint, the secondary glioblastomas emerging in astrocytomas need to be separated from 'primary' glioblastomas," in 1940, as he worked at the Institute Bunge in Antwerp, Belgium, as a member of the political exile. The majority of glioblastomas with protracted therapeutic duration are likely triggered by them. This was a groundbreaking discovery at that point, since the World Health Organization (WHO) failed to recognize glioblastoma as a type of astrocytic tumor until 1979, classifying it with a category of poorly distinguished and embryonal tumours as a substitute. Glioblastoma was completely classified into the category of astrocytic neoplasm with the advent of immunohistochemistry. However, the distinction between both primary and secondary glioblastomas stayed theoretical and was not used as an evaluation term, primarily because both of these subtypes are thought to be histopathologic ally identical. Over the last ten years, a growing body of research has demonstrated that they are separate medical

entities that impact patients in varying age ranges, following discrete genetic routes, have varying proteins and RNA development profiles, and may react differently to chemotherapy and radiation (Watanabe et al., 1996). According to estimates, gliomas account for roughly seventy percent of all brain tumors, while tumors that affect the central nervous system (CNS) represent for approximately two percent of all cancers (Ohgaki et al., 2004). There are three forms of gliomas that originate from supporting cells in the central nervous system: oligodendrogliomas, oligoastrocytomas, and astrocytic tumors. Despite being rare, glioma is lethal. After being diagnosed with gliomas, over fifty percent of patients live for fewer than five years. Numerous research projects have been undertaken in an effort to determine its causes and lower its mortality. The disease's cause is yet unknown, albeit. Although exposure to large amounts of ionizing radiation is the most prominent known threat to the environment factor, it only partially explains the root cause of a tiny percentage of cases. It is generally acknowledged that glioblastoma is a complex disease, independent of environmental variables. The etiology of gliomas is influenced by a number of elements, including as inflammatory reactions, hereditary factors, and how they relate (Parsons et al., 2008). The 2,938 base pairs (bps) of the IL-13 gene, which codes for interleukin-13 (IL-13), are found at chromosome 5q31. It is essential to an immunoregulatory mechanism of cancer immunosurveillance suppression that plays significant roles in allergies [7]. The IL-13 gene has been found to contain a number of single nucleotide polymorphisms (SNPs), such as rs1800925, rs25041, and rs1295686, which are strongly linked to the activity of IL-13 (Borger et al., 2012). It has been demonstrated that human malignant cell lines from glioma and main tumor cell cultures excessively express IL-13. The relationship among IL-13 gene polymorphisms and a vulnerability to breast cancer, bladder cancer, pancreatic cancer and lung cancer, and has been examined in earlier studies involving case-control subjects (Amaray et al., 2011). Up till now, numerous studies have looked into the relationship between familial glioma risk and the IL-13 gene polymorphism rs20541 (R130Q). Nevertheless, there were variations in the outcomes of these investigations. While some research did not find a significant link, others did. While earlier meta-analyses have attempted to elucidate the relationship, a number of recent case-control experiments have been reported (Liu et al., 2012).

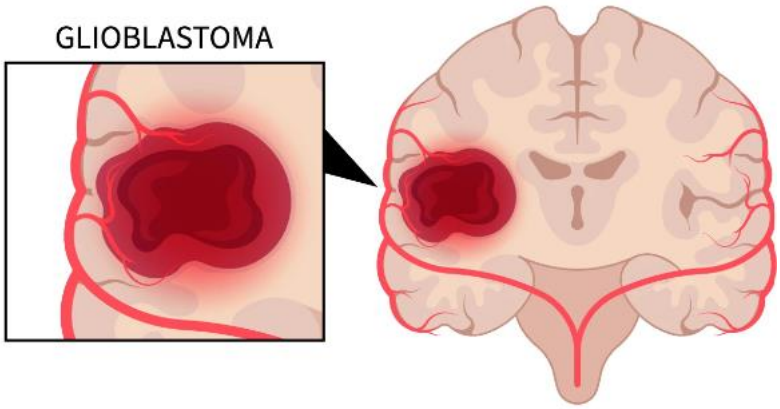

Figure 1.1 The figure illustrates the presence of GBM (Watanabe et al., 1996)

1.4 Epidemiology and Clinical feature:

The most common histological kind of brain tumor is glioblastoma (WHO grade IV), which accounts for 69% of occurrence instances of oligodendroglia and astrocytic tumors. In Switzerland, there are 3.55 new cases of glioblastoma per 100,000 people year, modified for the European Standard Population (Sasaki et al., 2012). After adjusting for the US Standard Population, the prevalence rate for glioblastomas in the US is 2.96 instances per 100,000 people annually.

Due to the fact that incident cases are limited to first diagnoses, they exclude secondary glioblastomas which developed from poor-quality or anaplastic gliomas. When primary glioblastomas are diagnosed, they are full-blown malignancies without any indication of a less-malignant underlying lesion in the form of radiological, clinical, or histological findings. Although they are also known as "de novo" glioblastomas, this does not imply a one-step change; rather, just like other kinds of human neoplasms, these are the outcome

of numerous genetic changes. Anaplastic astrocytoma (WHO grade III) or low-grade diffuse astrocytoma (WHO grade II) can advance slowly to secondary glioblastomas. Clinical (neuroimaging) or histology (bioptic) proof of a transition from a benign to a less malignant tumor is necessary for the confirmation of secondary glioblastoma (Liu et al., 2012).We discovered that, in terms of the community as a whole, just 5 percent of cases had secondary glioblastomas exhibiting histological proof of a poor-quality or anaplastic precursor astrocytoma. This is in line with findings from the University of Alabama, where 19 out of 392 (5%) instances of glioblastomas had previously been diagnosed with low-grade gliomas based on histology (Patel et al., 2011). Approximately up to three times as many low-grade and anaplastic astrocytomas occur as secondary glioblastomas. This could be partially explained by the reality that a sizable portion of individuals with anaplastic or low-grade astrocytomas pass away from their condition before it progresses to glioblastoma. It's possible that some cases that progressed extremely quickly from low-grade or anaplastic astrocytomas were mistakenly identified as primary glioblastomas. When contrasted with primary glioblastomas, secondary glioblastomas are a very uncommon condition, even accounting for this likelihood. Sixty-eight percent of individuals with primary glioblastomas in the community had a clinical history shorter than three months. The average time between the onset of symptoms and the histology confirmation was 6.3 months (Ohgaki et al., 2007).

1.5 Liver Cancer:

The term "liver cancer" refers to hepatic cancer, a deadly tumor that often develops alongside cirrhosis and chronic liver disease (Figure 2). Hepatocellular carcinoma (HCC), also known as primary liver cancer, is the 3rd most prevalent cause of death due to cancer globally and ranks fifth in cancer incidence among men and seventh in women (Ferlay et al., 2010). Prevalence of liver cancer is rising in the US; in 2005, it was 4.5 cases per 100,000 people annually. Liver cancer is still considered one of the most challenging malignancies to treat, even with advancements in medical care. Surgery, localized destructive therapy, and liver transplantation offer viable cures for people with early-stage HCC(Altekruse et al., 2009). Surgery, localized destructive therapy, and liver transplantation all offer viable cures for people with early-stage HCC. Even with curative treatment, HCC recurrence is still a significant issue—it reaches a frequency of over 70% after five years (Llovet et al., 2005). Surgically treated patients with early-stage, tiny HCC (<3 cm) have an unsatisfactory 5-year survival rate (47% to 53%). The majority of individuals with more severe HCC are not able to receive curative therapy, and the disease is typically identified at its most advanced stage. Furthermore, there are minimal survival advantages and poor effectiveness rates with conventional systemic chemotherapy (Poon et al., 2002). The approval of sorafenib, a multichines inhibitor, has demonstrated some benefit for survival in patients having advanced HCC who have retained liver function, indicating that molecular targeting to treat advanced HCC is an exciting possibility (Llovet et al., 2008). Hepatocellular carcinoma, the most common type of primary liver cancer, is still challenging to treat. Liver cancer mortality varies by region and is correlated with the incidence of viral hepatitis in different regions. Many staging methods that take into account the variability of primary liver cancer, local preferences, and differences in resect ability or suitability for transplantation have been created. Treatment options for this type of heterogeneous malignancy are multifaceted, and care guidelines differ depending on the specialty and geographical region for liver malignancies. The development of new therapeutic methods has combined with innovative therapy tactics. Considering liver cancer occurrence, classification, as well as therapy is the main goal .Today, the management of liver cancer involves multiple disciplines, and the selection of multimodal therapy choices is typically done on an individual basis, taking into account the intricate interactions between the patient's general condition, the current stage of the tumor, and the degree of underlying liver disease. Different specialties and geographical areas have different

guidelines about the care of liver malignancies.

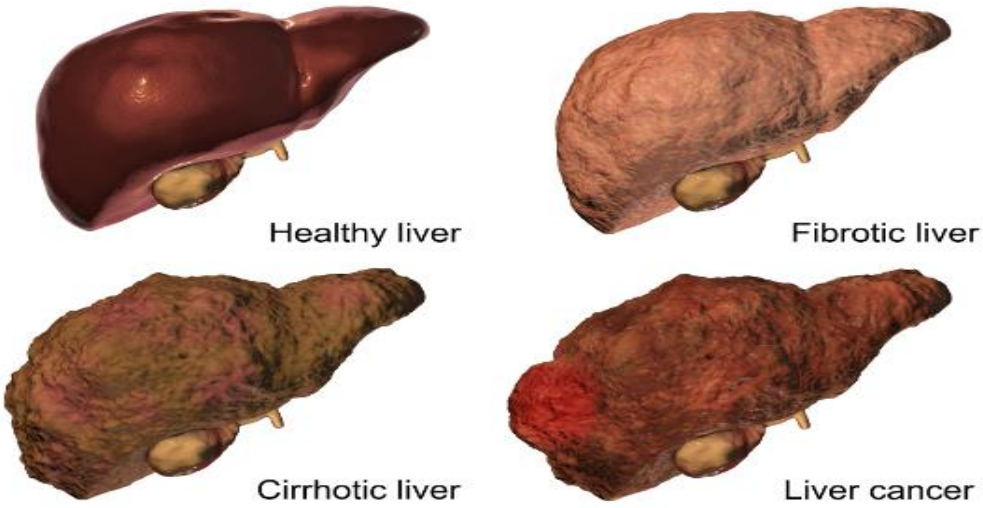

Figure 1.2 This figure depicts the stages of liver cancer (Pons et al., 2005)

The National Comprehensive Cancer Network [NCCN] in the United States, the European Association for the Study of the Liver/European Organization for Research and Treatment of Cancer [EASL-EORTC] in Europe, and the Asian Oncology Summit 2009 consensus statement in Asia all have different recommendations for the treatment of liver cancer (Poon et al., 2009).

1.6 Staging of liver cancer:

Numerous staging systems have been developed for the diagnosis of HCC, such as the widely used Cancer of the Liver Italian Program (CLIP) score, Okuda, and (BCLC) Barcelona Clinic Liver Cancer systems (Okuda et al., 1985). The diversity of these staging schemes is a reflection of the variability of HCC, local preferences, and regional differences in donation suitability or respectability. The dimension of the tumor, the degree of underlying liver illness, the extent to which the tumor has spread to adjacent organs, and tumor metastases are all significant survival factors that are taken into account by these methods (Pons et al., 2005). Other than the TNM system developed by the American Joint Committee on Cancer (AJCC), more recent staging systems have included tumor-dependent variables related to the extent of the HCC and patient-dependent variables like the seriousness of cirrhosis (Kudo et al., 2003). These systems include BCLC, CLIP, Chinese University Prognostic System (CUPI), Groupe d'Etude du Treatment du Carcinoma Hepatocellular (GRETCH), and Japan Integrated Staging (JIS) (Liu et al., 2015).

1.7 Cervical cancer:

The aberrant cells in the area known as the cervical area, which is the lowest portion of the uterus that binds it to the genitals can cause cervical cancer. The human papilloma virus, or HPV, is the cause of the majority of cervical malignancies. An infectious agent known as HPV is spread through sexual activity. Vaccination against viruses before exposure can significantly lower infection rates. Cervical cancer may arise as a result of HPV-induced precancerous alterations in cervix cells. Even though cervical cancer usually progresses slowly, it may advance to other bodily regions like the inner layers of the liver, abdomen, lungs or bladder if it is not discovered in time (Center et al., 2009).

Cervical cancer symptoms can range from none at all to include the following:

- Abnormal periods
- Vaginal Bleeding
- Pain during intercourse
- Abnormal periods

- Abnormal vaginal discharge

Cervical cancer can be prevented in some ways. There is currently a vaccine accessible to adolescents and kids that protects against the types of HPV that are known to cause cervical cancer. Consult your physician if this immunization is appropriate for you or a member of your family. When someone has been diagnosed with cancer of the cervical spine or has HPV, the vaccine cannot be given as a treatment. Cervical carcinoma is currently the second most prevalent malignancy reported in women worldwide, while becoming fewer prevalent in the industrialized world because to efficient screening initiatives (Marmol et al., 2017). There is substantial and well acknowledged proof suggesting an ongoing infection with the carcinogenic human papillomavirus inevitably precedes cervical cancer. Owing to the viral origin of cervical cancer and the heightened likelihood of anogenital cancers in immune-compromised groups like those who have received organ transplants and HIV positive individuals, it is probable that ailments associated with immunologic dysregulation augment a woman's susceptibility to cervical cancer. The overreaction of the immune system with common allergens in the environment causes allergic symptoms, which have been linked to an increased risk of lung cancer and a decreased risk of leukemia, pancreatic cancer and glioma, among other cancers. A single study found no correlation among childhood allergies with cervical cancer within young women within a British cohort, but no link has been found between an allergy history and the risk of the disease. The inverse link between allergens and many cancer types is explained by two widely accepted ideas, both of which may have bearing on the genesis of cervical carcinoma (Povey et al., 2000). According to the prophylactic idea, allergies aid in the removal of carcinogens, hence halting the development of cancers. The immune response associated with allergies would function as a preventative in the context of cervical cancer, eliminating carcinogenic HPV infection before an ongoing condition could arise. Tumor immunosurveillance is yet another possible mechanism, according to which allergy patients' heightened immune responses could target antigens that are associated with tumors and kill tumor cells before they grow (Liu et al., 1999). Most prevalent causes of allergy symptoms have a biological basis in an aberrant inflammatory response to typically benign external chemicals (pollen, for example). Interleukin (IL) 4, IL13 and IL5 produced by allergen-specific T-helper type 2 (Th2) cells mediate the formation of mucus, the growth of eosinophils, and the generation of allergen-specific IgE by B cells. When allergens are bound by IgE, the IgE transmitter signaling cascade is triggered. Most prevalent causes of allergy symptoms have a biological basis in an aberrant inflammatory response to typically benign external chemicals (pollen, for example). Interleukin (IL) 4, IL13 and IL5 produced by allergen-specific T-helper type 2 (Th2) cells mediate the formation of mucus, the growth of eosinophils, and the generation of IgE antibodies against allergens by B cells. When allergens are bound by IgE, the IgE transmitter signaling cascade is triggered (Caims et al., 2012). According to a recent study, pollen allergies can trigger a Th2-polarized response by attracting Th2 cells to the location of pollen exposures and triggering the migration of active dendritic cells (Sasali et al., 2012).

It is worthwhile to investigate how variation among the genes encoding Th2 cytokines may be associated to SCC as well as how that may impact the connection between SCC and allergy disease, since a Th2-polarized response typically results in a less efficient antitumor response. It's likely that allergy-related Th2 cytokine response compromises immune response against malignancies, although allergy-related eosinophil activation has been demonstrated to have immediate tumoricidal effects (Moertel et al., 1990).

1.7.1 In what ways is cervical cancer detected and assessed?

To identify cervical cancer, your physician might undertake the following:

Pap smear: The cervix is scraped in order to accomplish this inspection. After that, the cells are submitted to a lab for analysis to look for any anomalies.

Colposcopy: During this procedure, your doctor will utilize a low-powered microscope to see the cervix in order to sample the region and look for any anomalies. On the other hand, a biopsy can be carried out without a colposcopy.

Biopsy: A needle-based sample of tissues that may be impacted. In the event that cancer is found, your physician will assess the disease's local spread before deciding whether or not surgery is the best course of action.

To find out if the malignancy has spread, imaging is frequently helpful. The medical imaging tests listed below can be carried out:

Body CT scan: Through this process, several images or photos of the interior of the body are produced using advanced computers and specialized x-ray equipment. To determine whether the tumor has gone to the lungs, for instance, a CT scan across the chest is frequently performed.

Body MRI: A strong electromagnetic field, electromagnetic pulses, with a computer are used in this diagnostic exam to create detailed images of the body.

Chest X-ray: This examination yields simple x-ray pictures of the lungs.

PET scan: A tiny quantity of radioactive material is used during a nuclear medicine imaging test to assist assess the degree of cancer in the cervical cavity involvement. In order to provide unique views that can result in more exact or correct diagnoses, PET exams can be overlay alongside CT or MRI images (Bleeker et al., 2009).

In the event that cancer is found, your doctor might additionally prescribe a cystoscopy—a visual inspection of the bladder—or a proctoscopy—a visual inspection of the end of the colon—to ensure the disease is not affecting those organs. During a cystoscopy, the physician may look into the bladder due to a specialized camera at the extremity of a tube. During a proctoscopy, the doctor can look inside the rectum due to a specialized camera at the extremity of a tube (Jiao et al., 2012).

1.8 Breast cancer:

Among the most prevalent malignancies in women globally, breast cancer claimed around 570,000 lives in 2015. Worldwide, over 1.5 million women (or twenty-five percent of all women with cancer) receive the diagnosis of breast cancer each year. According to estimates, breast cancer accounted for 30% of all new instances of cancer (252,710) across women in the United States in 2017. Breast cancer is incurable mostly because it is a cancer with metastatic spread that frequently spreads to distant structures like as the brain, liver, bone and lung. A favorable outlook and a high chance of survival can result from early detection of the illness (Majeed et al., 2014). Because the disease is discovered early in North America, the 5-year overall survival rate for patients with breast cancer is over 80%. Mammography is a frequently used screening method for breast cancer detection that has been shown to successfully lower death rates. Over the past ten years, additional screening techniques have also been used and researched, including as Magnetic Resonance Imaging (MRI), that's more accurate than mammography. The chance of getting breast cancer can be increased by a number of factors, including sex, estrogen, aging, gene mutation, family history and an unhealthy lifestyle. The majority of instances of breast cancer take place in women, who also account for 100 times more cases than men. .Despite the fact that breast cancer is becoming more common in America, fewer people die from the disease as a result of broad early detection programs and cutting-edge medical treatments (Dunars et al., 2012). Recent developments in biological therapy have shown promise in treating breast cancer. Numerous nonpenetrated immune regulatory genes are among the identified and unidentified genetic and environmental influences that contribute to the susceptibility and advancement of breast cancer, which is a complex illness. Most naturally occurring killer T cells and activated TH2 lymphocytes release the immune regulatory cytokine interleukin-13. TH2 subtype cytokines have the ability to inhibit tumor rejection by decreasing TH1 responses that are anti-tumor (Zhang et al., 2017). According to recent reports, tumor resistance to recurrence is caused by the reduction in IL-13 production that occurs when NKT cells are absent in CD1 defective mice. Additionally, it has been noted that IL-13 may directly stimulate tumor cell proliferation or prevent apoptosis in B-chronic lymphocytic leukemia (B-CLL) and Hodgkin disease. Additionally, a recent study found that IL-13 produced by tumour-associated CD4 T cell-derived tumors may

directly stimulate breast tumor cells through pSTAT6, speeding up the growth of the tumor . Notwithstanding these roles in support of tumor progression, several in vivo investigations revealed that IL-13 exhibited strong anti-tumor effect in mice. Additionally, it has been observed that IL-13 inhibits the proliferation of multiple lineages of human cancer cells, including B lineage acute lymphoblastic leukemia, carcinoma of renal cells, and breast carcinoma (Valenti et al., 2017). 25 kb upstream of the IL-4 gene on chromosomal 5q is where the IL13 gene is found. Numerous polymorphisms within the coding and non-coding areas of IL13 have been found, including -1055 C to T in the promoter region of the gene and -1512 A to C in the coding region, which may have an impact on expression. The C-1055T dimorphism modifies the control of IL-13 production and is located close to the Nuclear Factor of Activated T cells (NFAT) binding location. The?2044 G to A variant, which is found in exon 4 and has a peptide substitution effect (arginine to glutamine) at codon 130, is another beneficial polymorphism that may have an impact on the stability of IL-13 mRNA and ligand-receptor association. Both of the earlier polymorphisms have been linked to asthmatic allergic atopy, and associated phenotypes such IgE production and allergic rhinitis, according to earlier studies.

