CAPITAL UNIVERSITY OF SCIENCE AND TECHNOLOGY, ISLAMABAD

Association Between IL-17A Polymorphisms (rs2275913 and rs3748067) and Cancer Risk in Asian Population: A Meta Analysis

by

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This thesis is dedicate to my parents, family and friends who is always support, encouragement, and constant love have sustained me throughout my life. I would like to dedicate this thesis to my supervisor Dr. Shaukat Iqbal.

CERTIFICATE OF APPROVAL

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Abstract

Single nucleotide polymorphism (SNP) in IL-17A might be associated with cancer risk. The aim of this study was to analyze the associations between the IL-17A rs2275913 and rs3748067 polymorphisms and the risk of cancer disease in Asian population by meta-analysis. Relevant articles were selected from electronic database Google Scholar, PUBMED, EMBAS, Web of science, Elsevier science direct, Springer and Wiley online library. Papers based on case-control studied in Asian population that meet inclusion criteria were selected. Odd ratio's with 95% CIs used for analysis of polymorphisms association with cancer. Software used to performed meta-analysis was Review Manager 5.4 (latest version 2020). Nineteen studies (19 for rs2275913 & 10 for rs3748067) involving 5,325 cases and 6,589 healthy controls for SNP rs2275913 and 3,227 cases and 4,247 healthy controls for SNP rs3748067 were selected. Both IL-17A polymorphisms showed different analysis results. Pooled OR with 95% CI indicated that the rs2275913 was associated with increased cancer risk under dominant model (OR =1.34, 95% CI =1.17-1.54, P<0.0001), homogeneous model (OR =1.71, 95% CI =1.44-2.03, P<0.00001), heterogeneous model (OR =1.29, 95% CI =1.19-1.39, P<0.00001) and allelic model (OR =1.31, 95% CI =1.24-1.39, P<0.00001), while recessive model (GG+AG vs AA; OR =0.67, 95% CI =0.60-0.74, P<0.00001) found to be associated with decreased risk of cancer. However, no significant relation was observed in the analysis of the rs3748067 with the risk of cancer. Almost same results were observed during cancer subgroup analysis for both polymorphisms. This meta-analysis concluded that IL-17A polymorphism rs2275913 is significantly associated with cancer and may increase or decrease risk of cancer in Asian population.

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Abbreviations

CC	Cervical Cancer
CI	Confidence Interval
CRC	Colorectal Cancer
DNA	Deoxyribonucleic Acid
GC	Gastric Cancer
IL	Interleukin
ILR	Interleukin Receptors
INF	Interferon
MDSC	Myeloid-Derived Suppressor Cells
NF-κB	Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B Cells
OR	Odd Ratio
SNP	Single Nucleotide Polymorphism
Thc	T Helper Cells
TLR	Toll-Like Receptors
TNF	Tumour Necrosis Factor
TRAIL	TNF-Related Apoptosis-Inducing Ligand
VEGF	Vascular Endothelial Growth Factor

Chapter 1

Introduction

1.1 Background

Cancer/carcinoma includes a number of diseases that can occur in any body part. Abnormal growth occurs that spread to surrounding parts and affect other cells. This uncontrolled growth known as metastasis that leads to death. A neoplasm and malignant tumour terms also used for cancer [1]. Asia accounts for about 60% of the global population and about 50% of the global burden of cancer. Cancer cases incidence is estimated to be increase from 6.1 million (2008) to 10.6 million (2030) due to various factors such as population growth, aging, lifestyle and some environmental changes. Dietary patterns, habits, sociocultural practices, human development index and variations in ethnicity in different regions affect the number and pattern of cases. Certain measures such as early diagnosis and main preventive measures contributed to considerable savings in treatment costs and better health outcomes [2]. Many cancer prevention measures have been developed in Asian regions. These preventive measures include development of national cancer registries, cancer screening planes, health behaviour improvement education schemes, elimination of infectious agent *Helicobacter pylori* and vaccination against hepatitis B and hepatitis C viruses. But, low and medium resources still need attention [3].

Cytokines are small proteins (5–20kDa) significant in cell signaling. Interleukins (IL) are a class of cytokines that played an essential role in defence system. Primarily interleukin stimulate growth, differentiation and activate immune cells during inflammation. Many proteins are crucial and performing their function by binding itself with the receptors presents on interleukin surface. Animal studies have been used to investigate interleukins aspects concerning to clinical medicine [4]. The role of immune system is largely dependent on interleukins and a number of them have been identified as an unusual deficiencies, all with autoimmune disorder or immune deficiencies. Some interleukins are synthesized by lymphocyte with the aid of CD4 T, as well as by leukocytes, phagocytes and endothelial cells and assist T and B Lymphocytes growth and differentiation of cells [5].

Interleukin 17 is a pro-inflammatory (cause inflammation) cytokine. This cytokine is generated by class of T cells Th17c (T helper 17 cells).T helper cell described by Rouvier et al in 1933. He isolated it from a rodent T-cell by using hybridoma technique [6]. IL-17 polypeptides encoded by IL-17A are building element of this cytokine family, and is highly homologous to viral protein [7]. Interleukin 17 is a biologically active component that interconnect with receptors present on its surface known as interleukin 17R. There are 3 variants of interleukin 17 receptors (IL-17RA, IL-17RB, IL-17RC) [8]. IL-17 initiate many signaling cascade when it binds with its receptors, which in turn contribute to chemokines induction. These chemokines act as chemoattractants inducing the immune cells at inflammation site. Usually these signaling pathway followed by a body when infected by micro-organism. IL-17 synergy with TNF (tumour necrosis factor) and IL-1 promote inflammation in infected individual [9, 10].

There are about 6 members in IL-17 family refereed as IL-17A-IL-17F. IL-17A-IL-17F all have homologous protein structure. Four cysteine residues present in IL-17 protein. These cysteine residues are conserved and have significant role in protein molecule shape. IL-17 members don't show sequence similarity with other interleukins but have homologous sequence among them. There is about 40-55% homology between IL-17F and Il-17A. While IL-17B have similarity with all of its family member except IL-17F. These cytokines sequence is highly conserved in

case of mammalians, such as mouse proteins have 62-88% similar sequence with that of human proteins [11]. In-spite of well known pro-inflammatory function, the main role of IL-17 and its family members in carcinoma not yet clear. While this cytokine show pro or anti-tumor effect[12].

It is still ambiguous that what is the primary role of IL-17A in development of tumour [13]. But recent evidences suggest that IL-17A have both inducing and suppressing affect on tumour growth. IL-17A start playing it's role right from the beginning of tumour development. IL-17A do so by combining two effects. First is releasing MDSCs (myeloid-derived suppressor cells) and the other is stimulation of pro-inflammatory cytokines. MDSCs decrease the immune system activities. Pro-inflammatory cytokines are stimulated systematically by NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) pathway and locally through CCL2 (chemokine ligand 2). Stimulation of these cytokines maintain inflammatory environment. As a result of combination of these two effects antiapoptic genes got expressed causing increase in survival of cell with protumorigenic potential [14].

Due to stimulation of MEK-ERK (mitogen-activated protein kinases, extra-cellular signal-regulated kinases) pathway tumour growth increase. MEK-ERK pathway stimulation is caused by IL-17A induced activation of NF-κB. In this way IL-17A further aid in tumour growth in certain cancer lymphocytes infiltration and microvascular densities got increase due to proangiogenesis effect of IL-17A. IL-17A induce this through expression of VEGF (vascular endothelial growth factor). An independent pathway of VEGF via NF-κB and MEK-12 signaling was also noted. This pathway through MDSCc abolish the response of immune system which was targeting cancer cells. During investigation of impact of IL-17 on tumour metastasis it become evident that through expression of VEGF, IL-17 enhance metastasis. Angiogenesis and lymphangeogenesis are induced by expression of VEGF resulting in metastasis of tumour. But, with decreased level of VEGF, an anti-angiogenesis was also found. Moreover, failure of chemotherapy was clearly linked with IL-17. Effects of anti-VEGF chemotherapy were regulated by tumour through expanded expression of G-CSF (Granulocyte-colony stimulating factor) and IL-17. Despite

this, a great suppression in tumour growth was observed when anti-VEGF therapy was used along with knocking out IL-17R [14].