1.9 Pathogenesis:

Breast tumors typically begin as capillary hyperproliferation and, after being continuously stimulated by several carcinogenic stimuli, progress into benign growths or even metastatic carcinomas (Sun et al., 2017). The initiation and course of breast cancer are significantly influenced by tumor microenvironments, including macrophages and epithelial effects. When carcinogens were only exposed to the stroma and not into the extracellular matrix or the epithelium, rats' mammary glands could develop neoplasms. Macrophages have the ability to create an inflammatory and mutagenic environment that can support angiogenesis and help cancer cells evade the immune system. The typical and tumor-associated microbial environments have different variations in DNA methylation, which suggests that epigenetic changes in the tumor's internal environment can encourage the development of cancer. Cancer stem cells (CSCs) are a novel subgroup of malignant cells found inside tumors that have just come to light and are linked to the development, spread, and recurrence of malignancies. This restricted number of cells possesses the capacity for renewal themselves and is immune to common treatments like radiation and chemotherapy. It may arise from embryonic or progenitor cells in regular tissues. Ai Hajj was the first to identify breast cancer stem cells (bCSCs), and in immunocompromised mice that were as low as 100 bCSCs might develop into new tumors (Dal et al., 2017). In addition to basal stem cells, hydrophilic epithelial progenitors are the much more likely source of bCSCs. Wnt, Notch, p53, Hedgehog, HIF and PI3K are among the signaling pathways that are involved in the spread, expansion, and renewal themselves of bCSCs (Baumann et al., 2008). To further comprehend bCSCs and create cutting-edge tactics to eradicate them directly, more research is necessary. The malignant stem cell model and the stochastic hypothesis are two conjectures on the origin and spread of breast cancer (Dabiri et al., 2016). According to the cancer embryonic stem cell theory, progenitor cells, also known as transit-amplifying cells, are the source of all tumor subgroups. Various tumor morphologies might result from acquired genetic and epigenetic alterations in embryonic or progenitor cells. According to the stochastic hypothesis, stem cells, progenitor cells, or differentiated cells are the single cell types from which each tumor subtype originates. Any breast cell can progressively become mutated randomly, and when enough mutations have collected, the cell will eventually turn into a tumor. The two hypotheses have a lot of data to back them up, but none of them can adequately explain how human breast cancer first developed (Rhiem et al., 2015).

1.10 Kaposi Sarcoma:

Dermatologist and physician Moritz Kaposi first reported Kaposi sarcoma (KS) in 1872 (Figure 3). He reported on multiple elderly European males who had a multiplex macular sarcoma of the skin; all of them passed away in less than two. Nowadays, four primary epidemiological types of KS are commonly acknowledged. The type of KS that Kaposi first recognized is referred to as classic or scattered KS. Unlike the instances first reported by Kaposi, classic KS usually affects the skin on the legs and usually affects elderly men of European or Jewish descent. It usually manifests as a slow-moving, prolonged clinical course (Kerur et al., 2016). Beginning in 1947, a number of studies detailed KS cases in Africa, particularly cases of lymphadenopathy in children; this kind of KS is now often known as endemic KS. The initial discovery

of highly violent KS affecting young men who engage in sexual activity with men (MSM), in 1981, arrived just before it was discovered that the men were seriously immunodeficient and subjected to opportunistic infections. This type of KS came onto the at the forefront of the public's attention at the beginning of the AIDS epidemic. These days, this kind of KS is referred to as epidemic or AIDS-related KS (Fuld et al., 2006). Though KS is more frequently linked to HIV-1 infection as compared to HIV-2 infection6, it should be noted that we refer to HIV generally in this article because it is possible that some of the studies reviewed involved people with HIV-2 infection (Li et al., 2016). Iatrogenic KS is the term for KS that also affects people with iatrogenic immunodeficiency, which includes those who receive organ transplants. Lastly, it is noteworthy that numerous cases of KS have been identified documented in MSM who have no history of HIV infection, and that KS in these individuals is gradually becoming acknowledged as a potential unique fifth variant of KS. The KS herpesvirus (KSHV; additionally referred to as human herpesvirus-8 (HHV-8)) was identified in 1994 as a result of a targeted search, which was prompted by epidemiologic hints that this malignancy had an inflammatory origin not associated with HIV (Cosocoy et al., 1016). Until then, the cause of KS remained unknown. It is now established that KSHV infection and compromised host immunity work together to generate KS. However, while AIDS-related KS and iatrogenic KS are linked to clearly established immunodeficiency, the compromised immunity in classic KS—which is thought to be connected to an aging immune system—and endemic KS—which is thought to be related to persistent infections and malnourishment—is not completely defined. Apart from KS, KSHV also causes KSHV inflammatory cytokines syndrome, several lymphoproliferative illnesses, primary effusion lymphoma (PEL), and multicentric Castleman disease (MCD) (Jacobs et al., 2013).

1.11 Epidemiology:

Prior to the beginning of the AIDS outbreak, KS was an uncommon disease. The reported prevalence of classic KS varied from 0.01 for every 100,000 individual years in the UK , 0.2 per 100,000 individual years in the USA, to 1.6 in each 100,000 person-years in Sardinia ; incidence was 2-3 times higher in men than in women worldwide. Prior to the AIDS epidemic, Uganda, Zaire, Cameroon and Tanzania, had reported anticipated incidence rates for endemic KS in Africa that were higher (>6 per 1,000 person-years) than those in southern and north Africa (0.5–1.5 per 1,000 person-years) (Burysek et al., 1999). Due to a lack of population-based studies, the majority of studies on KS in Africa so far (both endemic or AIDS-related KS) have identified KS as a fraction of all malignancies. According to reports, patients of solid organ transplantation currently have an occurrence of KS that is approximately 200 times higher than that among the population as a whole (iatrogenic KS). Additionally, depending on the transplanted recipient's locality, rates of classical KS and the incidence of KSHV are positively correlated with prevalence of iatrogenic KS in those receiving transplants. Additionally, iatrogenic KS is linked to male gender and advanced age. In fact, it is generally recognized that variations in the frequency of KSHV22 account for the majority of the geographic variance in the occurrence of KS (Wu et al., 2015).

CHAPTER 2:

LITERATURE REVIEW

Literature Review

The trillions of cells make up the body of an individual, and during the course of a person's life, these cells are able to multiply and proliferate as required. Cells that are new typically substitute existing ones once they begin to wear out or aged.
When anything goes wrong during this process and cells proceed to divide even when there are wholesome and worn-out cells present, malignancy results. When this proliferation gets out of hand, cells that are healthy have trouble operating normally. These extra cells may combine to form a malignant tumour, which is a mass of tissue. One kind of malignancy that doesn't end up in tumours is leukaemia. Certain cancer types cause the cells to grow slower than usual, whereas other kinds lead their proliferation to proliferate faster than usual.

The word "cancer" refers to a wide range of illnesses that can begin in practically any portion of the body. Typically, genetic changes that disrupt a cell's regular and ordered process are the cause of cancer. Unregulated division of cells may result in the formation of either malignant or not cancerous tumours. These tumours may remain localized or, in a condition known as metastatic disease, they may infiltrate and propagate to neighboring regions (Weinberg et al., 1996). Benign tumours, another name for non-cancerous tumours, typically do not spread to nearby tissues and does not regrow following excision.

As the following most common cause of mortality globally in 2018, an estimated 9.6 million deaths, or one in every six deaths, were linked to malignancy. Compared to women, those who are more inclined to acquire breast, colorectal cancer, lung, cervical, and thyroid cancer, men are more likely to be diagnosed with lung, prostate, colorectal, stomach, and liver cancer (Bailer et al., 1997).

2.1 Types of cancer:

Despite the fact that cancer comes in a wide variety of forms, we may divide it into five primary groups based on the kind of cells that it begins in.

2.2 Carcinoma

Cancers such as carcinoma originate in the tissue of the epithelium. Most the internal structures, including the one responsible for digestion, are lined by tissue called epithelial cells, which also coat the body's external surfaces like the skin. These cancer kinds are the most prevalent ones. A lot of carcinomas impact glands or secretory organs, including the breasts themselves, that generate milk. Different types of epithelial cells found in the human body can develop into numerous kinds of carcinomas, including carcinoma of squamous cells, transition cell carcinomas, adenocarcinomas, and basal cell carcinomas. Compared to carcinomas, tumours are more uncommon. Sarcomas can be classified into two primary categories: soft tissue sarcomas and bone sarcomas (Soussi et al., 2000).

2.3 Leukemia

Cancers called leukaemia start in the connective tissue of the bone marrow which generate blood. This kind of tumour results in an uncontrolled excess production of white blood cells in the blood and bone marrow rather than solid tumours. Both healthy blood cells and bone marrow structures are harmed by these abnormal white blood cells. Individuals with leukemia have no ability to produce red blood cells to deliver oxygen, white blood cells to combat infections, or platelets for blood clotting because of this damage that occurs. Each of the four primary types of leukaemia are acute lymphocytic leukaemia, chronic lymphocytic leukaemia, acute myeloid leukaemia, and chronic myeloid leukaemia (Bailer et al., 1997).

2.4 Lymphoma and myeloma

Carcinoma is the term for cancer that starts in the lymphocytes. The immune system's primary element is the lymphocyte. Aberrant cells proliferate throughout the body in cancer, particularly in the lymph nodes, lymph arteries, and several important organs. The primary cause of cancer is aberrant proliferation of certain lymphoid system white blood cells. Cells like this are unable to combat disease because they multiply prior to they are fully developed, or complete. The aberrant lymphocytes begin to gather in the lymph nodes or lymphatic arteries, and eventually develop into tumours (Clarke et al., 2000).

There are actually two primary varieties of lymphoma tumor: non-Hodgkin lymphomas that come from B or T cells, and Hodgkin lymphomas that start in the B cells. Myeloma is the name given to cancer that begins in cells called plasma cells. One kind of white blood cell produced in the bone marrow is called a plasma cell. By producing antibodies known as immunoglobulin, they aid in the battle against infection. Tumours in the bone along with other bodily tissues are caused by the accumulation of aberrant plasma cell populations in the marrow of the bone (Faghih et al., 2011).

2.5 Brain and Spinal Cord Tumors

Tumor can also start in cells that are part of the brain and spinal cord (Figure 4). Brain and spinal cord tumors can present in a variety of ways. The kind of cell that gave rise to these malignancies started and the area of the central nervous system in which the tumor showed up first serve to designate these malignancies. For instance, an astrocytic tumor originates from astrocytes, that help preserve the integrity of brain nerve cells. Tumors in the brain may be either benign (not cancerous) or malignant (cancerous). Other tumor forms include carcinoid tumors, neuroendocrine tumors, and germ cell tumors, among others (Hollier et al., 2001). Although there are certainly numerous warning signs for cancer, genetic mutation is the primary cause of the disease. Three primary gene categories are typically impacted by the mutations in genes that lead to malignancy. Proto-oncogenes, tumour suppressor genes, and DNA repair genes. Such modifications are occasionally referred to as "drivers" of cancer. Typically, proto-oncogenes play a role in the development and reproduction of cells. Such genes, nevertheless, may transform into genes that cause cancer if they undergo a change or becoming active more frequently than usual. This allows the cells to proliferate and flourish even when they shouldn't. The oncogene are the mutated forms of proto-oncogenes. Mutations like this typically result from interference with genes and cannot be hereditary. among the greatest prevalent instances of an oncogenic is the HERZ gene, particularly regulates breast cell proliferation and reproduction. Certain cells that cause cancer of the breast and ovary have these types of genes. Tumor suppressor genes play a similar role in regulating the division of cells and proliferation as proto-oncogenes. These kinds of genes can detect aberrant cell division and development in cancerous and injured tissues, and they can stop those cells from proliferating until the flaw is fixed. Tumor suppressor genes are crucial for the control of the transcription process, intercellular interactions, and repair of DNA in cells. Tumor suppressor genes that have mutations are unable to operate correctly, which will lead to the formation of tumors. Genes that inhibit certain kinds of cancer include p53, BRCA-1, and BRCA-2 (Heimer et al., 2012).

Genes that repair DNA are primarily responsible for repairing DNA that has been damaged. There have additional genes that decrease tumor growth. When the genes in question get mutated, cells around them will also become mutated. Errors in DNA will not be fixed if repair genes are mutated, that leads to in mutagenesis.
In addition to these instances, however are numerous additional risk variables such as smoking, handling hazardous chemicals, being exposed to radiation, inherited diseases, and interaction to specific viruses, among others.

2.6 Lungs Cancer

With nearly 158,900 deaths from lung disease in 1999, lung cancer is the most common cause fatalities in the United States for either man and women. Over a million individuals worldwide pass away from lung cancer each year. Numerous prospective epidemiologic studies unequivocally show that smoking cigarettes is the primary cause of lung cancer. According to estimates, smoking is the main reason for of 75–80% of lung cancer fatalities in the United States and 90% of lung cancer deaths in men each year (Hecht, 1999). Lung cancer is undoubtedly a significant and common illness that poses a serious threat to public health (Bray et al., 2016) (Figure 5). This wasn't always the case. It was a very rare condition about 150 years ago. Only 1% of all malignancies observed at postmortem in the Institute of Pathology at the Medical School of Dresden, Germany, in 1878 were aggressive lung tumors. The ratio increased to about ten percent by 1918 and to over 14% by 1927. It was carefully noted within the 1930 edition of the venerable Springer Handbook of Special Pathology that dangerous lung tumors had started to rise at the beginning of the century, and maybe even more so following World War I, as well as that they might still be rising. Notably, the majority of lung tumors were found in men, but the number in women appeared to be steadily rising (Chansky et al., 2017). The illness typically took between six months and two years to diagnose and result in death, and in almost all cases, a lengthy history of chronic bronchitis predated the illness. Why was there such a sharp rise in a rare illness? The manual goes into some detail about potential causative variables, such as increased air pollution from industrial gases and particles, road paving, increased car traffic, gas exposure during World War I, the 1918 epidemic of influenza, and using phenol or gasoline. Lung cancer did not increase in the 19th century following previous flu pandemics, but it did climb at the same pace in nations with fewer motor vehicles, less industry, asphalt roads, and workers who were not in contact with benzene and gasoline. Smoking was immediately brought up as a potential explanation in one or two phrases, but it was noted that while there were favorable results from many studies, there was also a high rate of failure to identify a link between cigarettes and lung cancer (Travis et al., 2013).To summarize, there was a degree of uncertainty, but not a strong suspicion, that cigarette smoking might be the primary reason for lung cancer rather than external chemicals. Interestingly, nevertheless, Fritz Lickint, a German physician, submitted a paper in 1929 (perhaps late enough to be published in the handbook) demonstrating the higher likelihood of smoking among patients with lung cancer. After that, he began a fight against smoking, which led to a real rise in anti-tobacco advocacy in Germany. The theories about the origins of lung cancer, which was continuing on the rise, had drastically changed by the time the guidebook was updated in 1969 (Lewis et al., 2014). Over a full twenty-five pages, the role of lighting up cigarettes has been examined in detail. Another factor that was brought up was air pollution; the suggestion of a city-rural gradient increasing lung cancer prevalence was significant. Additionally, it was now known that specific chemicals found in certain jobs, such as asbestos, chromium and nickel in coal and smelting workers, and chemicals including arsenic in wine producers, may cause lung cancer. Clinicians first became suspicious of the connection connecting cigarette smoking and the development of lung cancer in the 1930s after observing an upsurge in this "unusual" illness. Publications started to appear, and after around 20 years, smoking's position as a causal agent was well established. The exceptional surge in tobacco usage was the single most significant cause of the increasing prevalence of lung cancer, according to a case control study released in 1940 in Germany (Zhu et al., 2017). At this point, stomach cancer was the most common cause of cancer-related deaths, with lung cancer coming secondly. Only three of the 109 lung cancer patients were people who do not smoke according to a 1943 report published by the German Institute for Tobacco Hazards Research. This was a significantly lower percentage than that of the control group. More proof of a link between cancer of the lungs and smoking was offered in the 1950s by Doll and Hill in Uk and Cuyler Huntington and Ernest Wynder from the United States. However, it took a while for everyone to grasp the fact. Many doctors were among the smokers who found enjoyment in smoking cigarettes (Freedman et al., 2008). They would not want to consider, or perhaps they would not accept, that their habit—more accurate term would be addiction—was harmful to their health. In this perspective, it's noteworthy to note that two figures who, together with a few others, contributed to raising awareness about the potential cancer-causing effects of substances in the environment oddly overlooked the effects of smoking. Wilhelm C. Hue per began his career in company as a physician. He

gained the enmity of management by persistently and tenaciously drawing attention to potential connections between worker cancer rates and occupational exposure to chemicals during production procedures (Lisy et al., 2018). In reality, he was occasionally prohibited from demonstrating or debating his research results and conclusions. Nevertheless, he insisted that smoking had no role in the development of lung cancer in people. Tobacco smoke is never discussed by Rachel Carson, who throughout her book Silent Spring forewarned of the looming cancer tragedy brought on by pollutants from the environment. After then, smoke from cigarettes has emerged as the most significant carcinogen in our surroundings and is arguably the only one for which zero exposure is possible, as it is in many locations already (Hiscock et al., 2012).

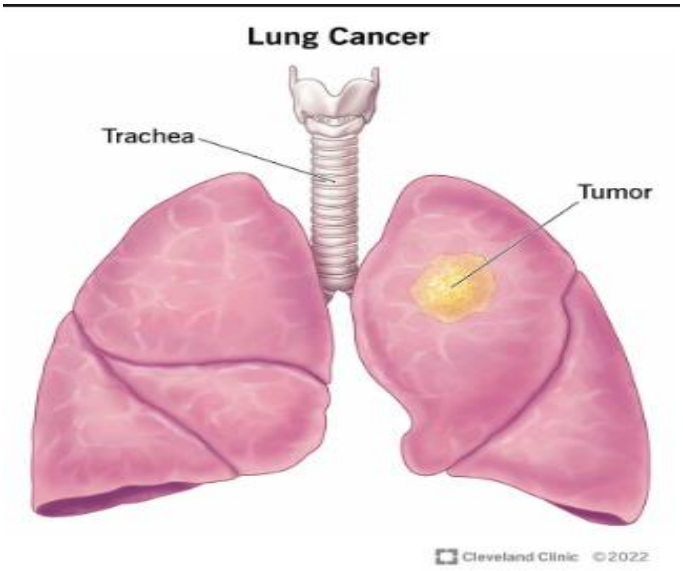

Figure 2.1 The figure shows the presence of cancer in Lungs (Lewis et al., 2014)

2.7 Colorectal cancer

The 3rd most frequent type of carcinoma and the fourth leading cause of death from cancer was colorectal cancer (CRC) (Figure 6). The majority of CRC cases are found in Western nations, and the disease is becoming more common there every year (Stintzing, 2014). The likelihood of having colorectal cancer is between 4% and 5%, and personal characteristics or behaviors including age, previous experience of chronic illness, and lifestyle choices are linked to the risk of acquiring CRC. The gut microbiota is important in this context, because conditions characterized by dysbiosis can cause chronic inflammation, which in turn can lead to colonic carcinogenesis (Marmol et al., 2017). Enteropathogenic Escherichia coli, Bacteroides fragilis, and Fusobacterium spp. are a few of the microorganisms that cause this multiphase procedure. Mutations affecting oncogenes, tumour suppression genes, and genes involved in DNA repair pathways are the cause of colorectal cancer (CRC). Colorectal tumors can be categorized as sporadic (70%), hereditary (5%) or familial (25%), based on where the mutation originated (Boyle et al., 2009). Three types of pathogenic processes, chromosomal instability (CIN), microsatellite instability (MSI), and CpG island methylator phenotype (CIMP), can be attributed to this condition. Many routes (WNT, MAPK/PI3K, TGF-β, TP53) have been shown to be impacted by common alterations, chromosomal abnormalities, and deletions within these types of colorectal cancer (CRC) (Center et al., 2009). Notably, genes like c-MYC, KRAS, BRAF, PIK3CA, PTEN, SMAD2, and SMAD4 can be utilized as predictive indicators for patient final result. Changes in non-coding RNAs (ncRNAs) including miRNA and lncRNA are additionally predictive when employed as biomarkers and can be involved in various stages of the tumorigenesis process in along with gene mutations. As a result, several gene and mRNA screens are being created to enhance the choice of treatment and prediction. When it comes to colorectal cancer (CRC), the initial line of treatment is determined by a multimodal approach that takes into account the specific features of the tumor (Oconnel et al., 2004). Typically, this involves surgical resection, subsequently followed by chemotherapy and monoclonal antibodies, which are antibodies or proteins that target the VEGF and EGFR receptors. In addition to

conventional chemotherapy, various treatments (including probiotics, medications that are anti-inflammatory, polymeric tumour macrobeads, and gold-based pharmaceuticals) are presently being researched to improve the efficacy of treatment and minimize side effects (Potter et al., 2009).

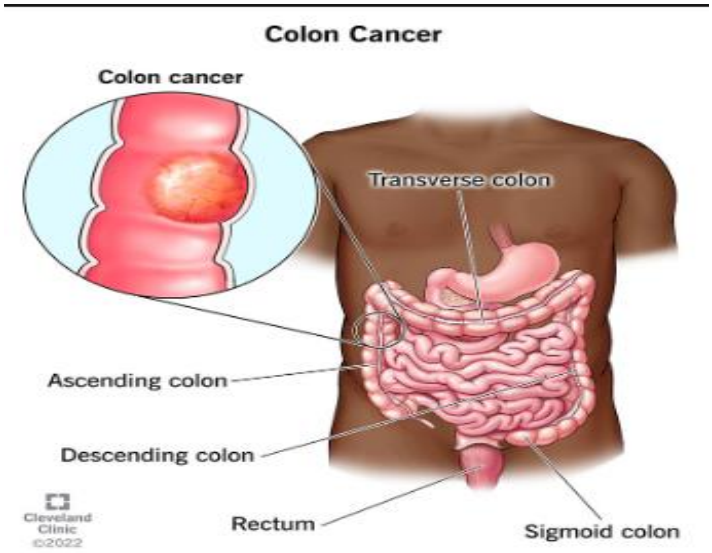

Figure 2.2 This figure shows the presence of tumors in colon (Stintzing, 2014)

2.8 Bladder Cancer

Bladder cancer ranks 9th globally in terms of frequency of aggressive forms and 13th out of 36 in terms of cancer-related deaths (Figure 7). In fact, it was estimated that 16,390 bladder cancer mortality rates and 76,960 new instances of bladder cancer will occur in the United States alone in 2016. 2012 had 165,084 bladder cancer passing away worldwide and 429,793 cases of the disease being diagnosed. The ratio of men to women afflicted is (3.2:0.9), and the incidence of the condition rises beyond age 40. Hematuria, or the presence of macroscopic or microscopic (visible) blood in the urine, is the most prevalent sign of carcinoma of the bladder (Kamat et al., 2016). It affects 13.7% and 78.3% of individuals, accordingly. Macroscopic hematuria is related with an intermediate histopathological stage in bladder patients suffering from cancer. But there's no current screening program for bladder cancer, and many people experiencing microscopic hematuria go untreated The epithelium (urothelium) covering the inner wall of the bladder is typically where bladder cancer begins, and urothelial carcinomas are among the most prevalent kind of bladder cancer (Oosterlinck et al., 2002). Carcinoma of the squamous cell, small-cell carcinoma, and adenocarcinoma are among the bladder malignancies that have been reported (10–25% of cases) with variation histology, or different histomorphological phenotypes. High-grade urothelial malignant tumors have the potential to differentiate into multiple histology, such as squamous and glandular, and may take on sarcomatous, micropapillary, nested, plasmacytoid, and microcystic forms. Bladder tumors with variable histology are linked to metastases, poorly responding to current treatments, and regionally aggressive disease; nevertheless, there is still debate over the actual impact of histology on prognosis (Black et al., 2009). Based on the scant literature now available, these individuals should generally receive tailored care. Muscle invasive bladder cancer (MIBC) is the term for tumors that invade the detrusor muscle. These tumors have a higher propensity to spread to lymph nodes or other areas of the body. Non-muscle-invasive bladder cancer (NMIBC) accounts for about 75% of newly identified patients, while MIBC or disseminated disease accounts for 25% (Figure 1). According to data gathered by the Surveillance, Epidemiology, and End Results (SEER) database in the United States, the level of disease at diagnostic of bladder cancer has remained unchanged over the last ten years although regular screening has not become accessible. Because metastatic illness has no known cure, death rates have remained unchanged. Bladder cancer research has been better understood thanks to the Cancer Genome Atlas project (TCGA) (Shah et al., 2013). In addition to shedding light on genetic causes that could potentially be used as therapeutic goals, the current research on the

molecular identification of MIBCs has also identified subgroups or groupings of invasive illness. These clusters may eventually represent a step toward customized patient care and be linked to prognostic variables and distinct therapy modalities. This primer covers the pathophysiology, epidemiology, diagnosis, prevention, screening, therapy, and overall quality of life concerns of bladder cancer, with a focus on urothelial (the predominant kind) (Gui et al., 2011).

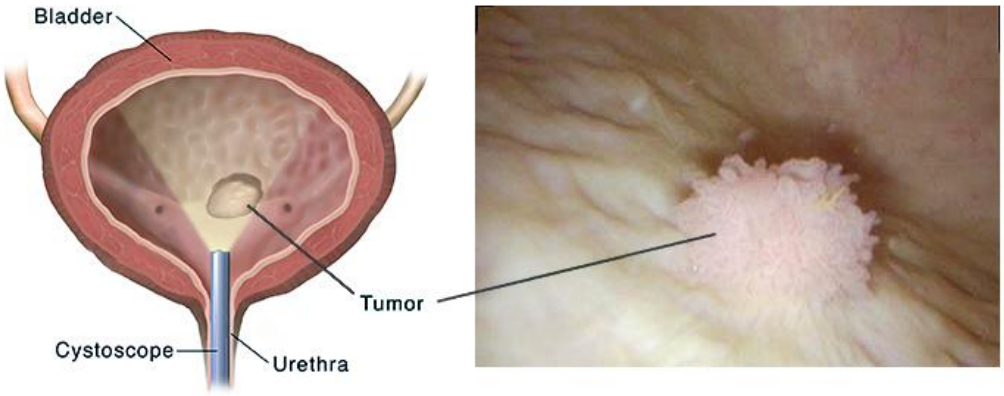

Figure 2.3 This figure depicts the presence of tumors in Bladder (Black et al., 2009)

2.9 NHL cancer

The majority of non-Hodgkin lymphomas (NHL) develop in the lymph nodes or similar lymphatic organs like the thymus, spleen, or Waldeyer's ring. Nonetheless, involvement of the referred to as extranodal organs is frequently discovered upon staging analysis, and a significant portion of NHL even begins at these locations (Figure 8). Primary extranodal NHL is a common term used to describe the latter kind. There is a paucity of literature on primary extranodal lymph nodes as a category, despite the fact that 25–40% of NHL individuals manifest with an initial extranodal lymphoma (Merrill et al., 2007). Many publications are being published on extranodal NHL that originates in almost each organ in the body. Furthermore, there is debate regarding the concept of first-line extranodal lymphoma, particularly in cases where patients have involvement from both nodal and extranodal locations. This issue is avoided in several primary extranodal NHL series by include only individuals with localized disease (Krol et al., 2003).These instances consequently provide an imperfect picture of extranodal NHL since initial extranodal lymphomas possess the propensity to spread. However, studies that include people who have widespread illness and employ more lenient criteria for extranodal NHL may inadvertently include individuals whose disease started in lymphatic vessels or other nodal locations. Overweight can affect cellular and humoral immunity, which could have a role in the emergence of non-Hodgkin lymphoma (NHL). An indirect indicator of obesity, body mass index (BMI), has been connected to the risk of NHL. Nevertheless, the outcomes of epidemiologic research have been mixed. A favorable correlation has been observed in certain studies, and both BMI and NHL risk, but no correlation was identified in other publications. The International Lymphoma Epidemiology Consortium recently aggregated data from 26,000 participants and found no correlation between BMI including the general likelihood of NHL and the majority of subcategories (Muller et al., 2005). Nevertheless, due to the notable heterogeneity of the included studies, the scientific reliability of an aggregated odds ratio is called into question. Some of the contradictory results may be explained by genetic variance. Cytokines are essential for controlling several immune system processes. The interferon-gamma (IFN-) and interleukin (IL-2) are produced by T helper 1 (Th1) lymphocyte cells, and they promote the immune system's response to combat intracellular infections and eradicate malignant cells.T helper 2 (Th2) lymphocyte cells, which have the ability to create immunoglobulin, and this can guard against external infections, and B-cell activation, are capable of producing IL-4, IL-5, IL-6, IL-10, and IL-13. One major possibility for the cause of NHL is immune system dysfunction brought on by unbalanced Th1 and Th2 cytokine production and regulation. It has been found that single nucleotide polymorphisms (SNPs) in a number of cytokine genes, including IL4, IL5, IL6, and IL10, are linked to an increased risk of NHL and one of its primary subtypes (Escalon et al.,

2005). The association between BMI and NHL risk may be altered by inherited variations affecting the Th1 and Th2 cytokine genes. To test the hypothesis, we thus carried out a based on populations, single-case control study among women in Connecticut. We also encountered the issues mentioned above with the criteria for detecting primary extranodal NHL in the Comprehensive Cancer Centre West (CCCW) NHL registry, particularly in patients having disseminated illness at the two neural and extranodal locations. A third form of presentation—extensive disease—was suggested for these kinds of individuals. The definition and importance of this NHL subgroup in extranodal, primary nodal and extensive involvement were investigated using data gathered from our registry. Its predictive importance was investigated by comparing it to prognostic components, effectiveness of therapy, along with survival, as well as the two additional classifications of systemic and extranodal NHL that are frequently utilized in the research community (Glass et al., 1997).

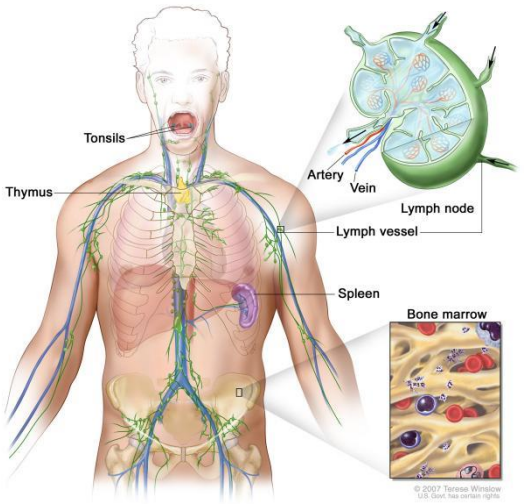

Figure 2.4 This figure shows the presence of NHL cancer (Cai et al., 2009)

2.10 MiRNA

Genes are composed of a lengthy strand of DNA that codes for signals in RNA. Intriguing genes that generate messenger RNA also exist. The production of proteins is the role of RNA, also known as messenger RNA. Other forms of RNA include tRNA, RNA, and snoRNA. These small RNAs assist messenger RNA to participate in producing proteins. While messenger RNA is constructed up of hundreds of thousands of nucleotides, smaller RNAs are found that have just a few hundred nucleotides or less. Extremely tiny RNA, sometimes referred to as microscopic RNA, are involved in a variety of processes within cells and have the ability to govern the actions of numerous various genes. MiRNAs are located in the non-coding areas of genes, corresponding to the parts of the genome that do not participate in the creation of proteins. MiRNA, which is are not generated in an operational state; instead, they must go through numerous phases of processing in order to operate properly. Once operational, they combine with proteins to regulate the expression of genes (Cai et al., 2009).

2.11 MiRNA and cancer

MiRNA play a significant part in an extensive variety of biological phenomena, primarily in the control of genes, the emergence of tumors, differentiation of cells, apoptosis, and numerous other processes (Ye et al., 2019). Roughly half of the miRNA genes are found in the chromosomal locations linked to malignancy. MiRNA, or messenger also significantly affects the makeup of cells and typical single nucleotide polymorphisms (SNPs) in genes or targets, which may raise a person's chances of developing a complicated ailment. Numerous genomic investigations have revealed the involvement of pre-miRNA polymorphism in malignancy, particularly lung, bladder, and breast cancers. Because miRNA functions as an oncogenic or tumor suppressor molecules, changes in the expression of miRNA have the potential to cause an aggressive

carcinoma of the prostate. SNPs affecting miRNA might be associated with an increased risk of cancers of the prostate and stomach (Gangwar., 2010). The research demonstrates the association between the likelihood of developing prostate cancer and cancer of the stomach and the presence of a trio of SNPs (rs1 1614913, rs2910164, and rs3746444) in the premiRNA regions of hsa-mir196a2, hsa-mir146a, and hsamir499 in prostatic cancer and gastrointestinal risk factors for cancer. Since the role of miRNA is to regulate genes involved in a variety of cellular activities, any alteration in miRNA can affect the functioning of DNA, and this in turn can alter an individual's appearance by causing diseases or other obvious modifications.

Melanoma is a dangerous condition brought on by changes in DNA replication and gene variants. Therefore, a mutation in the microbial RNA may cause tumor to start growing and spreading across various regions of the body. MiRNA is a play a critical role in the initiation, progression, and management of malignancy. The substances included in diet have an impact on the genes linked to miRNA. Therefore, eating habits of an individual affect's miRNA action, that can either raise or lower the risk of cancer.

The oncogene and genes that suppress tumors are also regulated by miRNA, which has the ability to regulate genes (Kunh et al., 2008). The alteration in the tumor suppressor gene causes unchecked division of cells, which in turn causes cancer, a dangerous condition that, unless caught swiftly, can be fatal. The cancer of the prostate is one of the most prevalent reason of malignant tumor diagnoses and cancer-related deaths among males. Given that miRNA plays an essential part in the control of genes, it was anticipated that miRNA related to carcinoma of the prostate will highlight the molecular alterations connected to the onset and progression of the disease. The messenger RNA 3 enzyme really produces the miRNAs, which are tiny, single-stranded, RNAs that don't code with an absolute minimum of 21–24 nucleotides (Gangwar., 2010).

The majority of miRNA, or messenger either through overexpression or under expression, represent the main reason of tumor development in the human body, as demonstrated by prostate tumors. Since a result, miRNA is also thought to be an early marker for carcinoma of the prostate. Numerous examinations, such as prostate-specific antigen (PSA) and cholesterol assessments, are carried out to find indicators in patients with cancer. MiRNAs are implicated in malignancy and are employed as indicators to identify malignancy in people. An individual might have malignancy if miRNA is found in the bloodstream or tissue. Since miRNA controls cell function, it is a useful targeting for therapy for cancer (Bavelloni et al., 2017).

2.12 Single Nucleotide Polymorphism (SNP)

One kind of sequencing of DNA polymorphism known as single nucleotide polymorphism results from changes made to a single nucleotide at the level of the genome. Disease progression may not be exclusively caused by SNPs. Polymorphism causes DNA sequence mutations that are irreversible. Just over one percent of alterations are caused by DNA polymorphism, and the majority of these mutations are harmful. Ethnicity and geography have an impact on the SNP prevalence (Vignal et al., 2002). Numerous genes which have been linked to the occurrence of malignancies are characterized by single nucleotide polymorphisms which can take place at exon, intron, promoter, or 3' and 5' sections. These variations affect the genetic components that, ultimately altered, result in malignancy (Ganal et al., 2009). The single nucleotide variant (SNP) is linked to tumors and is found in both the non-coding in nature area and the pathway of activity. Numerous SNP regions that code have been found to be connected to the emergence of numerous types of malignancies.

SNPs in the genetic material which are involved in the restoration of the genes have been linked to a variety of malignancies, including malignancies of the mouth, breast, prostate, and stomach. Additionally, SNPs are thought to be curative and biomarkers of diagnosis for a wide range of diseases such as cancer identification (Na Deng., 2017). SNPs at promoter locations affect gene transcription factors, and these changes in turn affect translational and modify proteins, resulting in the emergence of various diseases, particularly malignancy. MiRNA attaches to the 3' region of the transcript's not translated section to impede the translation, thereby weakens the messenger RNA interaction. Certain SNPs disrupt the workings of miRNA, and that in turn affects the amount of expression of miRNA on targets. SNPs located in the sequence's 5'

domain obstruct the intended target m RNA's ability to attach to miRNA. The SNPs rs 11614913, rs 2910164, and rs 3746444 linked to the miRNAs miR-196a2, miR-146a, and miR-499 have the potential to induce both stomach and cancers of the prostate.

The change in sequence of DNA base pair is rarely occur in 1% of population. The change in single base can cause cancer. Prostate cancer and gastric cancer have three common SNPs rs 11614913, rs2910164, rs3746444, which cause cancer in body.

In less than 1% of the overall population, the base combination in the human genome code changes. Tumor may result from just one base alteration. 3 SNPs which trigger malignancy in the body rs 11614913, rs 2910164, and rs 3746444 are shared by stomach and prostate cancers (Kim et al., 2007).

2.13 Aims and Objectives

Through a meta-analysis and mechanistic studies, these goals and objectives present a thorough strategy for investigating the effects of the microRNA genetic variant rs20541 on glioblastoma and its wider implications across many cancer types.

To investigate into the relationship between glioblastoma incidence and development and the microRNA genetic variant rs20541.

To carry out a meta-analysis in order to thoroughly investigate the connection between rs20541 and the likelihood of getting different kinds of cancer.

To better understand possible pathways via which rs20541 may affect the development and propensity to develop certain cancer types.

Collect and analyze pertinent clinical and genetic information from published research that looks into the relationship between rs20541 and cancer risk.

Examine the role that rs20541 plays in the biology of cancer by using pathway enrichment studies and bioinformatic analyses.

Make recommendations for future clinical uses and research directions based on the knowledge gathered from the mechanistic investigations and meta-analysis.

CHAPTER 3:

EXPERIMENTAL WORK

Experimental Work

The meta-analysis was performed according to PRISMA guidelines. The total number of studies identified by data base searching were three thousand eight hundred and seventy seven. Out of three thousand eight hundred and seven studies, seventy seven were taken from PubMed and three thousand and eight hundred were taken from Google scholar. This research did not include any other additional study that are identified by any other bases which may include contacting collaboration with external researchers.

After collecting data from PubMed and Google scholar, we removed the duplicate studies. Number of total studies obtained after removing the duplicates were one thousand and nine hundred and seventy-seven. That mean out of three thousand eight hundred and seventy-seven, nineteen hundred were duplicate.

In nineteen hundred duplicate studies, five hundred and ninety-nine were review article, three hundred and forty-five were book chapters, three were encyclopedia, one hundred and sixty were abstract, two were mini review, five were short communications and seven hundred and sixty-six were identified as other diseases. Full text articles that were actually included of data extraction were sixty-four from which thirty-seven were excluded because they had SNPs on which we are not working. So, in total we work on twenty studies; qualitatively and quantitatively. Graphical representation of PRISMA guidelines is given in the form of flow chart below Fig.

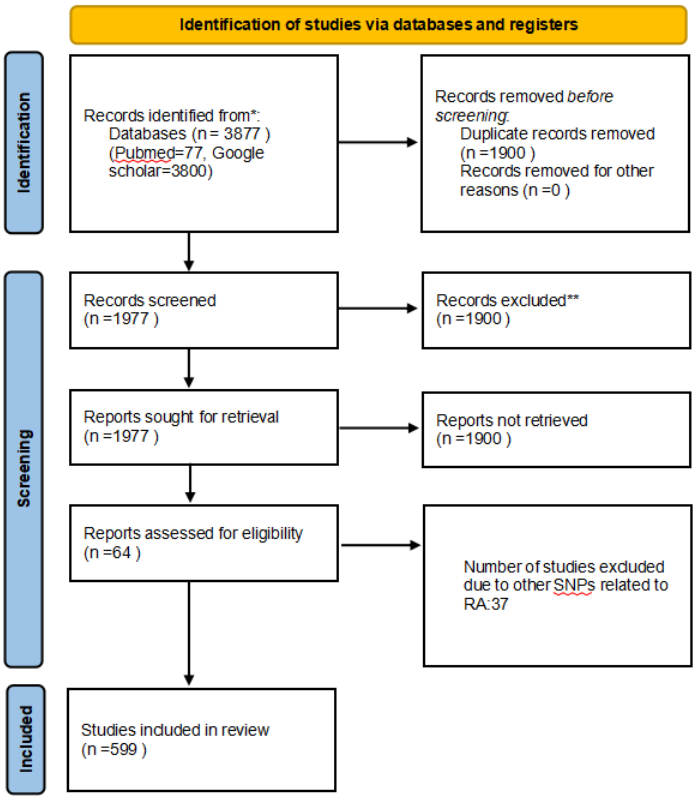

Figure 9: PRISMA flow graphic illustrating the methodology used when examining the literature across several relevant studies

After obtaining data from our studies on SNP rs20541 causing glioblastoma, colorectal, liver, cervical, breast and other cancers. Data, which was obtained from the literature review of the studies by PRISMA guidelines for glioblastoma, colorectal, liver, cervical, breast and other cancers is arranged in the form of table (table

1). These tables include name of the author of the articles, year of publication, ethnicity, genotyping method, case and controls, genotype of cases and controls (dominant, recessive, heterozygous and allelic) and their associated P value of all the three SNPs. Advanced statistical analysis was performed by using IBM SPSS software. After analyzing data in the SPSS, data files were made, which were then further analyzed by STATA. It includes test of association(OR, 95% CI, P value), test of heterogeneity (Model , I2 , P value) and publication bias P value (table 3).