To determine the association of genetic variants with different diseases or traits, association studies can be used significantly [15]. Genetic alteration such as the single nucleotide polymorphism (SNP) are a substitution of nucleotide sometimes very severe and change the normal structure and biological activities of gene encoded proteins. SNP can enhance or reduce the fabrication of relevant protein if occur in the gene region that initiate translation. Such type of inherited gene polymorphisms can make an individual more susceptible or resistant towards many diseases [16]. SNPs associated with a broad variety of human disorder such as tumor, infectious diseases, inflammatory, autoimmune and several other disorder and very significant as targets for pharmacogenomics therapy [17].

IL-17A SNPs (rs2275913 & rs3748067) association with different diseases previously studied that showed controversial results. Now a days many epidemiological studied were performed to find IL-17 (rs2275913 & rs3748067) SNPs association with different types of cancer such as Cervical [18-21], Gastric [22-28], Colorectal [29-31], Brest [32], Papillary thyroid [33], Bladder [34], Hepatocelluar carcinoma[35] and Laryngeal [36] cancer.

However, these findings are always remain inconsistent with previous articles. Because of sample size and ethnicity, individual study could not give precise result and fail to describe genetic relationship. To provide strong facts about effect of IL-17Ars2275913, rs3748067 polymorphisms on carcinoma, a meta-analysis performed by combining data from different paper.

1.2 Problem Statement

To find the association of interleukin 17A polymorphisms with cancer disease by meta analysis in Asian population.By knowing the genetic basis of cancer, it can

be possible to develop a better treatment by targeting the SNPs associated with cancer.

1.3 Aims and Objectives

The aim of study was to analyze the association between the genetic polymorphisms of interleukin-17A (IL-17A) and susceptibility to Cancer in Asian population. Objectives of current study were:

- To evaluate the IL-17A SNP (rs2275913) association with cancer by meta analysis of different case-control studies.
- To analyse the IL-17A SNP (rs3748067) association with cancer by meta analysis of different case-control studies.

Chapter 2

Literature Review

2.1 Introduction

Cancer/carcinoma includes a number of diseases that could occur in any part of the body. Abnormal growth occurs that spread to surrounding parts and affect other cells. This uncontrolled growth known as metastasis that leads to death. The other terms used for the cancer are neoplasm and malignant tumor [1]. Carcinoma is the second death causing disease, in 2018 it is estimated that about 9.5 million deaths occur due to cancer. Some cancers are common in men and some in women such as cervical, breast, colorectal and thyroid cancer are common in women while Hepatocellular carcinoma, lung cancer, colorectal cancer are common in man. With the passage of time cancer expand globally and increase physical, emotional and financial pressure on people, families, societies and health systems. Under-developed countries are facing problem to handle its burden because of least equipped medical system, there is difficult for large number of people to take access to reliable diagnostic and treatment approaches whereas in developed countries the medical system is strong, survival rates are high because of early stage detection and special cure availability [1]. Smoking is a risk of cancer and reason for more than 21% of cancer deaths [1]. About 10% die due to malnutrition, physical inactivity, excessive use of alcohol and obesity [1]. Other factors

include Infectious disease, exposure to dangerous radiation etc [37]. In the under developed countries infectious diseases are also major cause of cancer [1]. Cancer is epigenetic as well as it can assumed as a genetic disorder [38]. Nearly 5–10% of cancers are because of genetic defects that parents transfer to offspring [39]. Cancer might be diagnosed through screening tests [1] but medical imaging and biopsy require for investigation and confirmation of cancer [40]. Healthy lifestyle is affective to minimized cancer risk such as avoid smoking, acquiring a healthy weight, reduced or avoid alcohol consumption, eating healthy things and avoid rays from sun [41, 42]. First stage diagnosis of cervical and colorectal cancer by screening test is effective [43] while its use in breast cancer diagnosis are controversial [43, 44]. Radiation therapy, surgery, chemotherapy and targeted therapy are done during treatment individually or in combination depend on the cancer type or stage [3, 45]. At primary stage, its important how to handle sign and symptom and relax patient mentally and physically. People with advanced stage need palliative care [3].]. The survival rate is based on cancer and how the peoples are effected from it [42]. In the developed countries survival rate is about 80% of children if diagnosed under 15 [43].

2.2 Historical Background

Cancer has contentiously observed throughout the human history. Hippocrates described different forms of cancer, used the Greek word $\kappa\alpha\rho\kappa\zeta\nu o\varsigma$ (crab or crayfish) for cancer [46], the name given because of cut surface present on malignant cancer just like, the veins extended in all sides as the animal the crab has its feet [47]. According to Galen breast tumor taken its name from fanciful analogy to a crab provided by the lateral extensions of the cancer cell and the corresponding distended veins [48]. Celsus translated Greek word to Latin 'cancer' in between the period of 25 BC - 50AD the same meaning as the Greek word and suggested surgery for its treatment. Galen (2nd century AD) recommended purgatives instead of surgery for cancer treatment. These recommendations mainly remained for thousand years [46].

In the 15th, 16th and 17th centuries, doctors become allowed to find the reason behind the death by dissecting the dead body [49]. The main reason of breast cancer according to German professor Wilhelm Fabry, was clotted milk present in mammalian duct. Francois de la Boe Sylvius, hypothesized that all abnormalities was because of chemical reactions that leads to cancer. According to Nicolaes Tulp, cancer spreads same as poison and at the end became contagious [50]. In 1775 this statement further proceed by Percivall Pott that scrotum cancer common among chimney sweeps [51]. An English surgeon first one who described the cancer ability of metastasis (1871-1874) [52].

2.3 Epidemiology

Cancer is the major health issue and a reason of a large number of deaths Worldwide. According to a recent report on cancer incidence, there is more than 17 million new cases and 9.5 million deaths occur worldwide in 2018. The ratio of new cases and deaths due to cancer between males and females is different. Males are more susceptible than female [53]. Some tumors that are common, slowly progress and not fatal as other. In Asia and Europe, about 35% individual have not identified as cancer patients in their life. At the age of 80, 79% male found prostate cancer [54, 55]. Around 12.7 million cancers other than skin and non-invasive were identified. Lung, colorectal, liver, stomach and breast cancers were common in 2018 record. From this we can imagine that invasive cancer is a 1st reason of death in the underdeveloped countries and 2nd in developed countries [56].

In previous records more than 5 million peoples died because of cancer in 1990. This give an idea about cancer risk that going to increase with passage of time. The reason behind this may be changes in lifestyles [56, 57]. Robert A. Weinberg, commented on cancer that that "If we lived long enough, sooner or later we all would get cancer" [58]. In cancer risk factors age is very important for cancer growth and development. Although any individual acquire cancer because

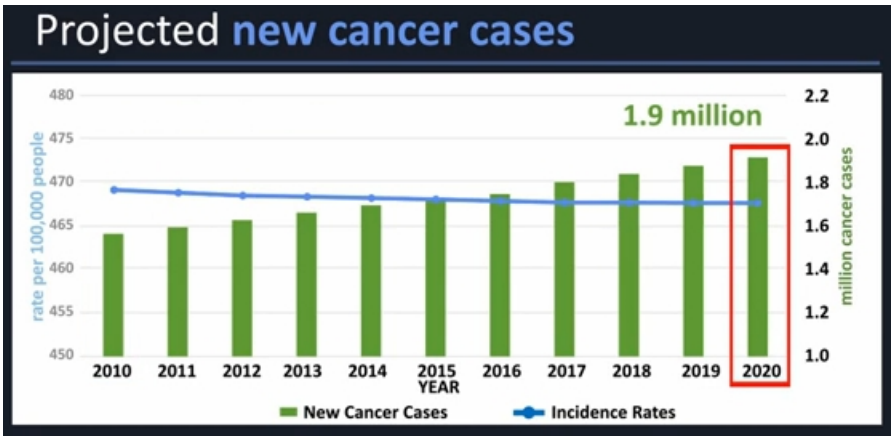


FIGURE 2.1: Projected Number of New Cancer Cases [77].