CHAPTER 4:

RESULTS AND DISCUSSION

4. Results and Discussion

The tabular data that follows was obtained using IBM SPSS and STATA. The data set provides information on the number of cases and controls for different ethnic groups. In addition to a graphical depiction of the number of studies featured in the form of a forest, our miRNA funnel graph illustrates the publication bias.

Table 4.1: Characteristics of all studies related to different cancers in the meta-analysis

Author	Year	Ethnicity	Genotyping Method	Cases	Controls	Genotype of cases GG	GA	AA	Genotype of control GG	GA	AA	Association P-value
Schwartz Baum et al	2007	Caucasian	PCR-RFLP	110	536	75	35	35	266	168	168	0.17
Schwartz Baum et al	2007	Caucasian	PCR-RFLP	111	422	70	37	37	308	151	151	0
Schwartz Baum et al	2007	Caucasian	PCR-RFLP	1008	381	42	24	24	383	212	212	0.23
Schwartz Baum et al	2007	Caucasian	PCR-RFLP	455	212	20	24	24	42	67	67	0.54
Raun et al	2011	Asian	TaqMan	677	698	316	293	63	300	319	74	0.07
Chen et al	2011	European	TaqMan	593	498	43	23	23	45	21	21	0.01
Sainz et al	2012	European	PCR-RFLP	1798	1810	1108	587	94	1151	552	68	0.30
Faghih et al	2009	European	PCR-RFLP	305	195	176	110	19	109	69	11	1
Wang et al	2009	Mixed	TaqMan	395	309	287	91	10	169	86	10	0
Chu et al	2012	Asian	PCR-RFLP	817	1141	134	29	84	44	56	99	0.97
Gunter et al	2006	European	PCR-RFLP	244	231	120	67	8	102	58	11	0.35
Wiemels et al	2007	European	TaqMan	248	289	247	123	15	281	169	18	0.39
Johnson et al	2011	European	PCR-RFLP	244	1258	178	85	18	325	164	22	0.01
Sameni et al	2009	European	PCR-RFLP	141	113	60	68	13	49	55	9	0.78
Brown et al	2006	European	PCR-RFLP	133	172	77	53	3	119	45	4	0.23

Haider A et al	2015	European	PCR-RFLP	453	543	86	9	1	19	13	8	0.41
Amirian et al	2010	European	TaqMan	139	365	60	68	13	35	43	22	0.06
Brenner et al	2007	European	TaqMan	431	611	107	46	6	295	128	17	0.42
Backes et al	2013	European	PCR-RFLP	139	407	84	50	5	278	116	13	0.00
Shamran	2015	Asian	PCR-RFLP	96	300	86	9	1	19	13	8	0.40

Table 4.2: Total and stratified group analysis according to ethnicity for the micro RNA rs20541 polymorphism

Genetic Model rs20541	**Comparison group and subgroup**		**Test of Association**			**Test of Heterogeneity**			**Publication Bias P value**
			OR	95%CI	P value	Model	I2	P value	
Dominant	20	Total	0.33	1.00-1.07	0.00	R	79.60	0.016	0.142
	7	Asian	1.14	1.06-1.22	0.12	R	83.43	0.00	0.652
	12	European	0.99	0.95-1.02	0.06	R	73.69	0.67	0
	11	Glioma	1.07	1.02-1.13	0.03	R	70.03	0.04	0.123
	9	Other cancer	1.01	0.97-1.05	0.34	R	85.5	0.49	0.275
Heterozygous	20	Total	0.96	0.91-1.01	0.01	R	66.93	0.169	0.254
	10	Asian	0.90	0.82-0.98	0.13	R	62.87	0.028	0
	12	European	1.01	0.95-1.08	0.01	R	65.74	0.491	0.385
	11	Glioma	0.94	0.87-1.01	0.04	R	61.04	0.148	0.157
	9	Other cancer	0.98	0.91-1.05	0.12	R	74.4	0.57	0.245
Recessive	20	Total	0.90	0.81-1.00	0.03	R	52.42	0.054	0.154
	8	Asian	0.87	0.77-0.98	0.33	F	12.7	0.028	0.617
	12	European	1.01	0.95-1.08	0.01	R	65.7	0.600	0
	11	Glioma	0.94	0.87-1.01	0.04	R	61.04	0.148	0.418

	9	Other cancer	0.97	0.83-1.13	0.01	R	56.30	0.76	0.234
Allele G	20	Total	1.02	1.00-1.04	0.12	R	86.37	0.02	0.115
	12	Asian	1.10	1.06-1.14	0.13	R	87.41	0.00	0
	8	European	1.10	1.06-1.14	0.05	R	82.08	0.00	0.125
	11	Glioma	1.04	1.01-1.07	0.06	R	79.31	0.01	0.234
	9	Other cancer	1.01	0.99-1.02	0.04	R	90.43	0.27	0.718
Allele A	20	Total	0.90	0.81-1.00	0.03	R	87.76	0.05	0.234
	12	Asian	0.85	0.80-0.90	0.03	R	86.04	0.00	0.231
	8	European	1.02	0.96-1.09	0.02	R	87.03	0.36	0
	11	Glioma	0.90	0.85-0.95	0.01	R	85.48	0.01	0.281
	9	Other cancer	0.96	0.91-1.02	0.13	R	90.86	0.26	0.154

4.1 Funnel plot for miRNA rs20541:

A funnel plot is a type of scatter plot used to compare the findings and accuracy of different studies, or how comparable the estimated impact size of a measure is to the genuine effect size. A scatterplot used to visually identify publication prejudice or variability based on the conventional error pattern of individual study results in a meta-analysis is called a funnel plot. A portion of the total is represented by every phase of the funnel. As a result, it takes on the shape of a funnel, with every phase getting narrower as it goes along and the initial stage being the widest and biggest. The "intake" stage, which is the initial step, is usually the biggest in size.

Meta-analysis of the relationship between miRNA rs20541 G>A polymorphism for (Dominant):

In Figure 4.1, there is notable deviation of the studies from the mean line, indicating increased variation and a higher publication bias value. The association of the SNP rs20541 with Glioblastoma for the dominant allele appears to be limited.

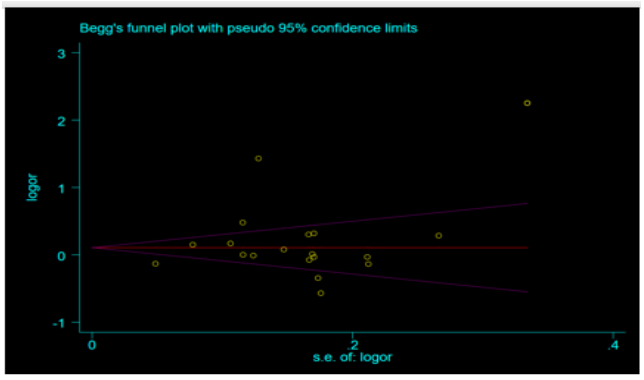

Fig 4.1: Meta-analysis of the relationship between miRNA rs20541 G>A polymorphism, Glioblastoma and various cancers for different region. (Dominant total)

Meta-analysis of miRNA rs20541 G>A polymorphism for Heterozygous allele:

In Figure 4.2, there is notable deviation of the studies from the mean line, indicating increased variation and a higher publication bias value. The association of the SNP rs20541 with Glioblastoma for the Heterozygous allele also appears to be limited.

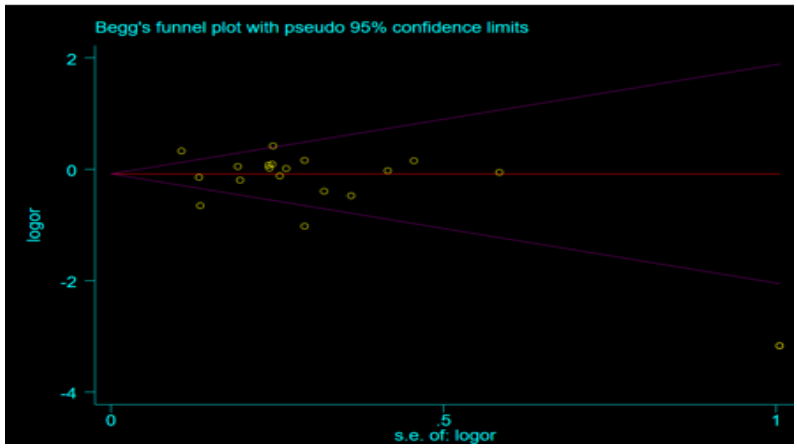

Fig 4.2: Meta-analysis of the relationship between miRNA rs20541 G>A polymorphism. (Heterozygous total)

Meta-analysis of miRNA rs20541 G>A polymorphism for G-allele:

In Figure 4.3, there is notable deviation of the studies from the mean line, indicating increased variation and a higher publication bias value. The association of the SNP rs20541 with Glioblastoma for the G- allele appears to be limited.

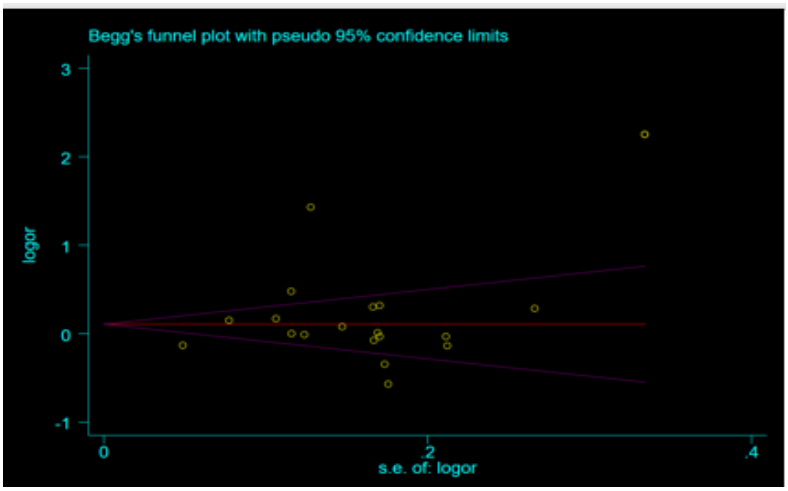

Fig 4.3: Meta-analysis of the relationship between miRNA rs20541 G>A polymorphism.

Meta-analysis of miRNA rs20541 G>A polymorphism for A-allele:

In Figure 4.4, there is notable deviation of the studies from the mean line, indicating increased variation and a higher publication bias value. The association of the SNP rs20541 with Glioblastoma for the A allele appears to be limited.

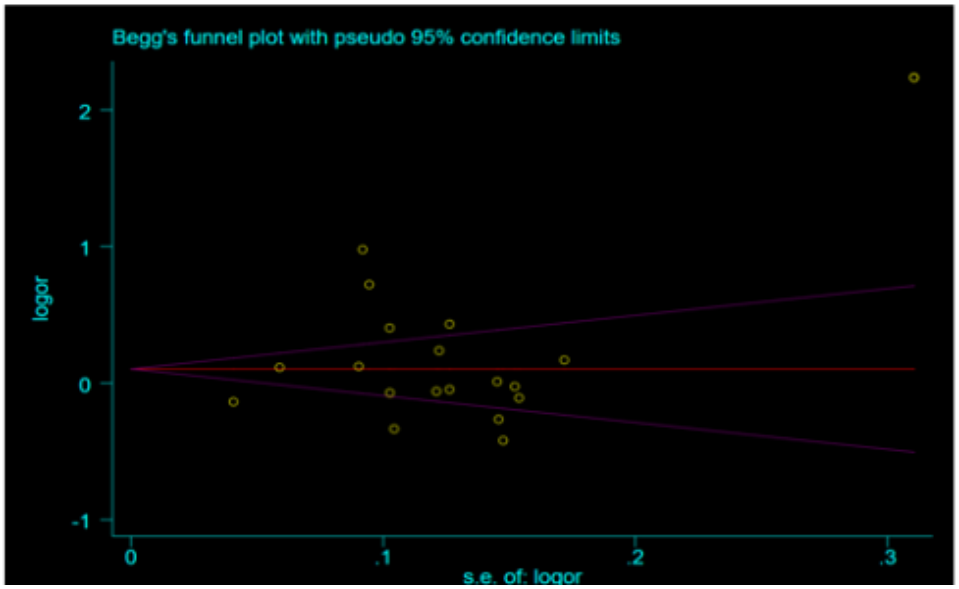

Fig 4.4: Meta-analysis of the miRNA rs20541 G>A polymorphism (A allele total)

Meta-analysis of miRNA rs20541 G>A polymorphism for Asian (Dominant):

In Figure 4.5, there is notable deviation of the studies from the mean line, indicating increased variation and a higher publication bias value. The association of the SNP rs20541 with Glioblastoma for the A allele appears to be limited.

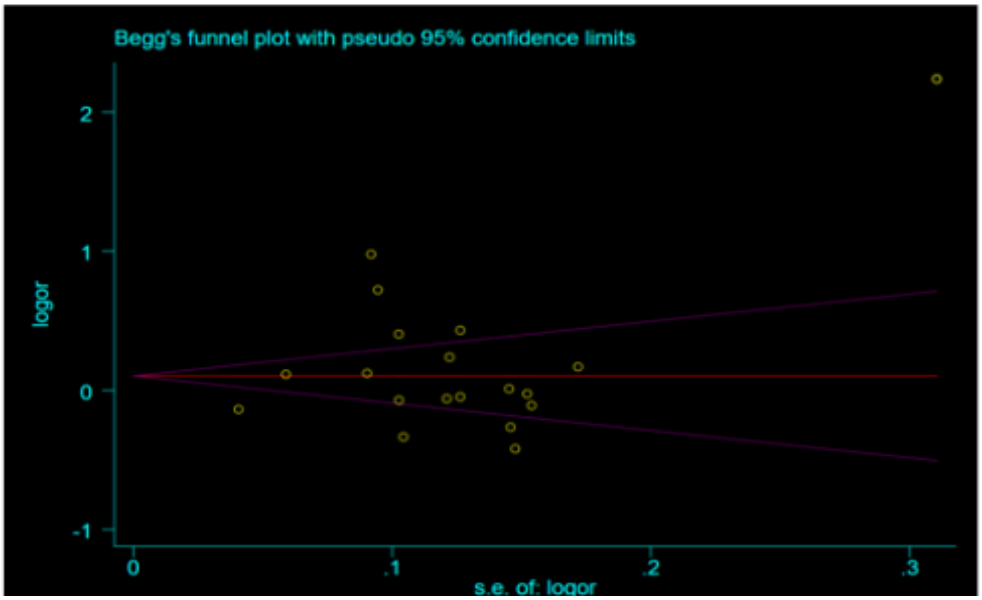

Fig 4.5: Meta-analysis of the relationship between miRNA rs20541 G>A polymorphism, Glioblastoma and various cancers for different region. (Dominant Asian total)

Meta-analysis of miRNA rs20541 G>A polymorphism for Asian (Heterozygous):

In Figure 4.6, there is notable deviation of the studies from the mean line, indicating increased variation and a higher publication bias value. The association of the SNP rs20541 with Glioblastoma for the heterozygous allele appears to be limited for Asian population.

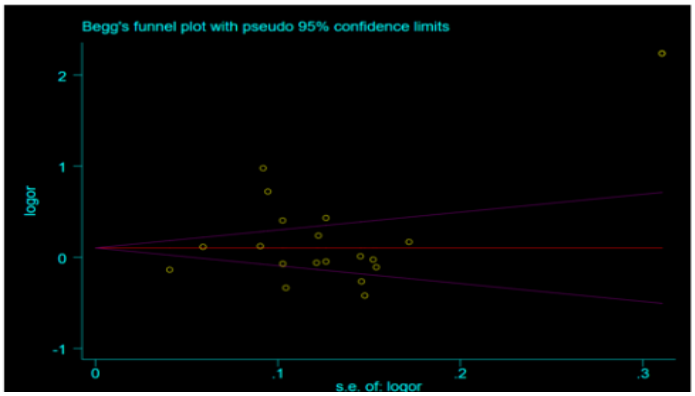

Fig 4.6: Meta-analysis of the relationship between miRNA rs20541 G>A polymorphism, Glioblastoma and various cancers for different region. (Heterozygous Asian total)

Meta-analysis of miRNA rs20541 G>A polymorphism for Asian (G allele):

In Figure 4.7, there is notable deviation of the studies from the mean line, indicating increased variation and a higher publication bias value. The association of the SNP rs20541 with Glioblastoma for the G allele appears to be limited for Asian population.

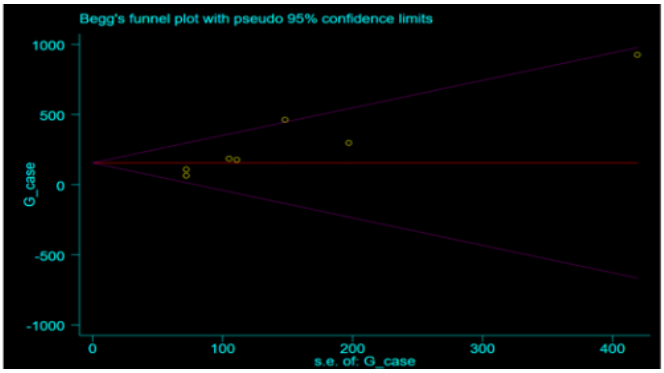

Fig 4.7: Meta-analysis of the relationship between miRNA rs20541 G>A polymorphism, Glioblastoma and various cancers for different region. (G allele Asian total)

Meta-analysis of miRNA rs20541 G>A polymorphism for Asian (A allele):

In Figure 4.8, there is prominent deviation of the studies from the mean line, depicting increased variation and a higher publication bias value. The association of the SNP rs20541 with Glioblastoma for the A allele appears to be limited for Asian population.

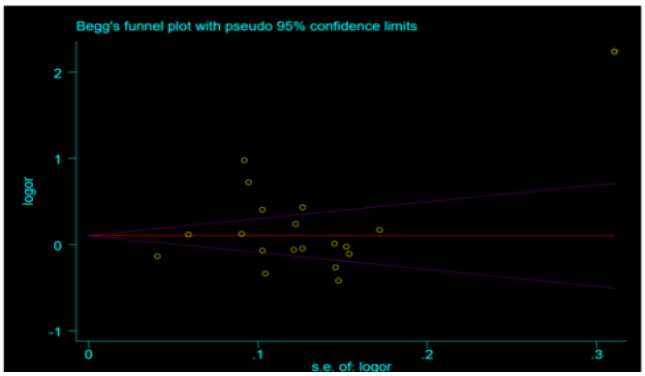

Fig 4.8: Meta-analysis of the relationship between miRNA rs20541 G>A polymorphism, Glioblastoma and various cancers for different region. (A allele Asian total)

Meta-analysis of miRNA rs20541 G>A polymorphism for European (Dominant):

In Figure 4.9, there is less deviation of the studies from the mean line, indicating decreased variation and a lower publication bias value. The association of the SNP rs20541 with Glioblastoma for the Dominant allele appears to be higher for European population.

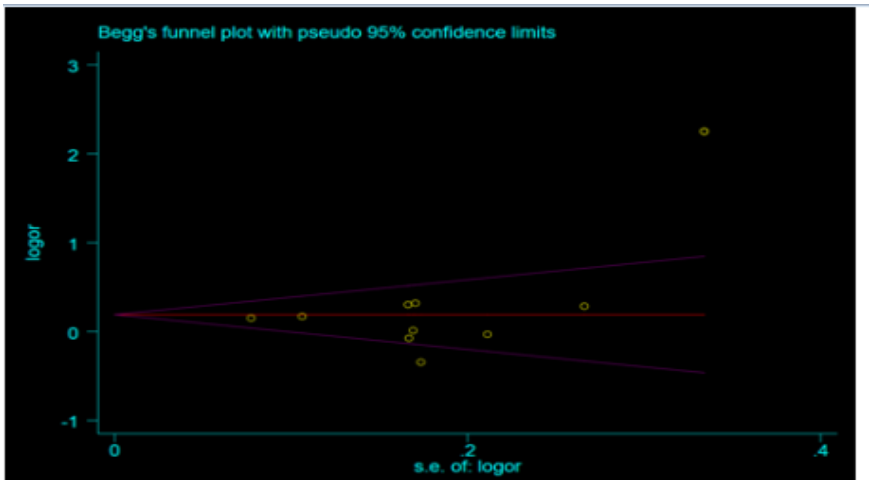

Fig 4.9: Meta-analysis of the relationship between miRNA rs20541 G>A polymorphism, Glioblastoma and various cancers for different region. (Dominant European total

Meta-analysis of miRNA rs20541 G>A polymorphism for European (Heterozygous):

In Figure 4.10, there is less deviation of the studies from the mean line, indicating decreased variation and a lower publication bias value. The association of the SNP rs20541 with Glioblastoma for the Dominant allele appears to be higher for European population.

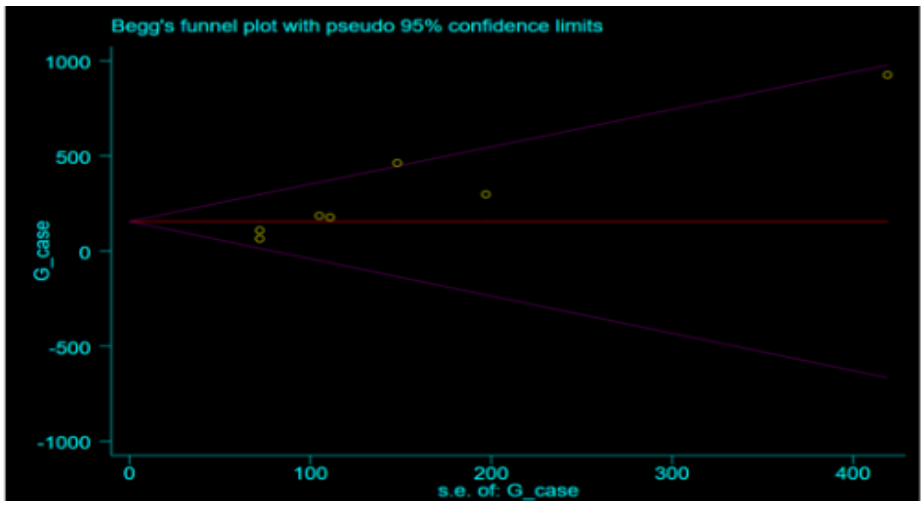

Fig 4.10: Meta-analysis of the relationship between miRNA rs20541 G>A polymorphism, Glioblastoma and various cancers for different region. (Heterozygous European total)

Meta-analysis of miRNA rs20541 G>A polymorphism for European (G allele):

In Figure 4.11, there is less deviation of the studies from the mean line, indicating decreased variation and a lower publication bias value. The association of the SNP rs20541 with Glioblastoma for the G allele appears to be higher for European population.

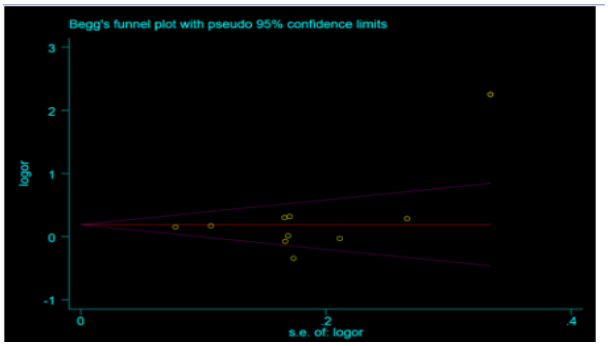

Fig 4.11: Meta-analysis of the relationship between miRNA rs20541 G>A polymorphism, Glioblastoma and various cancers for different region. (G allele European total)

Meta-analysis of miRNA rs20541 G>A polymorphism for European (A allele):

In Figure 4.12, there is less deviation of the studies from the mean line, indicating decreased variation and a lower publication bias value. The association of the SNP rs20541 with Glioblastoma for the A allele appears to be higher for European population.

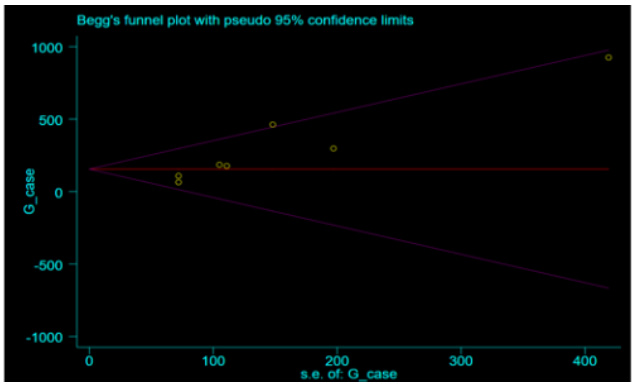

Fig 4.12: Meta-analysis of the relationship between miRNA rs20541 G>A polymorphism, Glioblastoma and various cancers for different region. (A allele European total)

Meta-analysis of miRNA rs20541 G>A polymorphism for Glioma (Dominant):

In Figure 4.13, there is a little deviation of the studies from the mean line, indicating decreased variation and a lower publication bias value. The association of the SNP rs20541 with Glioblastoma for the Glioma appears to be greater.

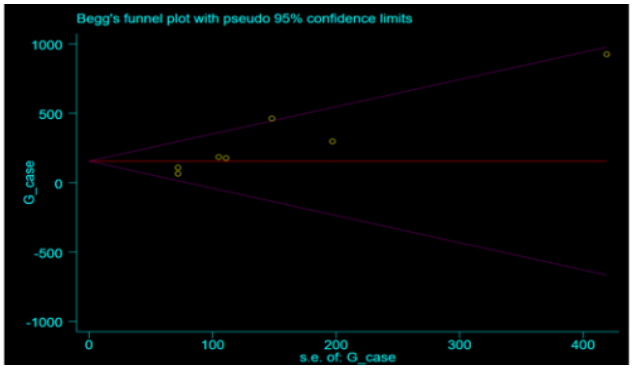

Fig 4.13: Meta-analysis of the relationship between miRNA rs20541 G>A polymorphism, Glioblastoma and various cancers for different region. (Dominant total Glioma)

Meta-analysis of miRNA rs20541 G>A polymorphism for Glioma (Heterozygous):

In Figure 4.14, there is a little deviation of the studies from the mean line, indicating decreased variation and a lower publication bias value. The association of the SNP rs20541 with Glioblastoma for the Glioma appears to be greater.

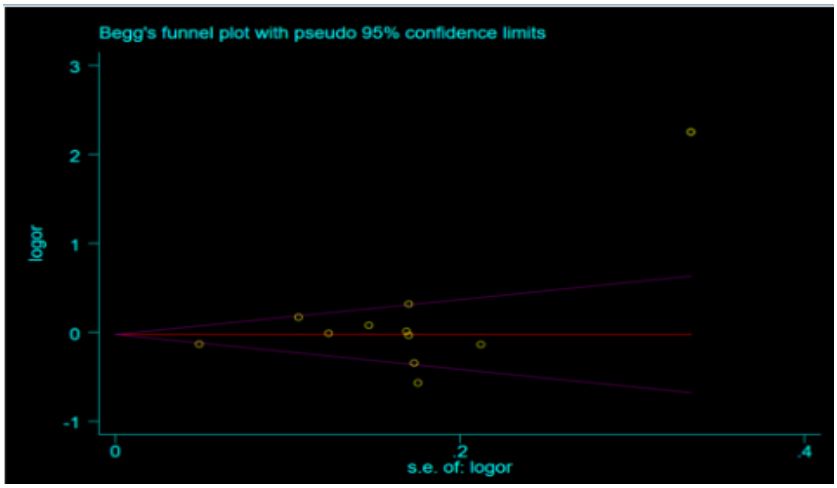

Fig 4.14: Meta-analysis of the relationship between miRNA rs20541 G>A polymorphism, Glioblastoma and various cancers for different region. (Heterozygous total Glioma)

Meta-analysis of miRNA rs20541 G>A polymorphism for Glioma (G allele):

In Figure 4.15, there is a little deviation of the studies from the mean line, depicting decreased variation and a lower publication bias value. The association of the SNP rs20541 with Glioblastoma for the G allele appears to be greater.

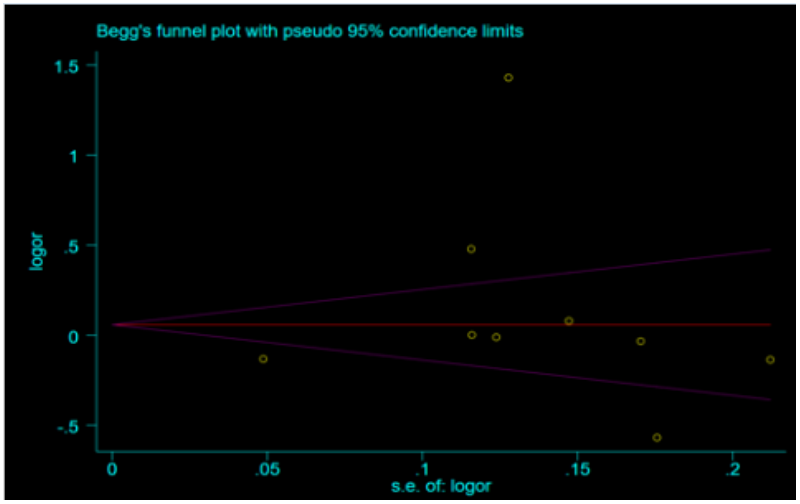

Fig 4.15: Meta-analysis of the relationship between miRNA rs20541 G>A polymorphism, Glioblastoma and various cancers for different region. (G allele Glioma)

Meta-analysis of miRNA rs20541 G>A polymorphism for Glioma (A allele):

In Figure 4.16, there is a little deviation of the studies from the mean line, depicting decreased variation and a lower publication bias value. The association of the SNP rs20541 with Glioblastoma for the G allele appears to be greater.

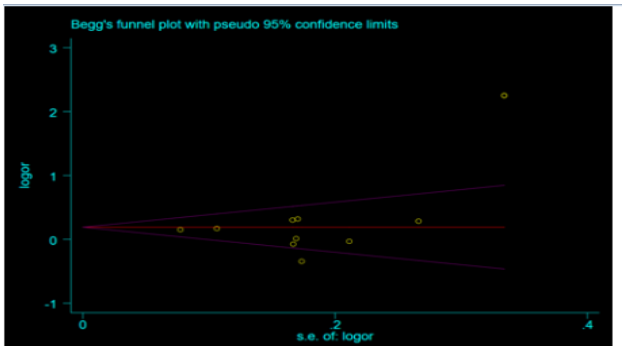

Fig 4.16: Meta-analysis of the relationship between miRNA rs20541 G>A polymorphism, Glioblastoma and various cancers for different region. (A allele Glioma)

Meta-analysis of miRNA rs20541 G>A polymorphism for Other cancer (Dominant):

In Figure 4.17, there is a little deviation of the studies from the mean line, depicting decreased variation and a lower publication bias value. The association of the SNP rs20541 with Glioblastoma for the dominant allele appears to be greater.

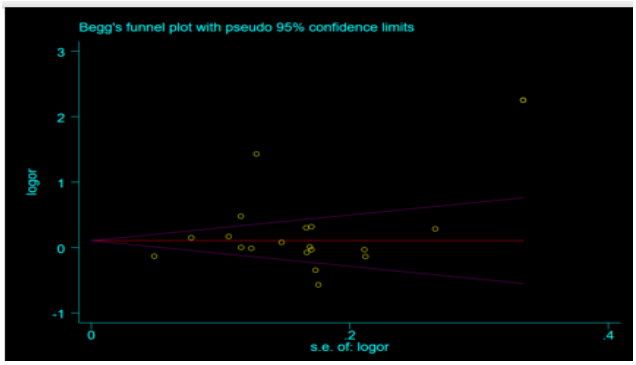

Fig 4.17: Meta-analysis of the relationship between miRNA rs20541 G>A polymorphism, Glioblastoma and various cancers for different region. (Dominant Other cancer)

Meta-analysis of miRNA rs20541 G>A polymorphism for Other cancer (Heterozygous):

In Figure 4.18, there is a little deviation of the studies from the mean line, depicting decreased variation and a lower publication bias value. The association of the SNP rs20541 with Glioblastoma for the heterozygous allele appears to be greater.

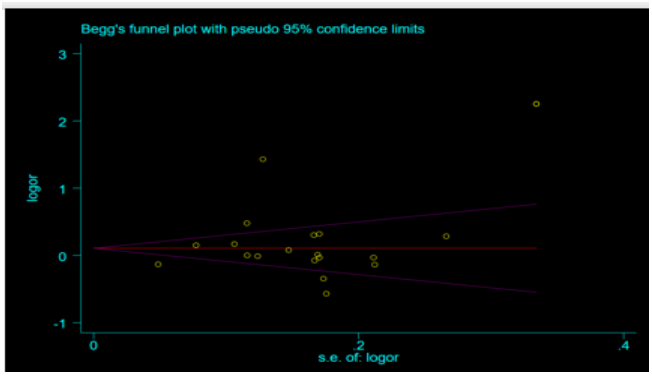

Fig 4.18: Meta-analysis of the relationship between miRNA rs20541 G>A polymorphism, Glioblastoma and various cancers for different region. (Heterozygous other cancer)

Meta-analysis of miRNA rs20541 G>A polymorphism for Other cancer (G allele):

In Figure 4.19, there is a little deviation of the studies from the mean line, depicting decreased variation and a lower publication bias value. The association of the SNP rs20541 with Glioblastoma for the G allele appears to be greater.

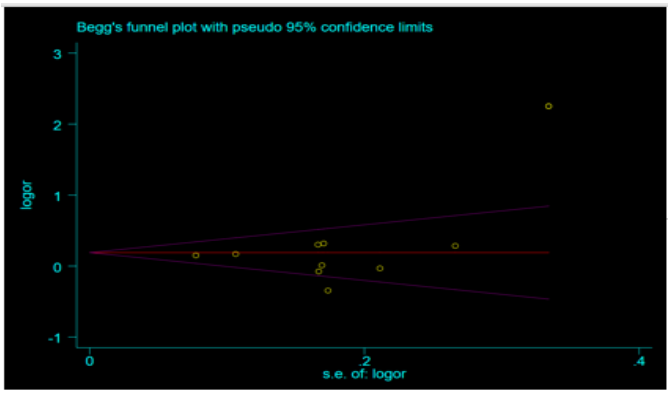

Fig 4.19: Meta-analysis of the relationship between miRNA rs20541 G>A polymorphism, Glioblastoma and various cancers for different region. (G allele Other cancer)

Meta-analysis of miRNA rs20541 G>A polymorphism for Other cancer (A allele):

In Figure 4.20, there is a little deviation of the studies from the mean line, depicting decreased variation and a lower publication bias value. The association of the SNP rs20541 with Glioblastoma for the A allele appears to be greater.

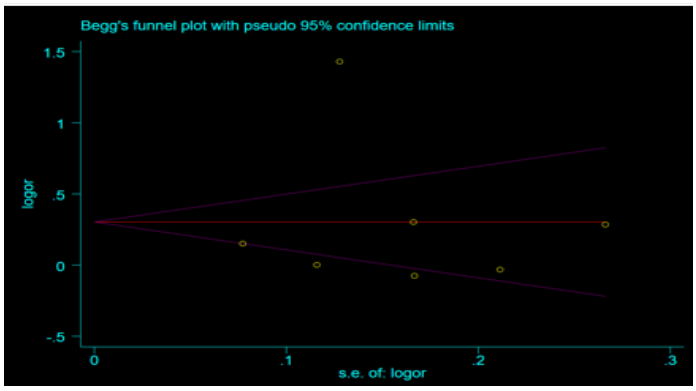

Fig 4.20: Meta-analysis of the relationship between miRNA rs20541 G>A polymorphism, Glioblastoma and various cancers for different region. (A allele Other cancer)

4.2 Forest plot for rs20541:

A forest plot represents a crucial tool for providing, in a single information, figure, on individual research data, a visual indication of the degree of study variability, and an approximate general effect. The total pooled effect across every of the included studies is represented by the diamond that is below the studies. The inclined "no effect" range, which appears in every forest plot, correlates to a number that is 1 for outcomes that are binary (such as the probability or odds ratios) and 0 for results that are continuous.

Meta-analysis of the miRNA rs20541 G>A polymorphism (Dominant):

In Figure 4.21, there is increase deviation of the studies from the mean line, depicting increased variation and an increased publication bias value. The association of the SNP rs20541 with Glioblastoma for the dominant allele appears to be greater.

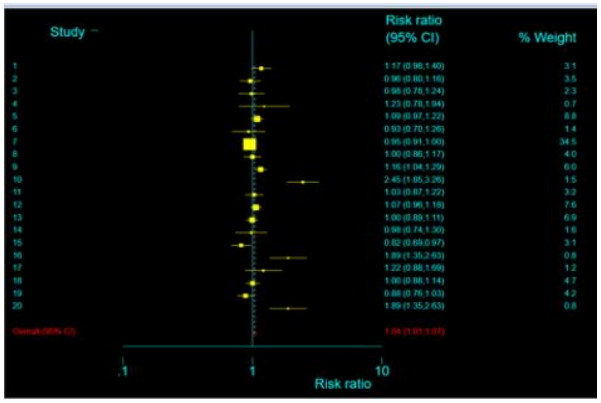

Fig 4.21: Meta-analysis of the relationship between miRNA rs20541 G>A polymorphism, Glioblastoma and various cancers for different region. (Dominant total cancer)

Meta-analysis of the miRNA rs20541 G>A polymorphism (Dominant):

In Figure 4.22, there is a little deviation of the studies from the mean line, depicting decreased variation and a lower publication bias value. The association of the SNP rs20541 with Glioblastoma for the Heterozygous allele appears to be greater.

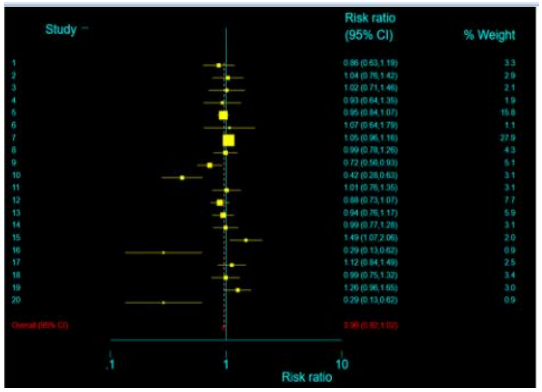

Fig 4.22: Meta-analysis of the relationship between miRNA rs20541 G>A polymorphism, Glioblastoma and various cancers for different region. (Heterozygous total cancer)

Meta-analysis of the miRNA rs20541 G>A polymorphism (G allele):

In Figure 4.23, there is increase deviation of the studies from the mean line, depicting decreased variation and a decreased publication bias value. The association of the SNP rs20541 with Glioblastoma for the G allele appears to be lower.

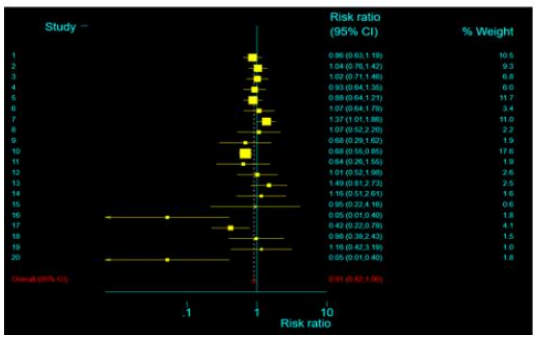

Fig 4.23: Meta-analysis of the relationship between miRNA rs20541 G>A polymorphism, Glioblastoma and various cancers for different region. (G allele total)

Meta-analysis of the miRNA rs20541 G>A polymorphism (A allele):

In Figure 4.24, there is low deviation of the studies from the mean line, depicting decreased variation and a decreased publication bias value. The association of the SNP rs20541 with Glioblastoma for the A allele appears to be lower.

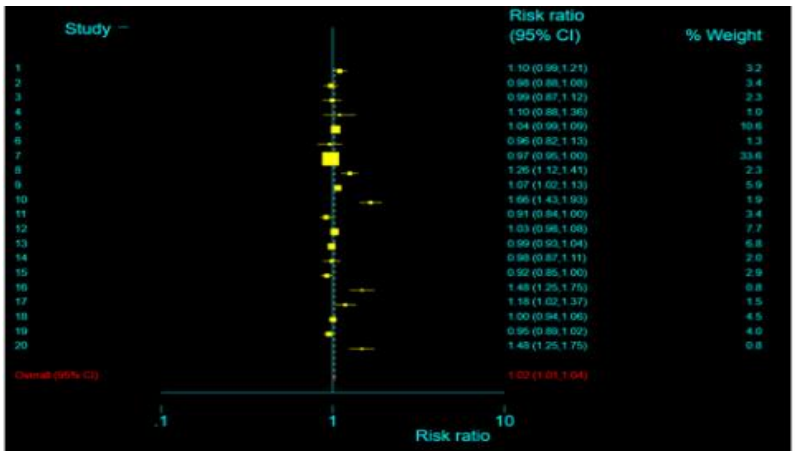

Fig 4.24: Meta-analysis of the relationship between miRNA rs20541 G>A polymorphism, Glioblastoma and various cancers for different region. (A allele total)

Meta-analysis of the miRNA rs20541 G>A polymorphism for Asian (Dominant):

In Figure 4.25, there is increase deviation of the studies from the mean line, depicting decreased variation and a decreased publication bias value. The association of the SNP rs20541 with Glioblastoma for the dominant allele for Asian population appears to be lower.