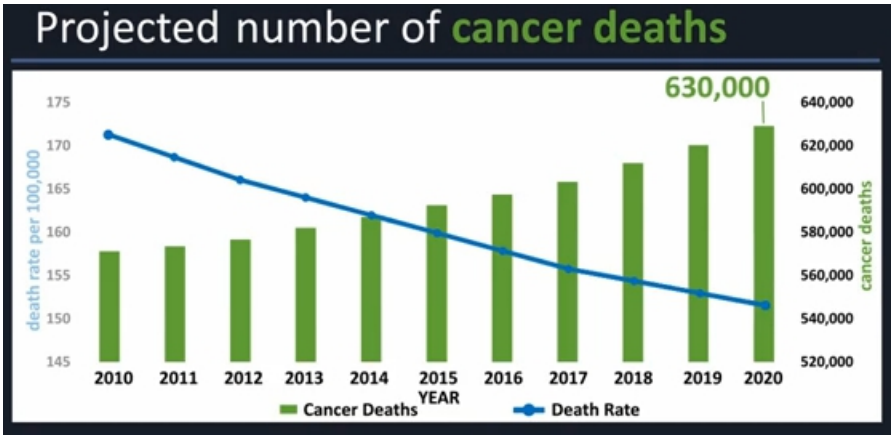


FIGURE 2.2: Projected Number of Cancer Deaths [77].

of genetic or environmental factors but, mostly patients are more than 60 [59]. Age susceptibility towards cancer is due to immune response against cancer [60]. DNA accumulated errors [61] and alteration due to age in the endocrine system [62] make individual more vulnerable towards cancer. Main complications in increasing risk related to age are DNA damage and inflammation [63]. Expected projected new cancer cases and deaths explained in figure (2.1 and 2.2) [64].

2.4 Cancer in Asian Countries

About 60% of the Global population account for Asia, that facing 50% global burden of cancer. It is estimated that rate of incidence of cancer increase from 6.1 million in 2008 to 10.6 million in 2030, because of lifestyle, socioeconomic change

and growing and ageing populations. In different regions the pattern and burden of cancer is due to variations in human development index, dietary pattern, ethnicity, habits and sociocultural practices. [2]. In typical economically developed Asian countries, the rate of incidences of prostate, colon and breast cancer are considerably increased, although incidence rates of breast and prostate cancer are lower compared to western countries, but are growing steadily. Infectious agent (*Helicobacter pylori*, palilloma virus, hepatitis B, hepatitis C) have great impact on this rate. Colorectal and breast cancer are common in Japanese and Korean population respectively. Excessive alcohol usage, exposure to toxic radiation, air pollutants are the risk factor for lung cancer, while risk of breast and colorectal cancer associated with the reproductive factors including; late marriage, menstruation problem, abortion pill intake, and short duration lactation [3].

In Asian region the cancer has clearly become raising health threat and must implemented cancer control programs actively and evaluated in this region. Many cancer prevention measures have been developed in Asian regions. These preventive measures include development of national cancer registries, cancer screening planes, health behavior improvement education schemes, elimination of infectious agent *Helicobacter pylori* and vaccination against hepatitis B and hepatitis C viruses. But, low and medium resources still need attention [3].

2.5 Sign & Symptoms

At the beginning, symptoms of cancer are less but after some time it show symptoms. Overall, sign and symptom depends on the cancer and the site of infection. It is not easy to detect and identify cancer, So it can be referred a “great imitator” [65].

Cancer do not show symptoms at start, with the passage of time cell abnormally grow and manifestation regarding cancer start to appear. Cancer types have some specific sign and symptoms but general symptoms normally appear in peoples who have not disease or affected by any other reason. It is difficult to detect

cancer because it mimics with other diseases. While diagnosis leads to anxiety and depression and people become hopeless [66].

2.5.1 Local Symptoms

Local symptoms arise because of mass of cancer cell or its pustule. In lung cancer abnormal growth obstruct the bronchus and cause pneumonia or wheeze. Esophageal stricture make swallowing uncomfortable resulting in esophageal cancer, and colorectal cancer because of obstruction of intestine that affect bowel behavior. Clumps in breasts or gonads may form detectable lumps. Wounds result is hemorrhage that show the symptoms of cancer, such as anemia (colon cancer), bleeding in cough (GC), in urine (BLC), and unusual vaginal bleeding (CC). At beginning cancer is painless but it is very painful at its developed stage [65].

2.5.2 Systemic Symptoms

When a body react under the influence of cancer result in systemic symptoms. These are tiredness, accidental weight loss, other body changes [40]. Some cancers can cause systematic inflammation that result cachexia [67]. Some tumor such as hepatocelluar carcinoma, Hodgkin disease, and leukemias can cause a prolonged illness [65].

Symptoms may be appear due to hormonal changes induced by cancer, called paraneoplastic syndromes that involve hypercalcemia [68].

2.5.3 Metastasis

Cancer may proliferate from its original location to distant location, phenomena known as metastasis. This happen through surrounding or lymphatic spread, through blood or fluid. Metastasis via blood, spread throughout the body but

based on the form of cancer it proliferates to limited area. Metastatic symptoms based on the site of cancer and include swollen lymph glands, hepatic failure, or splenomegaly, injured bone pain, neurological symptoms [65].

2.6 Pathophysiology

2.6.1 Genetics

Cancer is basically a disease of uncontrolled cell division. When genes that control cell development and differentiation undergoes mutation results in conversion of a normal cell to a cancerous cell [69]. Oncogenes and tumor suppressor genes are very important genes in cancer. Oncogenes are genes that have potential to cause cancer and stimulate cell growth and replication and genes that slow down division and cause apoptosis are tumor suppressor gene. Tumorigenesis may cause by production of novel oncogenes that may show different expression than normal one and disturb the activities and production of tumor related genes [70].

Oncogenesis is a multi-step activity that may also needed collaboration of cellular oncogenes. Normal growth is related to proto-oncogenes expression, while because of gene alteration, reshuffling, amplification and other actions may result change or over expression of oncogene related to tumor growth. Evolution of oncogenes and their derivatives in molecular biology is expected to leads advancement in tumor diagnosis and therapy [69]. Environmental condition also leads to the more likely production and spread of mutation. Repeated physical injury, heat, toxic radiation or hypoxia may be caused by the carcinogens which are disruptive substances [71].

2.6.2 Epigenetics

Both genetic and epigenetic events control cancer initiation and its progression. The complexity of carcinogenesis does not depend on genetic mutation; it also comes with epigenetic changes. Epigenetic mechanisms are not generation bound

means that these have ability to pass from generation to generation, moreover include modification in DNA methylation, histone alteration and small noncoding micro Ribonucleic acid alteration.

Disturbance of epigenetic processes may become a reason of altered gene production and malignant cellular neoplastic growth, and they are broadly described as crucial players in tumor progression. Recent studies which focus on these points in epigenetics offer a complete perception of the basic pathways of carcinogenesis and provide in depth information and comprehensive knowledge for development of putative cancer bio markers for first stage diagnosis, monitoring of cancer, prognosis, and risk estimation [72].

Epigenetic modification often occurs in cancers for example, one study identified polypeptide coding genes that were commonly changed during methylation in relation to colon cancer. There are two types of genes that is known as hyper-methylated and hypo-methylated genes. Out of 147 hyper-methylated genes, 10 were important in hundred percent of intestine cancers and other that are more than 100 were important in more than fifty percent of intestine cancers [73-74]. DNA modification may also lead to cancer that found in gene repair mechanism of DNA. These changes might be occurring early in development to tumor and are most probably leads to genomic variability of cancers (Figure: 2.3) [75-77].

An inherited mutation enhances the tumor risk by decreasing the expression of deficient DNA repair proteins. There are about 34 DNA repairing genes, p53 and some others are playing crucial role and mutation in these gene may lead to cancer [78]. Only about 1 percent of cancers are known to be caused by germ line DNA repair mutations [79]. Cancers is not caused by a single source often but is actually a disease which results by a confluence of mutations and some leads to confer a selective advantage resulting clonal expansion. In colon and breast tumor, there are about 60-70 protein altering mutation, out of these 3 to 4 act as a driver while others behaving as passengers [80].