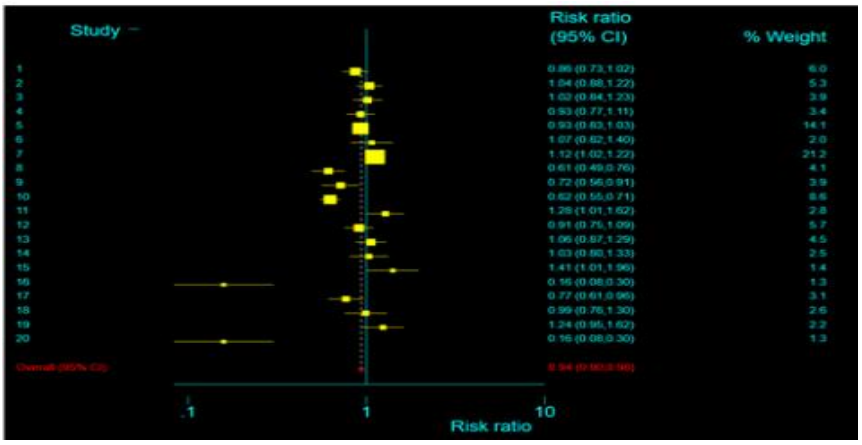

Fig 4.25: Meta-analysis of the relationship between miRNA rs20541 G>A polymorphism, Glioblastoma and various cancers for different region. (Dominant Asian total)

Meta-analysis of the miRNA rs20541 G>A polymorphism for Asian (Heterozygous):

In Figure 4.26, there is increase deviation of the studies from the mean line, depicting decreased variation and a decreased publication bias value. The association of the SNP rs20541 with Glioblastoma for the heterozygous allele for Asian population appears to be lower.

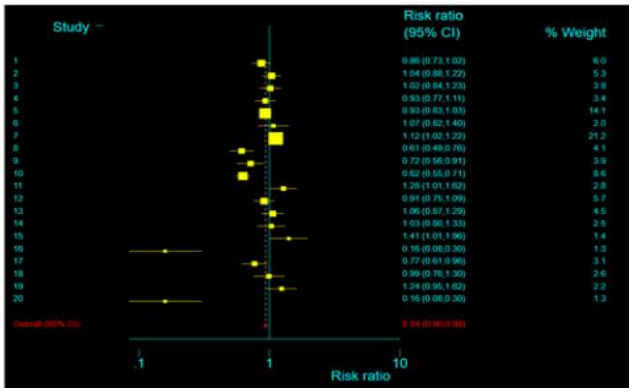

Fig 4.26: Meta-analysis of the relationship between miRNA rs20541 G>A polymorphism, Glioblastoma and various cancers for different region. (Heterozygous Asian total)

Meta-analysis of the miRNA rs20541 G>A polymorphism for Asian (G allele):

In Figure 4.27, there is increase deviation of the studies from the mean line, depicting decreased variation and a decreased publication bias value. The association of the SNP rs20541 with Glioblastoma for the G allele for Asian population appears to be lower.

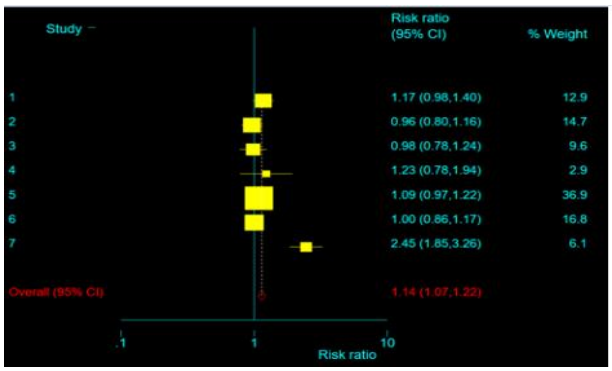

Fig 4.27: Meta-analysis of the relationship between miRNA rs20541 G>A polymorphism, Glioblastoma and various cancers for different region. (G allele Asian total)

Meta-analysis of the miRNA rs20541 G>A polymorphism for Asian (A allele):

In Figure 4.28, there is increase deviation of the studies from the mean line, depicting decreased variation and a decreased publication bias value. The association of the SNP rs20541 with Glioblastoma for the A allele for Asian population appears to be lower.

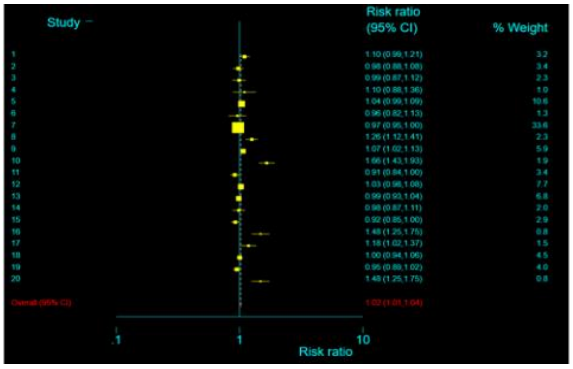

Fig 4.28: Meta-analysis of the relationship between miRNA rs20541 G>A polymorphism, Glioblastoma and various cancers for different region. (A allele Asian total)

Meta-analysis of the miRNA rs20541 G>A polymorphism for European (Dominant):

In Figure 4.29, there is increase deviation of the studies from the mean line, depicting decreased variation and a decreased publication bias value. The association of the SNP rs20541 with Glioblastoma for the Dominant allele for European population appears to be lower.

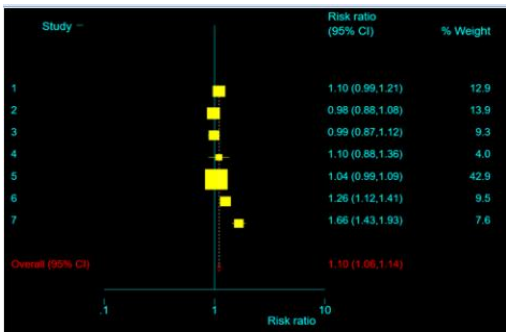

Fig 4.29: Meta-analysis of the relationship between miRNA rs20541 G>A polymorphism, Glioblastoma and various cancers for different region. (Dominant European total)

Meta-analysis of the miRNA rs20541 G>A polymorphism for European (Heterozygous):

In Figure 4.30, there is increase deviation of the studies from the mean line, depicting decreased variation and a decreased publication bias value. The association of the SNP rs20541 with Glioblastoma for the heterozygous allele for European population appears to be lower.

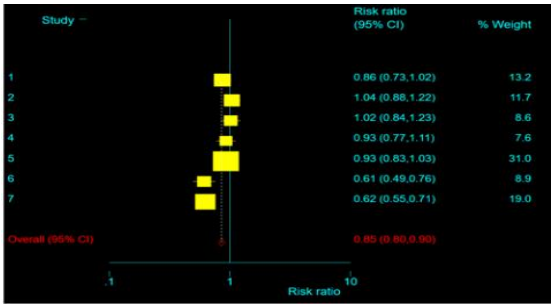

Fig 4.30: Meta-analysis of the relationship between miRNA rs20541 G>A polymorphism, Glioblastoma and various cancers for different region. (Heterozygous European total)

Meta-analysis of the miRNA rs20541 G>A polymorphism for European (G allele):

In Figure 4.31, there is a little deviation of the studies from the mean line, depicting decreased variation and a decreased publication bias value. The association of the SNP rs20541 with Glioblastoma for the G allele for European population appears to be higher.

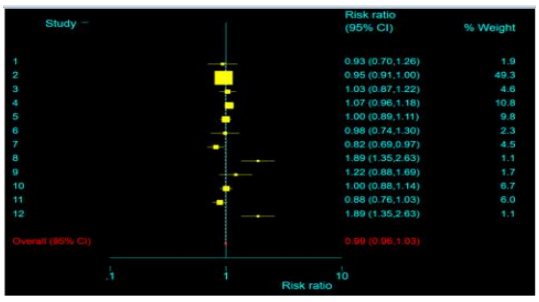

Fig 4.31: Meta-analysis of the relationship between miRNA rs20541 G>A polymorphism, Glioblastoma and various cancers for different region. (G allele European total)

Meta-analysis of the miRNA rs20541 G>A polymorphism for European (A allele):

In Figure 4.32, there is a little deviation of the studies from the mean line, depicting decreased variation and a decreased publication bias value. The association of the SNP rs20541 with Glioblastoma for the G allele for European population appears to be higher.

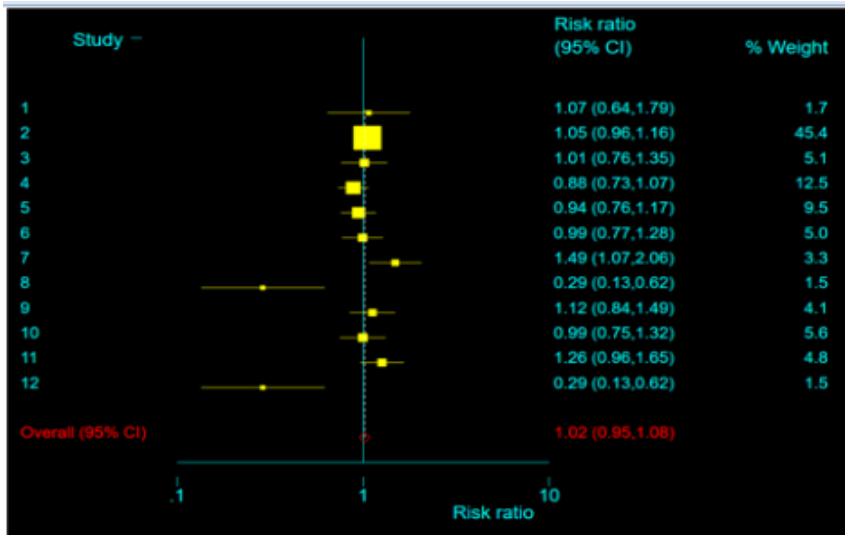

Fig 4.32: Meta-analysis of the relationship between miRNA rs20541 G>A polymorphism, Glioblastoma and various cancers for different region. (A allele European total)

Meta-analysis of the miRNA rs20541 G>A polymorphism for Glioma (Dominant):

In Figure 4.33, there is a little deviation of the studies from the mean line, depicting decreased variation and a decreased publication bias value. The association of the SNP rs20541 with Glioblastoma for the Dominant allele appears to be higher.

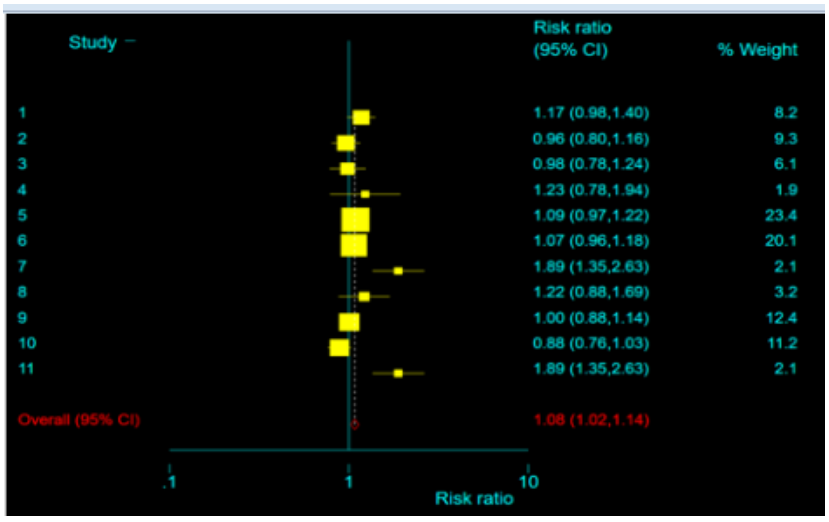

Fig 4.33: Meta-analysis of the relationship between miRNA rs20541 G>A polymorphism, Glioblastoma and various cancers for different region. (Dominant total Glioma)

Meta-analysis of the miRNA rs20541 G>A polymorphism for Glioma (Heterozygous):

In Figure 4.34, there is a little deviation of the studies from the mean line, depicting decreased variation and a decreased publication bias value. The association of the SNP rs20541 with Glioblastoma for the Heterozygous allele appears to be higher.

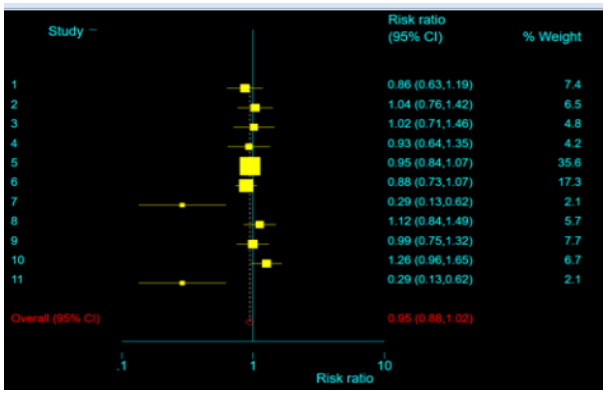

Fig 4.34: Meta-analysis of the relationship between miRNA rs20541 G>A polymorphism, Glioblastoma and various cancers for different region. (Heterozygous total Glioma)

Meta-analysis of the miRNA rs20541 G>A polymorphism for Glioma (G allele):

In Figure 4.35, there is a little deviation of the studies from the mean line, depicting decreased variation and a decreased publication bias value. The association of the SNP rs20541 with Glioblastoma for the G allele appears to be higher.

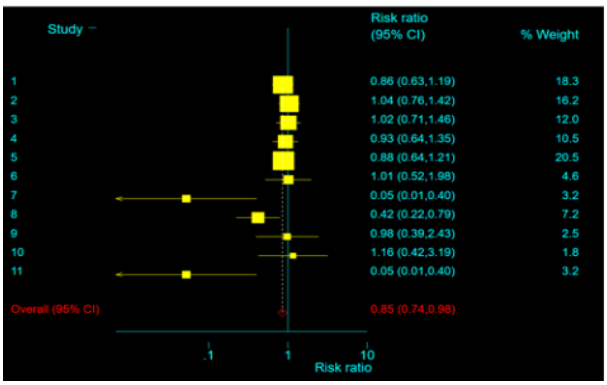

Fig 4.35: Meta-analysis of the relationship between miRNA rs20541 G>A polymorphism, Glioblastoma and various cancers for different region. (G allele Glioma)

Meta-analysis of the miRNA rs20541 G>A polymorphism for Glioma (A allele):

In Figure 4.36, there is a little deviation of the studies from the mean line, depicting decreased variation and a decreased publication bias value. The association of the SNP rs20541 with Glioblastoma for the A allele appears to be higher.

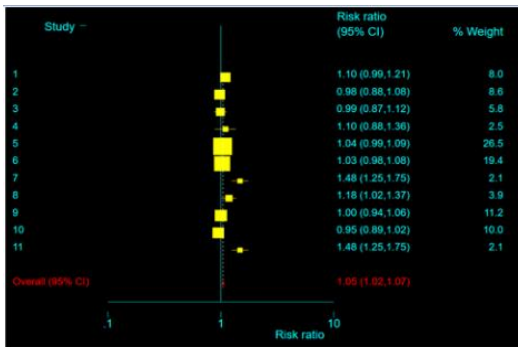

Fig 4.36: Meta-analysis of the relationship between miRNA rs20541 G>A polymorphism, Glioblastoma and various cancers for different region. (A allele Glioma)

Meta-analysis of the miRNA rs20541 G>A polymorphism for Other cancer (Dominant):

In Figure 4.37, there is a little deviation of the studies from the mean line, depicting decreased variation and a decreased publication bias value. The association of the SNP rs20541 with Glioblastoma for the dominant allele appears to be higher.

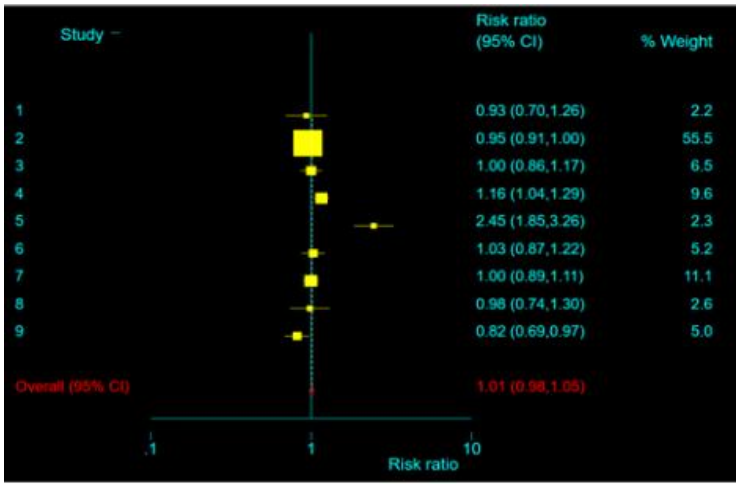

Fig 4.37: Meta-analysis of the relationship between miRNA rs20541 G>A polymorphism, Glioblastoma and various cancers for different region. (Dominant total other cancer)

Meta-analysis of the miRNA rs20541 G>A polymorphism for Other cancer (Heterozygous):

In Figure 4.38, there is a little deviation of the studies from the mean line, depicting decreased variation and a decreased publication bias value. The association of the SNP rs20541 with Glioblastoma for the heterozygous allele appears to be higher.

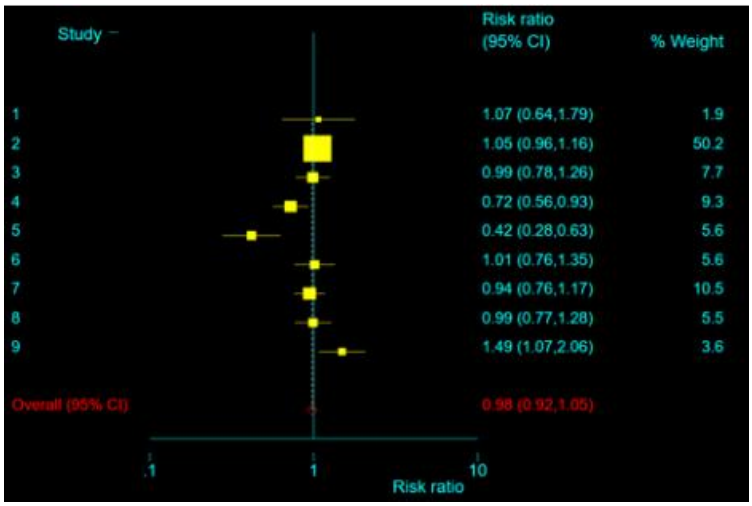

Fig 4.38: Meta-analysis of the relationship between miRNA rs20541 G>A polymorphism, Glioblastoma and various cancers for different region. (Heterozygous total other cancer)

Meta-analysis of the miRNA rs20541 G>A polymorphism for Other cancer(G allele):

In Figure 4.39, there is a little deviation of the studies from the mean line, depicting decreased variation and a decreased publication bias value. The association of the SNP rs20541 with Glioblastoma for the G allele appears to be higher.

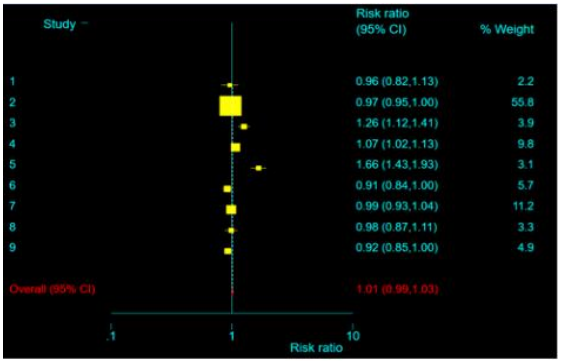

Fig 4.39: Meta-analysis of the relationship between miRNA rs20541 G>A polymorphism, Glioblastoma and various cancers for different region. (G allele other cancer)

Meta-analysis of the miRNA rs20541 G>A polymorphism for Other cancer(A allele):

In Figure 4.40, there is a little deviation of the studies from the mean line, depicting decreased variation and a decreased publication bias value. The association of the SNP rs20541 with Glioblastoma for the A allele appears to be higher.

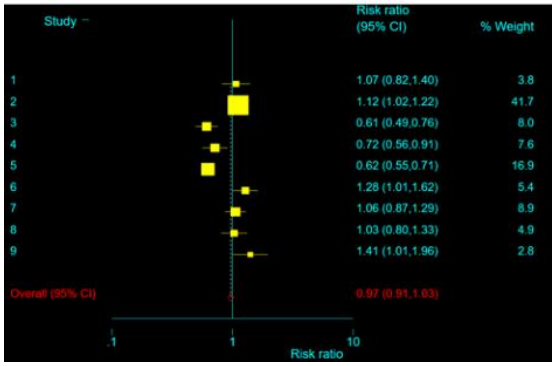

Fig 4.40: Meta-analysis of the relationship between miRNA rs20541 G>A polymorphism, Glioblastoma and various cancers for different region. (A allele other cancer)

4.2 Discussion

The main goal of this study is to conduct a meta-analysis of single nucleotide polymorphisms (SNPs) that have been linked to cancer in humans. One of the most important factors in determining a person's vulnerability to different diseases is genetic variability. Single nucleotide polymorphisms, or SNPs, are a major source of the genetic variability seen in humans and can significantly influence an individual's susceptibility to several diseases, including cancer (Amirian et al., 2011).Scholars have focused on examining the impact of single nucleotide polymorphisms (SNPs), specifically in precursor and mature microRNAs (miRNAs), on the development and course of various diseases. Their interest in this area has been aroused by the important implications these results have for comprehending the mechanisms underlying disease and possible treatments. The goal of this research is to provide a thorough understanding of the role of SNPs in cancer susceptibility by doing a meta-analysis. This will help identify prospective directions for further investigation and intervention techniques (Biggar et al., 2009).