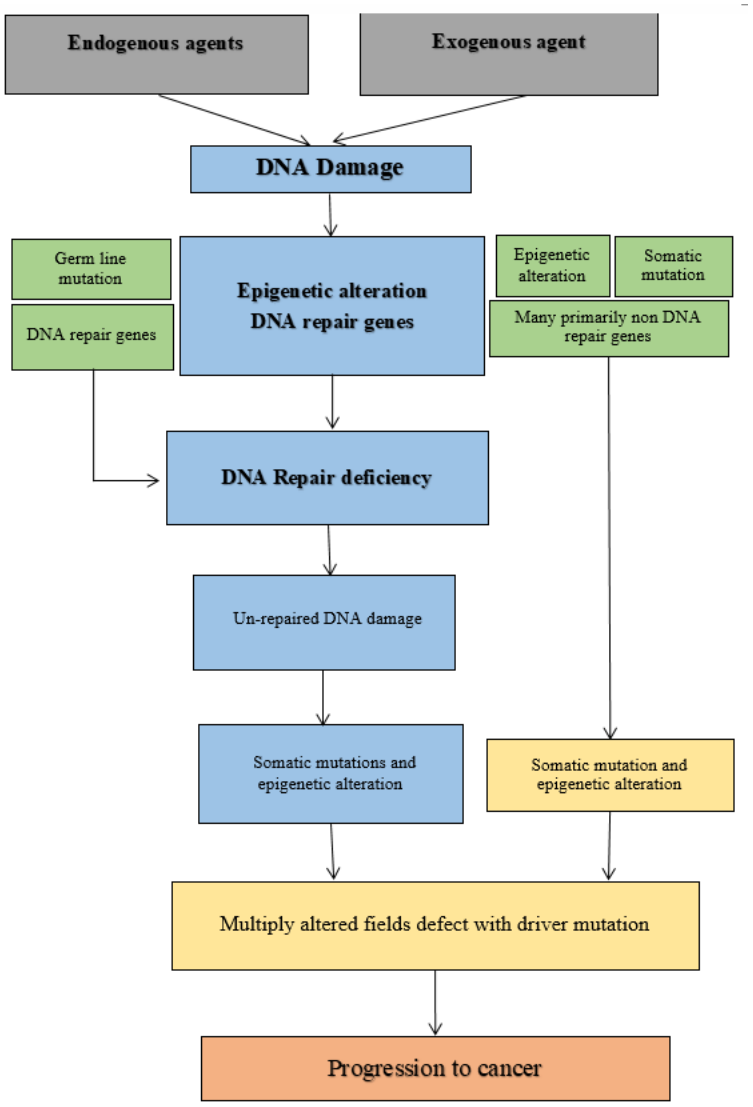


FIGURE 2.3: The Central Role of DNA Damage and Epigenetic Defects in DNA Repair Genes in Cancer Progression.

2.7 Cytokine and Cancer

Cytokines are protein having small size produced by cell and play important role in the activity of cell. These proteins cannot pass the cell lipid bilayer and enter to cytoplasm. Cytokines proteins include interleukins, TNF and chemokines. Cytokines have key effects on tumorigenesis and play both pro-tumor and anti-tumor effects, such as stimulate the immune effector mechanism that control development of tumor but at the same time support invasion and spread of cancer. In response to molecules that tumor cell produced Immune cells secreted cytokine. Along with these, malignant cells are also known to secrete proteins in identical

situation. A cytokine response that produced in site of tumor is judged with the help of arrangement of existing cytokines and their concentrations level [81]. Cytokines have also found a beneficial space in the field of carcinogenesis as many of them can be used for treatment of cancer in human beings explained in (Table 2.1) [81].

TABLE 2.1: Cytokines Application in Tumorigenesis.

Cytokine	**Clinical application/cancer**
IL-2	Melanocarcinoma, With peptide vaccine for melanoma, Plus adoptive cell transfer
TNF-a	CRC, ocular melanocarcinoma
IL-12	With peptide vaccine for melanocarcinoma
Flt3L	Colon, melanocarcinoma
FN-a	Melanoma 16, Hairy cell leukemia

2.7.1 Cytokine-Mediated Link Between Innate Immune System and Cancer

Infection and inflammation play significant role in tumor progression. For tumor growth process, inflammation provide favorable environmental condition and became a crucial participant. Cytokines that are generated by the animated innate immune cells enhance tumor development and progression. Moreover, tumor development further stimulated when inflammatory cells got activated and recruited by soluble mediators which are produced by cancer cells. But on the other hand, tumor growth can be decreased by cytokines produced by inflammatory cells [82].

Cytokines that are produced in response to tumor growth have pro-tumor or anti-tumor activity. Tumour necrosis factors α, Interleukin 6 and 17, are inflammatory mediators and play important role that leads to inhibition of immune response against cancer and enhance it's development, leading to eradication of anti-cancer activity and increase it's growth. Similarly, on the other hand there are some

mediators which can lead to suppression of tumor. These are TRAIL (TNF-related apoptosis-inducing ligand), IL-10, IL-12, and NK cells. TRAIL suppress tumor activity by causing programmed cell death of cancer cells, IL-10 by producing anti-inflammatory effect and IL-12 by cytotoxic mediators and by activation of cytotoxic T lymphocytes and natural killer cells. Besides these cytokines, there are some that show dual character in cancer development process like, TGF-β, IL-23 explain their dual roles (Figure: 2.4) [82].

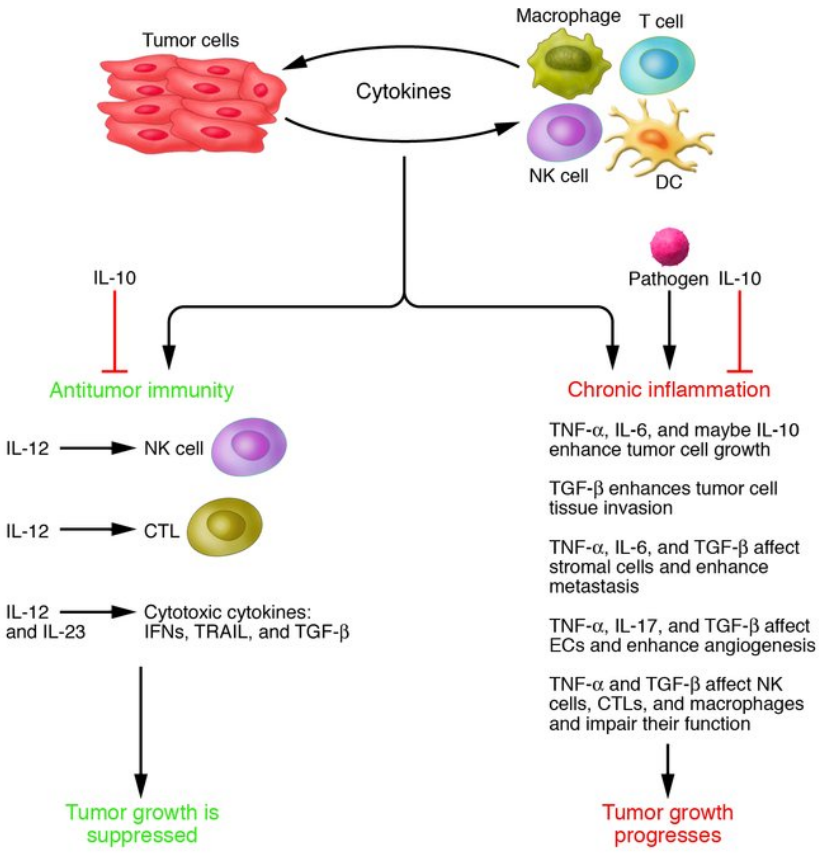


FIGURE 2.4: The Figure Present Two Consequences of Interactions Between Tumor Cells and Infiltrating Inflammatory and/or Immune Cells in the Tumor Micro Environment [82].

Tumor growth can increase by activation of TLR signaling by different mechanism. In a mouse model of transplanted metastatic cancers, intraperitoneal injection of bacterial Lipopolysaccharide (LPS) caused TLR4 activation which in turn stimulated the development of lung metastases [83-85]. Inflammatory cytokines, that are produced in response to TLR4 activation effected tumor growth. In this mouse model, host produced TNF-α by animation of NF-κB in the tumor cells found to

be main factor that cause increase in growth of lung metastasis [85]. But beside this, IFNs, cytokines were also produced that have anti-tumor effects. In this particular case, a TNF super family member named TRAIL was produced. Its production found to be caused by IFNs [85]. Although TRAIL cause tumor cell death [86], but in this transplanted metastatic cancer mouse, only after inhibition of NF-κB activity in the tumor cells, its tumoricidal activity was evident [85]. It can be inferred from these findings that different cytokines of opposite activities can be produced as a result of innate immunity activation (Figure: 2.5). Survival and development of tumor cells enhanced by TNF-α and tumor suppression due to cell death of tumor that is induced by TRAIL. However, balance shifted from activation of tumour development by TNF-α to tumor cell death by TRAIL is only due to inhibition of NF-κB activation in the tumor cells [85]. The signaling pathways (Fig:2.5) shown the immune response (positive/negative) on tumor cells [82].