According to research, Single nucleotide polymorphisms (SNPs) in mature and precursor miRNA sequences appear to be important in predisposing people to certain cancer forms. This effect results from changes that take place during the process of splicing and gene-coding. Notably, changes in miRNA precursor transcripts, that experience hairpin production via the removal of primary miRNAs by proteins like Drosha and DGCR8, have a major impact on the likelihood of cancer (Brown et al., 2006). Furthermore, the development process of miRNAs and the mutually beneficial interactions involving them and their targets play a key role in the

course of cancer, encompassing both the development of primary tumors as well as the propagation of metastatic ones. These results highlight how crucial it is to comprehend the complex mechanisms behind miRNA regulation in the growth of cancer. Researchers can find possible targets for medical treatments meant to reduce cancer susceptibility and development by clarifying the functions of SNPs in miRNA production and function (Chaouchi et al., 2012).

Significant correlations among variant genotypes (GA/AA) of the IL13 rs20541 polymorphisms with a lower risk of cancer, especially in glioma cases, were found by our meta-analysis. On the other hand, the IL13 rs1800925 polymorphism may have a protective effect against gliomas but did not significantly alter the overall risk during cancer. At codon 130, the IL13 rs20541 polymorphism, located in exon 4, causes an amino acid substitution from arginine to glutamine. Previous research has shown this polymorphism's physiological significance. For example, Graves et al. found that elevated serum IgE levels were strongly correlated with the IL13 rs20541 A allele, which codes for glutamine, in a variety of groups . Moreover, a number of research investigations have connected higher IgE levels to a lower risk of gliomas, non-Hodgkin lymphomas, and pancreatic cancer, among other cancers. This points to a probable process that indicates the IL13 rs20541 polymorphism, by influencing IgE levels, may provide protection against the formation of cancer, especially glioma (Chen et al., 2011).

There may be a connection between the polymorphisms in the IL13 gene and an increased risk of cancer since it is essential for both tumor immunosurveillance and IgE production. In particular, the IL13 rs20541 variation has demonstrated an antioxidant benefit against many cancers, including gliomas. Consistent epidemiological evidence suggests an inverse association among glioma risk and allergy disorders, which are frequently manifested by high IgE levels. For this reason, this finding is significant.

Furthermore, IL13 rs20541 has been implicated in asthma by prior meta-analyses, which lends additional biological credence to its relationship with glioma risk.
After more investigation, it was discovered that while the mitigating relationship of IL13 rs20541 variations was not significant in studies using hospital-based controls, it was observed in those using population-based controls.

This discrepancy could be the result of biases found in research conducted in hospitals, where the controls could be an unrepresentative fraction of the reference population. These controls might mostly consist of people who are seeking medical care, which could distort the outcomes. Population-based controls, on the other hand, are more likely to provide a more precise representation by reflecting a wider cross-section of the population (Chu et al., 2011).

All things considered, these results point to a complicated interaction between IL13 genetic variants, allergy symptoms, and cancer risk—especially when it comes to gliomas. Comprehending these correlations is imperative in elucidating the fundamental mechanisms propelling the development of cancer and may provide insights into preventive and therapeutic approaches, underscoring the need of taking demographic factors into account throughout the design and analysis of research. The most important way to reduce biases in genome association studies is to choose representative and suitable control people who do not have cancer. We found evidence of a correlation between IL13 rs20541 with cancer susceptibility in Europeans, but not in Asians, based on subgroup analysis conducted by ethnicity in our research. This ethnic gap may be caused by a number of variables, the main one being variations in genetic backgrounds (Graves et al., 2011).

In the beginning, the observed disparities could be explained by differences in genetic composition between populations. For example, there are differences in the minor frequency of alleles of the A allele (IL13 rs20541) among Asians and Europeans. The A allele is less common among Europeans (0.217) than in Asians, according to HapMap data, with frequencies of 0.302 for Han Chinese in Beijing (CHB) and 0.297 for Japanese in Tokyo (JPT). The observed relationships between IL13 rs20541 and cancer risk may be influenced by genetic variation among groups, as suggested by the variance in allele frequencies.

Furthermore, genetic variances involve wider genomic variations than just allele frequencies, which may account for ethnic differences in cancer risk. Different ethnic populations may experience distinct effects from IL13 rs20541 on cancer risk due to factors like the existence of population-specific genetic polymorphisms or changes in linkage disequilibrium patterns. The IL13 rs20541 polymorphisms may combine with these population-specific genetic variables to produce variable effects on cancer risk in distinct ethnic groupings.

To further compound ethnic variations in genotype-phenotype relationships, lifestyle and environmental variables might interact with inherited characteristics to affect cancer risk (Gunter et al., 2006). The impact of IL13 rs20541 polymorphisms on susceptibility to cancer may differ between Asian and European populations depending on differences in environmental exposures, dietary practices, socioeconomic factors and access to healthcare.

For example, variations in how much exposure to carcinogens in the environment or in factors related to lifestyle, like the incidence of smoking, may modify the impact of genetic polymorphisms on the occurrence of cancer in various ways among populations.

Moreover, the found correlations between IL13 rs20541 polymorphism and cancer susceptibility may possibly be impacted by variations in the healthcare infrastructure and availability to cancer diagnosis and treatment facilities between Asian and European populations. Inequalities in the availability and use of healthcare services may have an impact on the recognition and diagnosis of malignant tumor cases, which may have an impact on control group makeup and introduce biases into genetic association research (Johnson et al., 2011).

The correlation between cancer risk and IL13 rs20541 polymorphisms varies among ethnic groups, which highlights the significance of taking into account genetic and environmental factors particular to a population when conducting epidemiological studies.

Our meta-analysis revealed a statistically important (P=0.029) difference in the typical frequency of minor alleles of IL13 rs20541 between Europeans and Asians (0.237 versus 0.323). This disparity emphasizes how crucial it is to take genetic diversity into account when analyzing relationships between genetic variations and cancer incidence.

Furthermore, the observed variations in allele frequencies as well as the effect of IL13 rs20541 on susceptibility to cancer may be influenced by lifestyle and environmental variables that differ significantly among populations. The observed ethnic inequalities in our study could also be caused by other possible causes of bias, such as biased selection, variations in corresponding criteria, and small sample numbers, especially in the Asian subgroup where there are only four studies.

As a result, it's critical to exercise caution when interpreting these findings and acknowledge the necessity of additional extensive research to confirm and clarify the relationships between IL13 rs20541 polymorphisms as well as cancer risk in a variety of groups. We observed a protective correlation between glioma and the IL13 rs20541 mutation when we analyzed by type of malignancy. Notably, there is evidence linking this variation to an increased chance of developing asthma. Given the known linkage between glioma risk and asthma, as well as the effect of the rs20541 polymorphism for asthma susceptibility, more research is necessary to fully understand this relationship. Moreover, our analysis showed statistically significant relationships only in research utilizing population-based controls, while no significant relationships were found in research utilizing hospital-based controls (Johnson et al., 2011).

This discrepancy raises the possibility of biases in hospital-based research, as control groups might not fully reflect the broader population, thus distorting the associations that are found. Therefore, when comprehending genotype-phenotype relationships in cancer research, it is crucial to carefully consider study design and control selection criteria. This is made even more important by the differences in control selection

methods, which also highlight the need for thorough validation by means of more extensive investigations with broad control populations.

There could be underlying biases in the hospital-based controls studies, which could explain the differences in relationships between those studies and the population-based controls studies. Individuals seeking medical attention frequently make up hospital-based control groups, which may reflect a subgroup of the community with particular medical problems as compared to a representative sample. Because of this lack of representativeness, biases may be introduced and affect the observed relationships between genotype and phenotype. Thus, avoiding such biases in genetic association studies requires careful selection of appropriate, representative control patients free of cancer.

We found evidence of a connection between IL13 rs20541 and cancer susceptibility among Europeans, but not Asians, in our study that was stratified by ethnicity. This discrepancy can result from the genetic backgrounds of the various populations differing. Differences in the prevalence of alleles and linkage disequilibrium patterns across genetic diversity may account for the different ways that IL13 rs20541 affects cancer risk in different ethnic groups (Hershey et al., 2013).

These results emphasize the need for more research to fully understand the intricate interactions between genetic polymorphisms and cancer susceptibility across a range of populations, as well as the need of taking population-specific factors into account in genome-wide association studies.

There are multiple reasons for the observed differences between the ethnic groups in the relationship between IL13 rs20541 and risk for cancer. First, as seen by the disparities in minor allele frequencies between Asian and European populations, genetic background plays a major role. The A allele is less common in Europeans than in Asians, according to HapMap data, which is in line with our meta-analysis's conclusions. Moreover, the observed disparities are probably influenced by environmental and behavioral factors, which range greatly among people. The interaction between genetic predispositions and contextual circumstances can influence the risk of cancer. The observed ethnic inequalities may also be caused by other possible causes of prejudice, such as selection bias, different matching criteria, and small sample sizes—especially in Asian studies, where there were just four available. The makeup of the research populations and control groups may be impacted by these biases, which could skew the findings. Consequently, it's critical to exercise caution when interpreting these results and acknowledge the necessity of additional extensive research to confirm the links between IL13 rs20541 polymorphisms and cancer risk in a variety of groups. To improve the validity and generalization of findings, future research efforts should concentrate on resolving these constraints, using thorough research designs, and incorporating larger and more diversified study populations. It is possible for researchers to gain a deeper understanding of the intricate relationship between genetic variations and cancer susceptibility in diverse ethnic groups by taking into consideration environmental, genetic, and methodological aspects (Li et al., 2016).

The IL13 rs20541 polymorphism was not significantly associated with the overall cancer risk across all genetic models in our meta-analysis, nor was it in subgroup analyses depending on source of control or ethnicity. Nevertheless, a substantial protective impact of the IL13 rs20541 variation on gliomas was found upon stratification by cancer type. Since that similar polymorphism has been linked to an increased risk of asthma in other research, this discovery is especially intriguing. The correlation between glioma risk and asthma, along with the established influence of the IL13 rs20541 polymorphism on asthmatic susceptibility, indicates a potentially biological relationship. Glioma formation and asthma share identical pathophysiological pathways, with both conditions marked by persistent inflammation and immunological dysfunction. By reducing inflammatory processes or boosting immunosurveillance against tumor cells, the IL13 rs20541 polymorphism, which is known to affect immunological responses and inflammatory response through its regulation of interleukin-13 (IL-13) activity, might therefore provide protective benefits against glioma. This finding emphasizes the intricate relationship that exists between immune system performance, genetic variations, and cancer risk. It is necessary to conduct more study to clarify the precise mechanisms underlying the correlation between the IL13 rs1800925 polymorphism and glioma risk. Gaining

knowledge of these pathways may help develop new treatment approaches for gliomas and possibly other malignancies linked to inflammation (Fagihih et al., 2009).

Furthermore, these findings suggest that various cancer types may have distinct etiologies. It is important to note a few of the current meta-analysis's limitations. Firstly, the quantity of published research gathered for our study was insufficient for a thorough examination. Second, because interactions between genes and the environment as well as different polymorphic regions of the same genes can influence cancer risk, our ability to further evaluate potential interactions was limited by the absence of original data from the included studies. Examples of these interactions include those between IL13 variability and allergic conditions, cigarette smoking, and drinking status, correspondingly. Third, if individual data, such as age and sex, are available, a more exact analysis must be done as our results were based on uncorrected estimates. Inadequate data for the analysis could result in significant confounding bias. However, benefits in our meta-analysis should also be mentioned. Firstly, a comprehensive analysis of the relationship between glioma risk and IL13 polymorphisms is statistically stronger than a single study. Secondly, the case-control studies that were incorporated into our meta-analysis had a satisfactory quality and fulfilled our selection criteria. For example, no heterogeneity was found for the IL13 rs20541 in any of the comparisons, and no publication bias was found for the two polymorphisms, suggesting that the pooled data should be impartial and consistent (Li et al., 2011).

4.2 Conclusion

In conclusion, the IL13 rs20541 polymorphism may be linked to an increased risk of developing cancer, according to our meta-analysis. Furthermore, our results imply that the IL13 rs20541 polymorphism variant genotypes may provide protection against the development of gliomas. It is imperative to acknowledge, though, that additional validation of these findings would require larger trials with well-matched controls and uniform, impartial patient populations. Further investigations into the combined impact of gene-gene and gene-environment interactions are also necessary to fully comprehend the significance of IL13 polymorphisms in the genesis of cancer. By looking at these variables, we might be able to learn more about the mechanisms behind cancer susceptibility and even find new targets for treatment or preventative measures. All things considered, our work emphasizes the significance of genetic variations, like the IL13 rs20541 polymorphism, in cancer susceptibility and emphasizes the necessity of further research in this field to advance our knowledge and treatment of cancer. These results also imply that different cancer types can have different etiologies. A number of the limitations of the present meta-analyses should be noted. First off, there was not enough published research to do a comprehensive analysis with the amount of data we acquired for our study. Second, the lack of initial information from the research included hampered our capacity to further assess potential interactions, since interactions among genes and the environment as well as various polymorphism regions of the identical genes can influence the likelihood of developing cancer. IL13 variability and allergy diseases, cigarette smoking, and drinking status are a few examples of these relationships. Third, as the findings were based on erroneous estimates, a more precise study needs to be done if individual data, including gender and age, are available. Significant confusion bias could arise from using insufficient data for the analysis. Benefits from our meta-analysis, however, should also be highlighted. First off, a thorough examination of the connection between IL13 polymorphisms and glioma risk is statistically superior to a single study. Our meta-analysis suggests that the variant allele present(A) in IL13 rs20541 polymorphism is highly significant in Asian population and European population as depicted by the P-values. It is also significantly associated or present in Gliomas as compared with other cancer. Further validation of our findings would need larger, future investigations using well-matched groups and standardized, impartial, homogenous patients.

References

Alte kruse, S. F., McGlynn, K. A., & Reichman, M. E. (2009). Hepatocellular carcinoma incidence, mortality, and survival trends in the United States from 1975 to 2005. Journal of clinical oncology, 27(9), 1485.

Amary, M. F., Bacsi, K., Maggiani, F., Damato, S., Halai, D., Berisha, F., ... & Flanagan, A. M. (2011). IDH1 and IDH2 mutations are frequent events in central chondrosarcoma and central and periosteal chondromas but not in other mesenchymal tumours. The Journal of pathology, 224(3), 334-343.

Amirian, E. S., Ittmann, M. M., & Scheurer, M. E. (2011). Associations between arachidonic acid metabolism gene polymorphisms and prostate cancer risk. The Prostate, 71(13), 1382-1389.

Amirian, E. S., Scheurer, M. E., Liu, Y., D'Amelio Jr, A. M., Houlston, R. S., Etzel, C. J., ... & Bondy, M. L. (2011). A novel approach to exploring potential interactions among single-nucleotide polymorphisms of inflammation genes in gliomagenesis: an exploratory case-only study. Cancer epidemiology, biomarkers & prevention, 20(8), 1683-1689.

Bailar, J. C., & Gornik, H. L. (1997). Cancer undefeated. New England Journal of Medicine, 336(22), 1569-1574.

Baumann, M., Krause, M., & Hill, R. (2008). Exploring the role of cancer stem cells in radio resistance. Nature Reviews Cancer, 8(7), 545-554.

Bavelloni, A., Ramazzotti, G., Poli, A., Piazzi, M., Focaccia, E., Blalock, W., & Faenza, I. (2017). MiRNA-210: a current overview. Anticancer research, 37(12), 6511-6521.

Biggar, R. J., Christiansen, M., Rostgaard, K., Smedby, K. E., Adami, H. O., Glimelius, B., ... & Melbye, M. (2009). Immunoglobulin subclass levels in patients with non-Hodgkin lymphoma. International journal of cancer, 124(11), 2616-2620.

Black, P. C., Brown, G. A., & Dinney, C. P. (2009, January). The impact of variant histology on the outcome of bladder cancer treated with curative intent. In Urologic Oncology: Seminars and Original Investigations (Vol. 27, No. 1, pp. 3-7). Elsevier.

Bleeker, F. E., Lamba, S., Leenstra, S., Troost, D., Hulsebos, T., Vandertop, W. P., ... & Bardelli, A. (2009). IDH1 mutations at residue p. R132 (IDH1R132) occur frequently in high-grade gliomas but not in other solid tumors. Human mutation, 30(1), 7-11.

Borger, D. R., Tanabe, K. K., Fan, K. C., Lopez, H. U., Fantin, V. R., Straley, K. S., ... & Iafrate, A. J. (2012). Frequent mutation of isocitrate dehydrogenase (IDH) 1 and IDH2 in cholangiocarcinoma identified through broad-based tumor genotyping. The oncologist, 17(1), 72-79.

Boyle, P., & Leon, M. E. (2002). Epidemiology of colorectal cancer. British medical bulletin, 64(1), 1-25.

Bray, F., Ferlay, J., Soerjomataram, I., Siegel, R. L., Torre, L. A., & Jemal, A. (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.

Brown, E. E., Fallin, D., Ruczinski, I., Hutchinson, A., Staats, B., Vitale, F., ... & Kaposi Sarcoma Working Group. (2006). Associations of classic Kaposi sarcoma with common variants in genes that modulate host immunity. Cancer Epidemiology Biomarkers & Prevention, 15(5), 926-934.

Burýšek, L., Yeow, W. S., Lubyová, B., Kellum, M., Schafer, S. L., Huang, Y. Q., & Pitha, P. M. (1999). Functional analysis of human herpesvirus 8-encoded viral interferon regulatory factor 1 and its association with cellular interferon regulatory factors and p300. Journal of virology, 73(9), 7334-7342.

Cai, Y., Yu, X., Hu, S., & Yu, J. (2009). A brief review on the mechanisms of miRNA regulation. Genomics, Proteomics and Bioinformatics, 7(4), 147-154.

Cairns, R. A., Iqbal, J., Lemonnier, F., Kucuk, C., De Leval, L., Jais, J. P., ... & Mak, T. W. (2012). IDH2 mutations are frequent in angioimmunoblastic T-cell lymphoma. Blood, The Journal of the American Society of Hematology, 119(8), 1901-1903.

Center, M. M., Jemal, A., Smith, R. A., & Ward, E. (2009). Worldwide variations in colorectal cancer. CA: a cancer journal for clinicians, 59(6), 366-378.

Center, M. M., Jemal, A., Smith, R. A., & Ward, E. (2009). Worldwide variations in colorectal cancer. CA: a cancer journal for clinicians, 59(6), 366-378.

Chansky, K., Detterbeck, F. C., Nicholson, A. G., Rusch, V. W., Vallières, E., Groome, P., ... & Yokoi, K. (2017). The IASLC lung cancer staging project: external validation of the revision of the TNM stage groupings in the eighth edition of the TNM classification of lung cancer. Journal of Thoracic Oncology, 12(7), 1109-1121.

Chaouchi, N., Wallon, C., Goujard, C., Tertian, G., Rudent, A., Caput, D., ... & Delfraissy, J. F. (1996). Interleukin-13 inhibits interleukin-2-induced proliferation and protects chronic lymphocytic leukemia B cells from in vitro apoptosis.

Chaouchi, N., Wallon, C., Goujard, C., Tertian, G., Rudent, A., Caput, D., ... & Delfraissy, J. F. (1996). Interleukin-13 inhibits interleukin-2-induced proliferation and protects chronic lymphocytic leukemia B cells from in vitro apoptosis.

Chen YingTai, C. Y., Zheng TongZhang, Z. T., Lan Qing, L. Q., Foss, F., Kim, C., Chen XueZhong, C. X., ... & Zhang YaWei, Z. Y. (2011). Cytokine polymorphisms in Th1/Th2 pathway genes, body mass index, and risk of non-Hodgkin lymphoma.

Chen, D. T., Jiang, X., Akula, N., Shugart, Y. Y., Wendland, J. R., Steele, C. J. M., ... & Mcmahon, F. J. (2013). Genome-wide association study meta-analysis of European and Asian-ancestry samples identifies three novel loci associated with bipolar disorder. Molecular psychiatry, 18(2), 195-205.