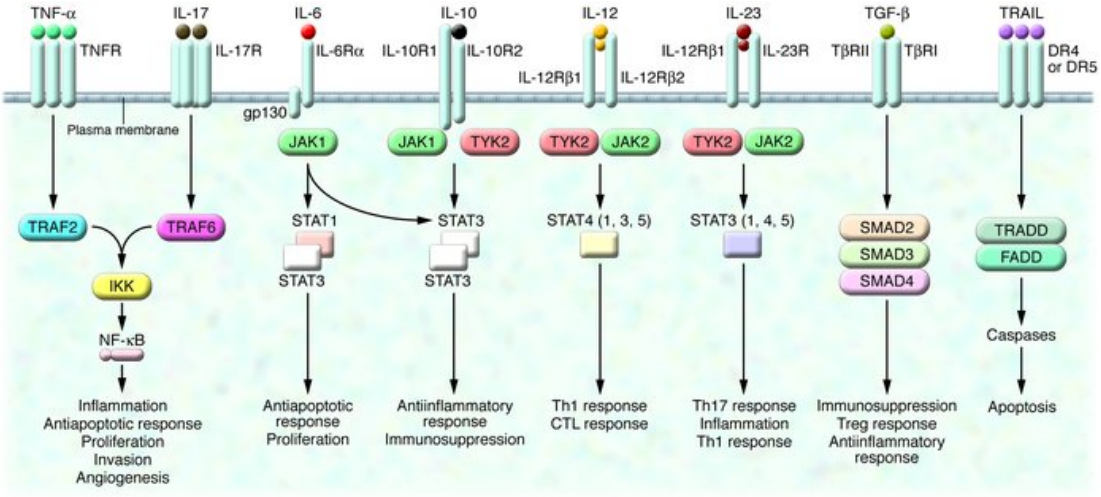


FIGURE 2.5: Signal Transmission Pathways and Cytokine-Mediated Link Between Inflammation and Cancer [82].

2.8 Interleukin 17 Biology

Interleukin 17 is actually a pro-inflammatory cytokine that secreted by T helper 17cells. Th17c first described by Rouvier et al in 1933, isolated during rodent

T-cell hybridoma [6]. IL17 protein encoded by IL-17A have similarity with a viral protein [7].

IL-17 the biologically active component that interconnect with receptors present on its surface known as interleukin 17R. There are 3 variants of interleukin 17 receptors (IL-17RA, IL-17RB, IL-17RC) [8]. IL-17 initiate many signaling cascade when it binds with its receptors, which in turn contribute to chemokines induction. These chemokines act as chemoattractants inducing the immune cells at inflammation site. Usually these signaling pathway of a body when infected by micro-organism, IL-17 function in combination with tumor necrosis factor (TNF) and IL-1 in promoting the inflammation [9, 10].

There are six members in IL-17 family such as interleukin (17A, 17B, 17C, 17D, 17E, 17F) IL17A-IL17F (Table 2.2). IL-25 also referred as IL-17E. In IL-17A-IL-17F all have similar protein structure. Four cysteine residues present in protein, these cysteine residues are conserved and have significant role in protein molecule shape. IL-17 members don't show sequence similarity with other interleukins but have homologous sequence among them.

There is about 40-55% similarity between IL-17F and IL-17A.While IL-17B have homology with all of its family member except IL-17F. These cytokines sequence is highly conserved in case of mammalians, such as mouse proteins have 62-88% similar sequence with that of human proteins [11].

Table 2.2: Overview of the Human IL-17 Family of Cytokines [8].

IL-17 Subtype	**Size (kDA)**	**AminoAcid (aa) Numbers (length)**	**Chromosomal site**	**Homology**
A	35	155	6p12	62
B	41	180	5q32-34	88
C	40	197	16q24	83
D	52	202	13q12.11	78
E	34	161	14q11.2	81
F	44	153	6p12	77

2.9 Interleukin 17A Structure and Protein

There are three exons in Interleukin 17A gene having 4252 base-pairs. The IL17A gene length is about 4252 bp, consisting of three exons. The transcript has 5 prime untranslated regions (UTR)1859 base-pairs and 3 prime untranslated region 1346 bp. Over the genome there is no pseudogenes homologous to IL-17A gene present (Figure 2.4) [87].

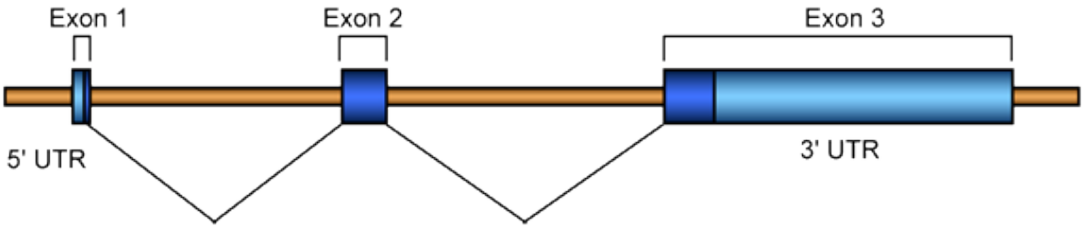


FIGURE 2.6: IL17A Gene Structure [98].

The IL17A protein is a glycoprotein that make a disulfide-linked homodimer or a heterodimer to the protein of IL17F (Figure 2.5). All IL-17 family members (IL17A-F) protein have four very conserved cysteine residues on all monomer [11, 88].

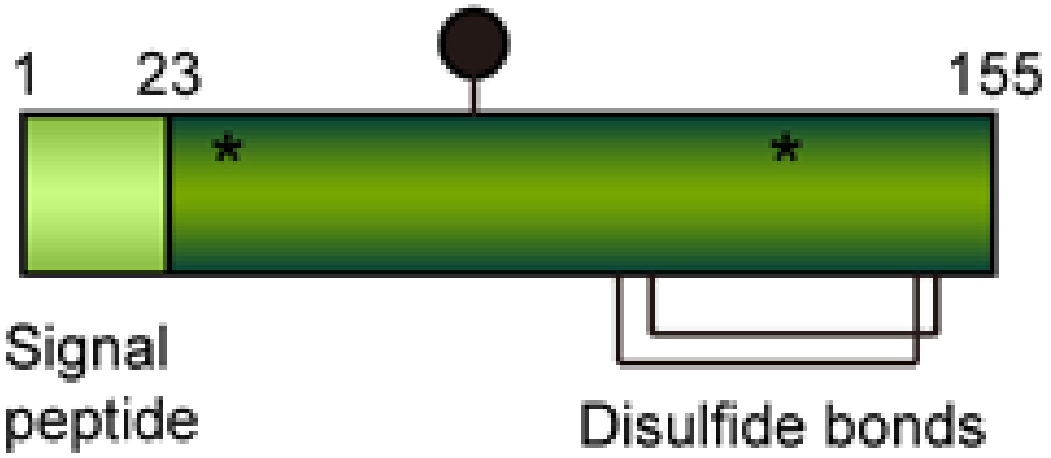


FIGURE 2.7: Interleukin 17A Protein Structure [87].

Structural examination of the IL-17A protein showed that these four cysteine residues contribute in the generation of characteristic cysteine-knot [89], but one

of the canonical disulfides of the cysteine-knot is absent from the IL-17 protein family [90]. Cysteine residues help in homodimer formation.

2.10 IL-17 Role in Cancer/Tumor

2.10.1 Tumorigenesis

Interleukin 17 start to playing its role from the early stage of tumorigenesis. Tumor growth increase due to IL-17 involvement within micro environment of affected cell. [91]. Its role as protumour was emphasized in its effective association with increased tumors malignancy [92]. This may be because of huge accumulation of IL-17 releasing Foxp3+ cells bearing both regulation of T-cell function and proinflammation function in the tumor microenvironment [93]. It is done through blocking the entry of MDSCs and cytotoxic CD8 T cells, that contributed to change the local environment and then reduces the immune response towards tumor cells [94]. After the entry of MDSCs in the environment, they respond to the release of heat shock protein (HSP) 72 on exosomes, that comes from tumor cells and also mediate the immune dampening effects of MDSCs. Because of the greater entry and preceding functions of MDSCs, it results in less survival in the renal cell carcinoma [93, 95].

As a result, increase in IL-17 can stimulate the secretion of pro-inflammatory cytokine IL-6 which result in STAT3 (Signal Transducer and Activator) [96]. Production of proinflammatory cytokines is interlinked with NF-κB pathway activation which in turn associated with STAT3 activation [97, 98]. IL-17, however, has been also shown to activate NF-κB in combination with TNF-via the IL-17B receptor [99, 100]. Entry of IL-17 is endorsed by CCL2 (chemokine ligand 2) which express monocytes.

These monocytes make their contribution in local inflammatory reaction. In these reactions tumor cells can maintain the local inflammatory response [101]. In

prostate cancer cells, it is assumed that maintainense of pro-inflammatory reactions and continuation of tumor growth stimulation are controlled by tumors ability [102].

2.10.2 Tumor Proliferation

Along with setting environment for tumor formation and forming base for tumor; IL-17 also causes growth of tumor cells. In rheumatoid arthritis, synovial cell proliferation (via mTOR pathway) occur due to involvement of NF-κB pathway in it [103]. To support this there is further evidence of association of IL-17 with increase proportion of myeloma cell which act on haematopoietic cells as a result myeloma cells spread significantly [104]. To summarize this IL-17 regulate the production of reactive oxygen species in human bone marrow-derived mesenchymal stem cells (hMSc). As a result MEK-ER pathway got activated which cause proliferation [105].

2.10.3 Tumor Immune-Resistance

2.10.3.1 Anti-tumor Effects

Antitumor response is initiated by the IL-17 and also reduces the size of the tumor, particularly when added via immunization. The immunization of Th17 cells into surrounding of cancer lead to stimulation of cytotoxic CD8+ T-cells was demonstrated [106]. The stimulation of this is connected with tumor shrinkage through IL-2 and major histocompatibility complex/peptide (pMHC)-I [107]. This allows local immunity to be activated via activation of anti-tumor T- cell response [108].

In an in vitro malignancy model in which malignant cells are inoculated in the mice, endogenous T cells are also effective against reduction of tumor size [109]. It is important to note, however, that non autologous TH17 and colon cancer cells

were used in both cases and that's why it may represent the clinical picture less accurately.

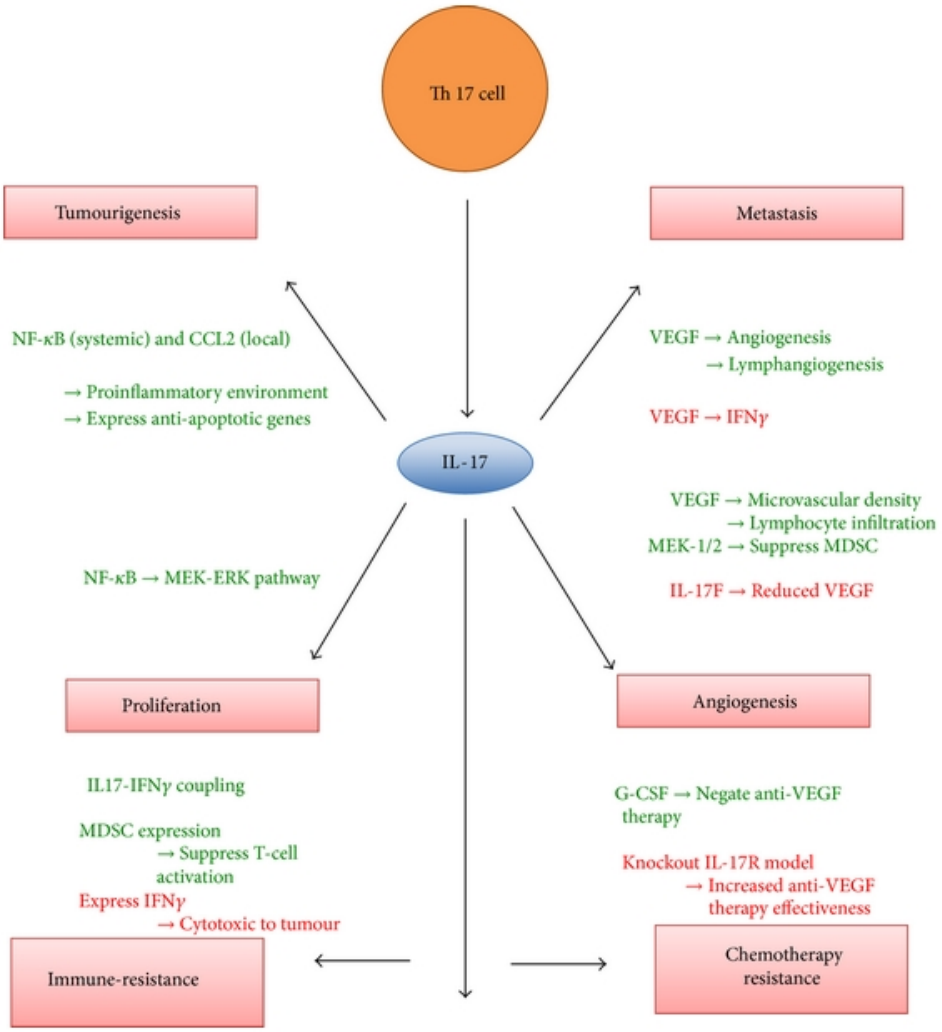


FIGURE 2.8: Pro-Tumor (Green) and Anti-Tumor (Red) Role of IL-17 [14].

2.10.3.2 Pro-tumor Effects

Cancer forbid the differentiation of immature myeloid derived cells into the mature myeloid derived cells, that results in amplification of MDSC population [110]. He et al. [104] reported that during the comparison of IL-17R knockouts with their wild type, IL-17 exhibit an important role in the synthesis of MDSCs. It has been reported that the functional IL-17 enhanced the synthesis of MDSCs but it reduces

the CD8+ T-cells, that lead to their finding of mediated growth of tumor [111]. It has been reported that the IL-17-IFN-coupling showed essential tumor promoting role in comparison to other researchers done on different cancers models [108, 112]. Increased amount of MDSCs that is related with the decreased activity of T-cell, lead to increased immunosuppressive activity of MDSCs [112]. Furthermore, the IL-17 is a key mediator in microenvironment of tumor that may contributed to promote the formation of tumor, angiogenesis and hence metastasis.

2.11 Interleukin 17A Association with Cancer Disease

IL-17 is a unique family of cytokine and have significant role in defense system. There are about 6 members in IL-17 family and 5 receptors that work in synergy [11, 113]. Interleukin-17 (IL-17) cytokine is a risk factor for number of diseases. It shows association with carcinoma as well. Published papers showed high IL-17 level in a large group of human malignant tumors [18].

2.11.1 Cervical Cancer (CC)

Cervical cancer (CC) is a serious health issue and cause great number of deaths in woman globally. IL-7A expression may increase the migration and invasiveness of cervical cancer cells through activation of signal pathway. Mutation in a single nucleotide can affect gene activity and expression of protein [21]. IL-17A polymorphism have affect on cervical cancer. In Quan, et all. Study, analyses showed the polymorphism of rs2275913 association with cervical cancer in Chinese population and shown that this may be a risk factor for CC [18].

2.11.2 Gastric Cancer (GC)

Gastric cancer is a well-known malignant tumors and cause a great number of deaths globally, especially in progressing countries [114]. The main cause of gastric cancer is Helicobacter pylori, and its infection is the main cause of GC and almost half of the population of world infected by H. pylori [115, 116]. In addition to H. pylori many environmental factor and lifestyle for example dehydrated food may be containing toxic substance, smoking, drinking alcohol and obesity also contribute to gastric cancer development [115]. Wang, et al. during case-control study examine that cancer cases in addition to H. pylori infection were cigarette smoker, alcohol consumption and also have cancer history. Cases with IL-17 (rs2275913) GA, AA genotype, and A allele were more susceptible to GC than the others [22]. However, Gao, et all. Study suggest that rs2275913 have no affect on GC [23]. While IL-17 SNP rs3748067 found associated with gastric cancer. However, Gao, et al. study has not found any association between rs3748067 polymorphisms and threat of developing GC [22, 23].

2.11.3 Breast Cancer (BC)

One of the notorious cancer from many types is breast cancer which is the most common and most threatening malignancy in females around the globe and its rate is still raising day by day, in both developed as well as in developing nations [121]. The etiology of breast cancer is very complex and to this date is not completely traced, but many modern studies have now paying attention on the participation of immunity as well as inflammation [122]. Previous study showed that SNPs in IL-17A showed association with breast cancer [32].