Chen, Y., Zheng, T., Lan, Q., Foss, F., Kim, C., Chen, X., ... & Zhang, Y. (2011). Cytokine polymorphisms in Th1/Th2 pathway genes, body mass index, and risk of non-Hodgkin lymphoma. Blood, The Journal of the American Society of Hematology, 117(2), 585-590.

Chu, H., Ma, L., Wang, M., Shi, D., Qin, C., Yuan, L., ... & Zhang, Z. (2012). The polymorphisms of IL-4, IL-4R and IL-13 genes and bladder cancer risk in a Chinese population: a case–control study. Molecular biology reports, 39, 5349-5357.

Clarke, E., & O'Malley, C. D. (1996). The human brain and spinal cord: A historical study illustrated by writings from antiquity to the twentieth century (No. 2). Norman Publishing

Coscoy, L., & Ganem, D. (2000). Kaposi's sarcoma-associated herpesvirus encodes two proteins that block cell surface display of MHC class I chains by enhancing their endocytosis. Proceedings of the National Academy of Sciences, 97(14), 8051-8056.

Dabiri, S., Aghtaei, M. M., Shahryari, J., Meymandi, M. S., Amirpour-Rostami, S., & Ardekani, R. F. (2016). Maspin gene expression in invasive ductal carcinoma of breast. Iranian journal of pathology, 11(2), 104.

Dall, G. V., & Britt, K. L. (2017). Estrogen effects on the mammary gland in early and late life and breast cancer risk. Frontiers in oncology, 7, 110.

Dumars, C., Ngyuen, J. M., Gaultier, A., Lanel, R., Corradini, N., Gouin, F., ... & Heymann, M. F. (2016). Dysregulation of macrophage polarization is associated with the metastatic process in osteosarcoma. Oncotarget, 7(48), 78343.

Escalón, M. P., Liu, N. S., Yang, Y., Hess, M., Walker, P. L., Smith, T. L., & Dang, N. H. (2005). Prognostic factors and treatment of patients with T-cell non-Hodgkin lymphoma: the MD Anderson Cancer Center experience. Cancer: Interdisciplinary International Journal of the American Cancer Society, 103(10), 2091-2098.

Faghih, Z., Erfani, N., Razmkhah, M., Sameni, S., Talei, A., & Ghaderi, A. (2009). Interleukin13 haplotypes and susceptibility of Iranian women to breast cancer. Molecular biology reports, 36, 1923-1928.

Ferlay, J., Parkin, D. M., & Steliarova-Foucher, E. (2010). Estimates of cancer incidence and mortality in Europe in 2008. European journal of cancer, 46(4), 765-781.

Freedman, N. D., Leitzmann, M. F., Hollenbeck, A. R., Schatzkin, A., & Abnet, C. C. (2008). Cigarette smoking and subsequent risk of lung cancer in men and women: analysis of a prospective cohort study. The lancet oncology, 9(7), 649-656.

Fujisawa, H., Reis, R. M., Nakamura, M., Colella, S., Yonekawa, Y., Kleihues, P., & Ohgaki, H. (2000). Loss of heterozygosity on chromosome 10 is more extensive in primary (de novo) than in secondary glioblastomas. Laboratory investigation, 80(1), 65-72.

Fuld, S., Cunningham, C., Klucher, K., Davison, A. J., & Blackbourn, D. J. (2006). Inhibition of interferon signaling by the Kaposi's sarcoma-associated herpesvirus full-length viral interferon regulatory factor 2 protein. Journal of virology, 80(6), 3092-3097.

Ganal, M. W., Altmann, T., & Röder, M. S. (2009). SNP identification in crop plants. Current opinion in plant biology, 12(2), 211-217.

Glass, A. G., Karnell, L. H., & Menck, H. R. (1997). The national cancer data base report on non-hodgkin's lymphoma. Cancer: Interdisciplinary International Journal of the American Cancer Society, 80(12), 2311-2320.

Graves, P. E., Kabesch, M., Halonen, M., Holberg, C. J., Baldini, M., Fritzsch, C., ... & Martinez, F. D. (2000). A cluster of seven tightly linked polymorphisms in the IL-13 gene is associated with total serum IgE levels in three populations of white children. Journal of Allergy and Clinical Immunology, 105(3), 506-513.

Gui, Y., Guo, G., Huang, Y., Hu, X., Tang, A., Gao, S., ... & Cai, Z. (2011). Frequent mutations of chromatin remodeling genes in transitional cell carcinoma of the bladder. Nature genetics, 43(9), 875-878.

Gunter, M. J., Canzian, F., Landi, S., Chanock, S. J., Sinha, R., & Rothman, N. (2006). Inflammation-related gene polymorphisms and colorectal adenoma. Cancer Epidemiology Biomarkers & Prevention, 15(6), 1126-1131.

Heimer, L. (2012). The human brain and spinal cord: functional neuroanatomy and dissection guide. Springer Science & Business Media.

Hershey, G. K. K. (2003). IL-13 receptors and signaling pathways: an evolving web. Journal of Allergy and Clinical Immunology, 111(4), 677-690.

Hershey, G. K. K. (2003). IL-13 receptors and signaling pathways: an evolving web. Journal of Allergy and Clinical Immunology, 111(4), 677-690.

Hiscock, R., Bauld, L., Amos, A., Fidler, J. A., & Munafò, M. (2012). Socioeconomic status and smoking: a review. Annals of the New York Academy of Sciences, 1248(1), 107-123.

Hollier, L. H. (1987). Protecting the brain and spinal cord. Journal of Vascular Surgery, 5(3), 524-528.

Iscovich, J., & Howe, G. R. (1998). Cancer incidence patterns (1972-91) among migrants from the Soviet Union to Israel. Cancer Causes & Control, 9, 29-36.

Jacobs, S. R., Gregory, S. M., West, J. A., Wollish, A. C., Bennett, C. L., Blackbourn, D. J., ... & Damania, B. (2013). The viral interferon regulatory factors of kaposi's sarcoma-associated herpesvirus differ in their inhibition of interferon activation mediated by toll-like receptor 3. Journal of virology, 87(2), 798-806.

Jiao, Y., Killela, P. J., Reitman, Z. J., Rasheed, B. A., Heaphy, C. M., De Wilde, R. F., ... & Yan, H. (2012). Frequent ATRX, CIC, FUBP1 and IDH1 mutations refine the classification of malignant gliomas. Oncotarget, 3(7), 709.

Johnson, L. G., Schwartz, S. M., Malkki, M., Du, Q., Petersdorf, E. W., Galloway, D. A., & Madeleine, M. M. (2011). Risk of cervical cancer associated with allergies and polymorphisms in genes in the chromosome 5 cytokine cluster. Cancer epidemiology, biomarkers & prevention, 20(1), 199-207.

Kamat, A. M., Hahn, N. M., Efstathiou, J. A., Lerner, S. P., Malmström, P. U., Choi, W., ... & Kassouf, W. (2016). Bladder cancer. The Lancet, 388(10061), 2796-2810.

Kerur, N., Veettil, M. V., Sharma-Walia, N., Bottero, V., Sadagopan, S., Otageri, P., & Chandran, B. (2011). IFI16 acts as a nuclear pathogen sensor to induce the inflammasome in response to Kaposi Sarcoma-associated herpesvirus infection. Cell host & microbe, 9(5), 363-375.

Kim, S., & Misra, A. (2007). SNP genotyping: technologies and biomedical applications. Annu. Rev. Biomed. Eng., 9, 289-320.

Krol, A. D. G., Le Cessie, S., Snijder, S., Kluin-Nelemans, J. C., Kluin, P. M., & Noordijk, E. M. (2003). Primary extranodal non-Hodgkin's lymphoma (NHL): the impact of alternative definitions tested in the Comprehensive Cancer Centre West population-based NHL registry. Annals of oncology, 14(1), 131-139.

Kudo, M., Chung, H., & Osaki, Y. (2003). Prognostic staging system for hepatocellular carcinoma (CLIP score): its value and limitations, and a proposal for a new staging system, the Japan Integrated Staging Score (JIS score). Journal of gastroenterology, 38, 207-215.

Kuhn, D. E., Martin, M. M., Feldman, D. S., Terry Jr, A. V., Nuovo, G. J., & Elton, T. S. (2008). Experimental validation of miRNA targets. Methods, 44(1), 47-54.

Lewis, D. R., Check, D. P., Caporaso, N. E., Travis, W. D., & Devesa, S. S. (2014). US lung cancer trends by histologic type. Cancer, 120(18), 2883-2892.

Li ShanQu, L. S., Jin TianBo, J. T., Zhang JiaYi, Z. J., Lou HuiLing, L. H., Yang Bo, Y. B., Li Yang, L. Y., ... & Zhang Yong Sheng, Z. Y. (2012). Polymorphisms of TREH, IL4R and CCDC26 genes associated with risk of glioma.

Li, W., Avey, D., Fu, B., Wu, J. J., Ma, S., Liu, X., & Zhu, F. (2016). Kaposi's sarcoma-associated herpesvirus inhibitor of cGAS (KicGAS), encoded by ORF52, is an abundant tegument protein and is required for production of infectious progeny viruses. Journal of virology, 90(11), 5329-5342.

Lin, W. W., & Karin, M. (2007). A cytokine-mediated link between innate immunity, inflammation, and cancer. The Journal of clinical investigation, 117(5), 1175-1183.

Lisy, K., Peters, M. D., Schofield, P., & Jefford, M. (2018). Experiences and unmet needs of lesbian, gay, and bisexual people with cancer care: A systematic review and meta-synthesis. Psycho-oncology, 27(6), 1480-1489.

Liu, B., Jiang, J. W., Wilson, B. C., Du, L., Yang, S. N., Wang, J. Y., ... & Hong, J. S. (2000). Systemic infusion of naloxone reduces degeneration of rat substantia nigral dopaminergic neurons induced by intranigral injection of lipopolysaccharide. Journal of Pharmacology and Experimental Therapeutics, 295(1), 125-132.

Liu, C. Y., Chen, K. F., & Chen, P. J. (2015). Treatment of liver cancer. Cold Spring Harbor perspectives in medicine, 5(9), a021535.

Liu, L. U., Holt, P. R., Krivosheyev, V., & Moss, S. F. (1999). Human right and left colon differ in epithelial cell apoptosis and in expression of Bak, a pro-apoptotic Bcl-2 homologue. Gut, 45(1), 45-50.

Liu, X. Y., Gergs, N., Korshunov, A., Sabha, N., Khuong-Quang, D. A., Fontebasso, A. M., ... & Jabado, N. (2012). Frequent ATRX mutations and loss of expression in adult diffuse astrocytic tumors carrying IDH1/IDH2 and TP53 mutations. Acta neuropathologica, 124, 615-625.

Liu, X. Y., Gerges, N., Korshunov, A., Sabha, N., Khuong-Quang, D. A., Fontebasso, A. M., ... & Jabado, N. (2012). Frequent ATRX mutations and loss of expression in adult diffuse astrocytic tumors carrying IDH1/IDH2 and TP53 mutations. Acta neuropathologica, 124, 615-625.

Llovet, J. M., & Bruix, J. (2008). Novel advancements in the management of hepatocellular carcinoma in 2008. Journal of hepatology, 48, S20-S37.

Llovet, J. M., Schwartz, M., & Mazzaferro, V. (2005, May). Resection and liver transplantation for hepatocellular carcinoma. In Seminars in liver disease (Vol. 25, No. 02, pp. 181-200). Copyright© 2005 by Thieme Medical Publishers, Inc., 333 Seventh Avenue, New York, NY 10001, USA..

Majeed, W., Aslam, B., Javed, I., Khaliq, T., Muhammad, F., Ali, A., & Raza, A. (2014). Breast cancer: major risk factors and recent developments in treatment. Asian Pacific Journal of Cancer Prevention, 15(8), 3353-3358.

Mármol, I., Sánchez-de-Diego, C., Pradilla Dieste, A., Cerrada, E., & Rodriguez Yoldi, M. J. (2017). Colorectal carcinoma: a general overview and future perspectives in colorectal cancer. International journal of molecular sciences, 18(1), 197.

Mármol, I., Sánchez-de-Diego, C., Pradilla Dieste, A., Cerrada, E., & Rodriguez Yoldi, M. J. (2017). Colorectal carcinoma: a general overview and future perspectives in colorectal cancer. International journal of molecular sciences, 18(1), 197.

Merrill, R. M., Isakson, R. T., & Beck, R. E. (2007). The association between allergies and cancer: what is currently known?. Annals of Allergy, Asthma & Immunology, 99(2), 102-117.

Moertel, C. G., Fleming, T. R., Macdonald, J. S., Haller, D. G., Laurie, J. A., Goodman, P. J., ... & Mailliard, J. A. (1990). Levamisole and fluorouracil for adjuvant therapy of resected colon carcinoma. New England Journal of Medicine, 322(6), 352-358.

Müller, A. M., Ihorst, G., Mertelsmann, R., & Engelhardt, M. (2005). Epidemiology of non-Hodgkin's lymphoma (NHL): trends, geographic distribution, and etiology. Annals of hematology, 84, 1-12.

O'Connell, J. B., Maggard, M. A., Livingston, E. H., & Cifford, K. Y. (2004). Colorectal cancer in the young. The American journal of surgery, 187(3), 343-348.

Ohgaki, H., & Kleihues, P. (2007). Genetic pathways to primary and secondary glioblastoma. The American journal of pathology, 170(5), 1445-1453.

Ohgaki, H., & Kleihues, P. (2013). The definition of primary and secondary glioblastoma. Clinical cancer research, 19(4), 764-772.

Ohgaki, H., Dessen, P., Jourde, B., Horstmann, S., Nishikawa, T., Di Patre, P. L., ... & Kleihues, P. (2004). Genetic pathways to glioblastoma: a population-based study. Cancer research, 64(19), 6892-6899.

Okuda, K., Ohtsuki, T., Obata, H., Tomimatsu, M., Okazaki, N., Hasegawa, H., ... & Ohnishi, K. (1985). Natural history of hepatocellular carcinoma and prognosis in relation to treatment study of 850 patients. Cancer, 56(4), 918-928.

Oosterlinck, W., Lobel, B., Jakse, G., Malmström, P. U., Stöckle, M., Sternberg, C., & EAU Working Group on Oncological Urology. (2002). Guidelines on bladder cancer. European urology, 41(2), 105-112.

Palmer, S. C., Navaneethan, S. D., Craig, J. C., Johnson, D. W., Tonelli, M., Garg, A. X., ... & Strippoli, G. F. (2010). Meta-analysis: erythropoiesis-stimulating agents in patients with chronic kidney disease. Annals of internal medicine, 153(1), 23-33.

Parsons, D. W., Jones, S., Zhang, X., Lin, J. C. H., Leary, R. J., Angenendt, P., ... & Kinzler, K. W. (2008). An integrated genomic analysis of human glioblastoma multiforme. science, 321(5897), 1807-1812.

Patel, K. P., Ravandi, F., Ma, D., Paladugu, A., Barkoh, B. A., Medeiros, L. J., & Luthra, R. (2011). Acute myeloid leukemia with IDH1 or IDH2 mutation: frequency and clinicopathologic features. American journal of clinical pathology, 135(1), 35-45.

Peiffer, J., & Kleihues, P. (1999). Hans-Joachim Scherer (1906-1945), Pioneer in Glioma Research. Brain pathology, 9(2), 241-245.

Pharoah, P. D., Dunning, A. M., Ponder, B. A., & Easton, D. F. (2004). Association studies for finding cancer-susceptibility genetic variants. Nature Reviews Cancer, 4(11), 850-860.

Pons, F., Varela, M., & Llovet, J. M. (2005). Staging systems in hepatocellular carcinoma. Hpb, 7(1), 35-41.

Poon, D., Anderson, B. O., Chen, L. T., Tanaka, K., Lau, W. Y., Van Cutsem, E., ... & Koo, W. H. (2009). Management of hepatocellular carcinoma in Asia: consensus statement from the Asian Oncology Summit 2009. The lancet oncology, 10(11), 1111-1118.

Povey, A. C., Hall, C. N., Badawi, A. F., Cooper, D. P., & O'Connor, P. J. (2000). Elevated levels of the pro-carcinogenic adduct, O 6-methylguanine, in normal DNA from the cancer prone regions of the large bowel. Gut, 47(3), 362-365.

Reid-Lombardo, K. M., Fridley, B. L., Bamlet, W. R., Cunningham, J. M., Sarr, M. G., & Petersen, G. M. (2011). Inflammation-related gene variants as risk factors for pancreatic cancer. Cancer epidemiology, biomarkers & prevention, 20(6), 1251-1254.

Rhiem, K., & Schmutzler, R. K. (2015). Risk factors and prevention of breast cancer. Der Onkologe, 21, 202-210.

Sasaki, M., Knobbe, C. B., Itsumi, M., Elia, A. J., Harris, I. S., Chio, I. I. C., ... & Mak, T. W. (2012). D-2-hydroxyglutarate produced by mutant IDH1 perturbs collagen maturation and basement membrane function. Genes & development, 26(18), 2038-2049.

Sasaki, M., Knobbe, C. B., Munger, J. C., Lind, E. F., Brenner, D., Brüstle, A., ... & Mak, T. W. (2012). IDH1 (R132H) mutation increases murine haematopoietic progenitors and alters epigenetics. Nature, 488(7413), 656-659.

Scherer, H. J. (1940). Cerebral astrocytomas and their derivatives. The American Journal of Cancer, 40(2), 159-198.

Shah, R. B., Montgomery, J. S., Montie, J. E., & Kunju, L. P. (2013, November). Variant (divergent) histologic differentiation in urothelial carcinoma is under-recognized in community practice: impact of

mandatory central pathology review at a large referral hospital. In Urologic Oncology: Seminars and Original Investigations (Vol. 31, No. 8, pp. 1650-1655). Elsevier.

Skinnider, B. F., & Mak, T. W. (2002). The role of cytokines in classical Hodgkin lymphoma. Blood, The Journal of the American Society of Hematology, 99(12), 4283-4297.

Soussi, T. (2000). p53 Antibodies in the sera of patients with various types of cancer: a review. Cancer research, 60(7), 1777-1788.

Stintzing, S. (2014). Management of colorectal cancer. F1000prime reports, 6.

Sun, Y. S., Zhao, Z., Yang, Z. N., Xu, F., Lu, H. J., Zhu, Z. Y., ... & Zhu, H. P. (2017). Risk factors and preventions of breast cancer. International journal of biological sciences, 13(11), 1387.

Terabe, M., & Berzofsky, J. A. (2004). Immunoregulatory T cells in tumor immunity. Current opinion in immunology, 16(2), 157-162.

Travis, W. D., Brambilla, E., & Riely, G. J. (2013). New pathologic classification of lung cancer: relevance for clinical practice and clinical trials. J Clin Oncol, 31(8), 992-1001.

Valenti, G., Quinn, H. M., Heynen, G. J., Lan, L., Holland, J. D., Vogel, R., ... & Birchmeier, W. (2017). Cancer stem cells regulate cancer-associated fibroblasts via activation of hedgehog signaling in mammary gland tumors. Cancer research, 77(8), 2134-2147.

Van der Pouw Kraan, T. C., Snijders, A., Boeije, L. C., de Groot, E. R., Alewijnse, A. E., Leurs, R., & Aarden, L. A. (1998). Histamine inhibits the production of interleukin-12 through interaction with H2 receptors. The Journal of clinical investigation, 102(10), 1866-1873.

Vignal, A., Milan, D., SanCristobal, M., & Eggen, A. (2002). A review on SNP and other types of molecular markers and their use in animal genetics. Genetics selection evolution, 34(3), 275-305.

Watanabe, K., Tachibana, O., Sato, K., Yonekawa, Y., Kleihues, P., & Ohgaki, H. (1996). Overexpression of the EGF receptor and p53 mutations are mutually exclusive in the evolution of primary and secondary glioblastomas. Brain pathology, 6(3), 217-223.

Weinberg, R. A. (1996). How cancer arises. Scientific American, 275(3), 62-70.

Wu, J. J., Li, W., Shao, Y., Avey, D., Fu, B., Gillen, J., ... & Zhu, F. (2015). Inhibition of cGAS DNA sensing by a herpesvirus virion protein. Cell host & microbe, 18(3), 333-344.

Ye, J., Xu, M., Tian, X., Cai, S., & Zeng, S. (2019). Research advances in the detection of miRNA. Journal of pharmaceutical analysis, 9(4), 217-226.

Zhang, M., Lee, A. V., & Rosen, J. M. (2017). The cellular origin and evolution of breast cancer. Cold Spring Harbor perspectives in medicine, 7(3), a027128.

Zhu, Q. G., Zhang, S. M., Ding, X. X., He, B., & Zhang, H. Q. (2017). Driver genes in non-small cell lung cancer: characteristics, detection methods, and targeted therapies. Oncotarget, 8(34), 57680.