2.11.4 Colorectal Cancer (CRC)

Colorectal cancer (CRC) is the 3rd most common cancer sub-type globally [117], about 1.4 million cases with an alarming 694,000 deaths have been reported for

the year 2012 [118]. In Malaysia, it is at second position in all caner diseases to cause death. 63% of the patients diagnosed at Stages II and IV. The relationship between inflammation and cancers, including CRC, has been long described and chronic inflammation might be associated with the promotion of tumor growth, angiogenesis, and metastasis [84,119]. The molecular mechanisms by which chronic inflammation promotes cancer include increased expression of pro inflammatory cytokines, matrix metalloproteinases, cyclooxygenase 2 and transcription factors. Host genetic factors such as cytokine gene polymorphisms can also influence the inflammatory and immune responses resulting in differences in susceptibility to diseases [120]. In previous study by Samiei, et al. no relation was found between of IL-17A polymorphism and tumor [29]. Al Obeed, et al. Study showed that IL-17A G197A, which is actually a variant might be helpful to asses colorectal cancer risk [30].

2.11.5 Laryngeal Cancer (LC)

The other common type of cancer is the laryngeal cancer (LC) that falls in the category of respiratory cancer. Its number is second to lung cancer in affecting the individuals. With the passage of time, more cases of LC are reported globally and their raising number is due to consumption of alcohol as well as tobacco. Comparatively, men are more affected than women [123]. In patients, frequencies of IL-17A rs2275913 genotype as well as allele were prominently different in controls. In Chinese population, the rs2275913 IL-17A (197 G/A) showed association with the increase risk of laryngeal cancer and the AA and GA+AA genotypes are considered to be high risk for laryngeal cancer [36].

2.12 Meta-Analysis

A statistical analysis that perform to combines the previous published result to make accurate and authentic result known as meta-analysis. There are some

requirements that should take into account before performing meta-analysis. All the research papers that are used should discussed the same topic, with results from all included studies reporting that are supposed to have some degree of error. Then statistical approaches according to nature and requirements of study used to derive the outcome. Established meta-analysis methodologies provide a weighted average from the outcomes of the single studies, and what varies is the way in which these are distributed and also way in which the unpredictability is measured. In addition to providing us better understanding about a confusion, it has the potential to identify patterns among study results, cause of difference among those outcomes [124]. General framework of MetaLab (Figure 2.9).

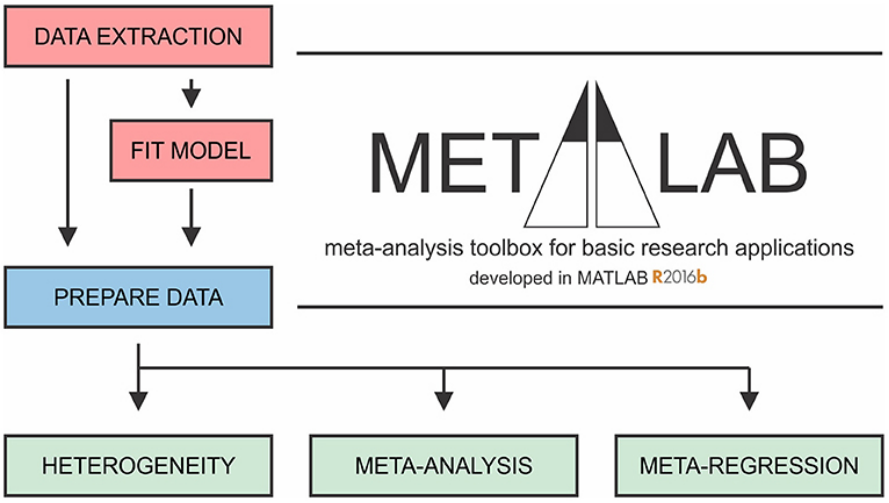


FIGURE 2.9: General Framework of MetaLab [125].

2.13 Application of Meta-Analysis in Modern Science

Application of Meta-analysis in modern science Individual study weakness can be minimized and corrected by statistical analysis of multiple studies. Other uses of meta-analytic are validation of clinical prediction models, and analyze the generalizability model [126, 127]. Meta-analysis may be carried out both for individual-subject design and for multiple-subject research design. This is significant because a lot of study has already been done on single/individual-subject

design. There is substantial debate about the most effective meta-analysis approach for individual-subject design. [128]. Meta-analysis leads to a shift of stress from single to multiple studies. It illustrates the functional value of the scale of the effect size rather than statistical relevance of individual approach. The outcomes of a meta-analysis are often expressed in a forest plot. Studies outcomes shared using various techniques, one of them that is used in meta-analysis is known as 'method'. Small sample studies that have more random variation given low weight than bigger one. Mantel–Haenszel is also a method used for result analysis [129]. MicroRNA techniques were used to classify deferentially expressed microRNAs in specific body part/cell. A meta-analysis was conducted to draw new hypothesis and verify the established findings [130].

Chapter 3

Material and Methods

3.1 Research Methodology

Overview of methodology adopted for project is summarized in figure 3.1 below.

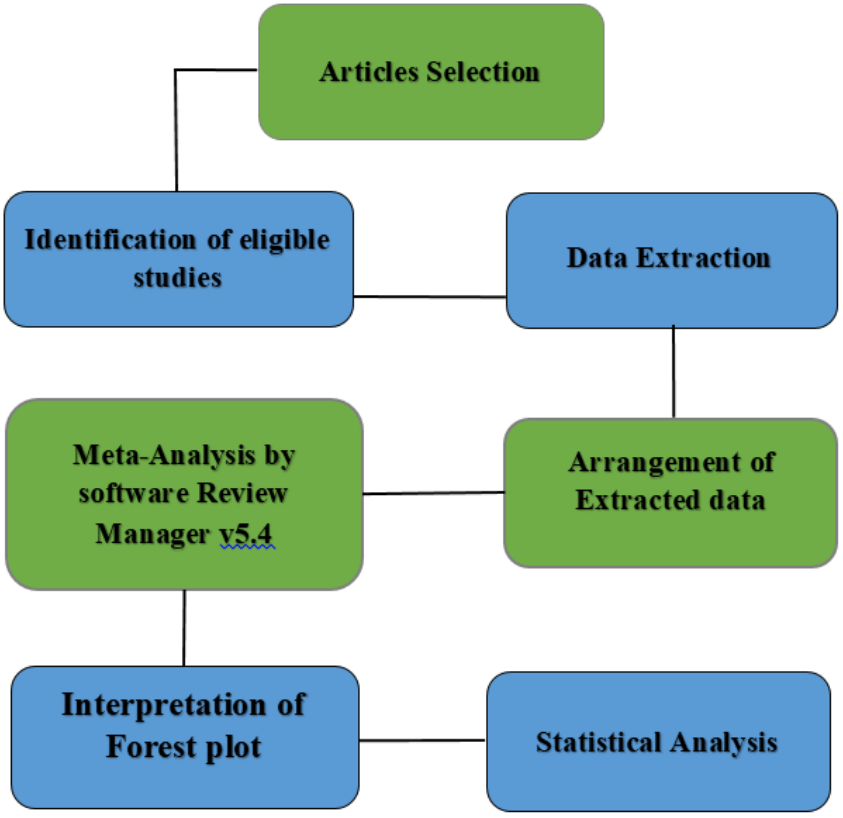


FIGURE 3.1: Methodology Overview.

3.2 Identification of Eligible Study

Literature search made by using different electronic database such as Google Scholar, PUBMED, EMBASE, Web of science, Elsevier science direct, Springer, Wiley online library. . Specified terms used during search included "Interleukin 17A" ,or "IL-17A" or "IL17A" or "SNP" or "single nucleotide polymorphism" or "tumour" or "cancer" or "carcinoma" or "case-control" as well as their combination. Search was limited to human beings. Selected articles published during period of March 2012 and October 2019. and examined carefully. There was no need of ethical approval.

3.3 Inclusion and Exclusion Criteria

3.3.1 Inclusion Criteria

First of all relevant articles titles and abstract were saved and reviewed. After that full text reviewed. Only those articles chosen that approached the following criteria:

1. Case-control study design
2. Researches that based on Asian population.
3. Study based on IL-17A SNP (rs2275913 & rs3748067) association or susceptibility to cancer
4. Cancer patient participated in case-control study must be diagnosed by specific test
5. The paper provided with the sufficient data to calculate odds ratio with 95% confidence intervals and P-value that could be used to infer the results
6. Publication language limited to English

3.3.2 Exclusion Criteria

The Exclusion criteria were:

1. Research articles other than case-control
2. Research articles that contain incomplete information
3. Review or only abstract
4. Unpublished data
5. Caucasian study

3.4 Data Extraction

We extracted the data separately by two authors with the help of data-collecting form in accordance with our inclusion criteria. The third author checked the original extracted data and if any discrepancy was found, it was solved by discussion among the three authors. Standard protocol was used to extract the data which meet our inclusion criteria and then save them into database. The data extracted from articles to perform meta analysis was as follows: first author, year of publication, ethnicity (Asian), population on which study was performed, cancer type, number of cases and control and particular SNP involved and allele & genotype distribution.

3.5 Statistical Analysis

Statistical analysis done with the aid of software Review Manager v5.4 (The latest version 2020 Cochrane Collaboration). The association between IL-17A SNPs and cancer was analyze by crude ORs with 95% CIs. The significance of the OR was determined using the Z-test ($P < 0.05$ was considered significant). Overall association of all genetic models (dominant, recessive, homogeneous, heterogeneous and

allelic) were calculated. First combined ORs calculated. ORs for dominant model (AA+AG vs GG), recessive model (BB vs. AA+AB), homogeneous comparison (AA vs GG), heterogeneous comparison (AG vs GG) and allele comparison (A vs G) in case of of rs2275913 and dominant model (TT+CT vs CC), recessive model (CC+CT vs TT), homogeneous model (TT vs CC), heterogeneous model (CT vs CC) and allelic model (T vs C) for rs3748067 were calculated.

The heterogeneity assumption was assessed by using the Chi-squared statistic test and the I-squared test. The heterogeneity between (25%-75%) was considered significant and below or above this range was not significant. Heterogeneity is the estimation of deviation between studies. I^2 is a most reliable test for heterogeneity. The Chi-square-based statistic was used to evaluate heterogeneity among the studies. On the basis of heterogeneity, the pooled ORs were estimated. If heterogeneity were more than fifty percent than random effect model used, if less than fifty percent than fixed effect model were used. To evaluate the multiple forms of cancer, subgroup analysis were conducted by cancer types and five different ORs also calculated for subgroup analysis separately.

Chapter 4

Result and Analysis

4.1 Study Characteristics

A total of 120 applicable articles were included according to selection criteria. The step by step selection procedure was shown in Figure 4.1. At the end we selected 19 studies with required data for further study.

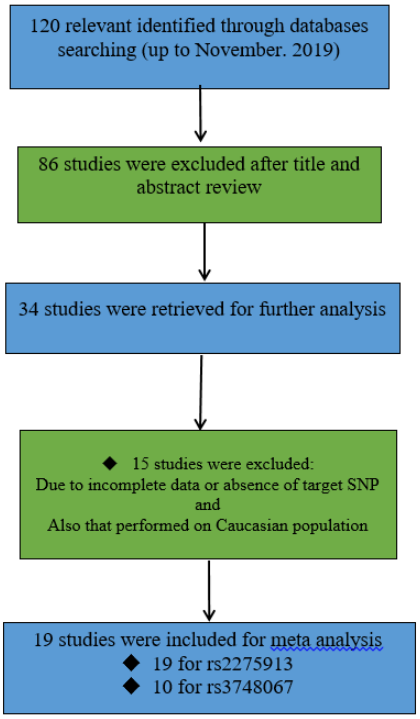


FIGURE 4.1: Flow Chart of the Selection Process.

After screening total 19 papers were included in current meta analysis. 5,325 cases 6,589 healthy controls involved. All papers were based on IL-17A (rs2275913) SNP association with cancer risk, of which four papers were involved in susceptibility of IL-17A with cervical cancer, seven papers were involved in susceptibility of IL-17A with gastric cancer while three papers involved association of IL-17 with colorectal cancer and remaining five paper related to other cancer. For IL-17A rs3748067 ten studies selected to find association of IL-17A rs3748067 C/T and cancer risk. Out of these ten, six studied related to gastric, three cervical cancer and one for laryngeal cancer. The included studies published during the period 2012 to 2019. The particular features of the selected studies are listed in Table 4.1 for rs2275913 and Table 4.2 for rs3748067 (see Table 4.1 & 4.2 for details).

TABLE 4.1: Studies Included in the Meta-Analyses of Association Between IL-17 (rs2275913) SNP and Cancer Risk.

Sr No.	**Authors**	**Population**	**Diseases**
1	Al Obeed,et al., 2018	Saudi Arabia	CRC
2	Feng, et al., 2019	Chinese	CRC
3	Gao, et al., 2015	Chinese	GC
4	Hou, et al., 2015	Chinese	GC
5	Lee, et al., 2015	Korea	PTC
6	Li, et ql., 2015	Chinese	CC
7	Lv, et al., 2015	Chinese	CC
8	Niu, et al., 2016	Chinese	CC
9	Qi, et al., 2016	Chinese	GC
10	Qinghai, et al., 2014	Chines	GC
11	Quan, et al., 2012	Chinese	CC
12	Samiei,et al., 2018	Malaysia	CRC
13	Si, et al., 2017	Chinese	LC
14	Wang, et al., 2012	Chinese Han	BC
15	Wang, et al., 2014	Chinese	GC
16	Xi, et al., 2015	Chinese	HCC
17	Yang, et al., 2016	Chinese Han	GC

18	Zhao, et al., 2016	Chinese	GC
19	Zhou, et al., 3013	Chinese Han	BLC

Sr No.	**Patient Number**	**GG**	**GA**	**AA**
1	117	60	40	17
2	352	160	154	37
3	572	239	250	83
4	326	121	149	56
5	94	28	42	24
6	216	91	94	31
7	264	110	117	37
8	185	95	60	30
9	252	100	110	42
10	239	126	122	45
11	311	93	76	142
12	70	10	33	27
13	325	121	148	56
14	491	165	234	92
15	462	160	211	91
16	155	38	71	46
17	386	200	128	58
18	153	51	76	26
19	301	79	154	68

Sr No.	**Control Number**	**GG**	**GA**	**AA**
1	100	70	23	7
2	433	231	169	31
3	572	260	241	72
4	326	161	136	29
5	260	76	137	47
6	432	222	171	38

7	264	139	105	20
8	370	202	117	51
9	252	122	105	25
10	550	273	216	61
11	463	168	80	215
12	80	27	41	12
13	325	155	146	24
14	502	198	245	58
15	462	214	190	58
16	171	35	90	46
17	374	203	123	48
18	207	95	94	18
19	446	164	204	78

Abbreviations: CRC: Colorectal Cancer; GC: Gastric Cancer; PTC: Papillary Thyroid Cancer; CC: Cervical Cancer; LC: Laryngeal Cancer; HCC: Hepatocellular Carcinoma; BC: Breast Cancer; BLC: Bladder Cancer.

As shown in Table 4.1, Nineteen studies reported association between IL-17A rs2275913 G/A and susceptibility to cancer. In order to find association, meta-analysis was done under five genetic models such as Dominant Model (AA+AG vs GG), Recessive Model (GG+AG vs AA), Homogeneous Model (AA vs GG), Heterogeneous Model (AG vs GG) and Allelic Model (A vs G).

4.2 Association Between IL-17A rs2275913 G/A Polymorphism and Cancer Risk

As shown in Table 4.1, Nineteen studies reported relation between IL-17A rs 2275913 G/A and susceptibility to cancer. To find association meta-analysis done for five genetic models; Dominant (AA+AG vs GG), Recessive (GG+AG vs AA),

Homogeneous (AA vs GG), Heterogeneous (AG vs GG) and Allelic (A vs G). Analysis results showed significant association between IL-17A (rs2275913G/A) polymorphism and cancer risk under the dominant model (AA+AG vs GG; OR =1.34, 95% CI =1.17-1.54, P<0.0001), homogeneous model (AA vs GG; OR =1.86, 95% CI =1.53-2.25, P<0.0001), heterogeneous model (AG vs GG; OR =1.29, 95% CI =1.19–1.39, P<0.00001) and allelic model (A vs G; OR =1.31, 95% CI =1.24–1.39, P<0.01). These all had significant P value and diamond favoured the cases. Recessive model (GG+AG vs AA; OR =0.67, 95% CI =0.60-0.74, P< 0.00001) also showed significant P value but diamond position in forest plot showed that this model favoured controls and this might be associated with reduced risk of cancer.

TABLE 4.2: Studies Included in the Meta-Analyses of Association Between IL-17A (rs3748067) and Cancer Risk.

Sr No.	**Authors**	**Population**	**Diseases**
1	Si, et al., 2017	Chinese	LC
2	Niu, et al., 2016	Chinese	CC
3	Qi, et al., 2016	Chinese	GC
4	Yang, et al., 2016	Chinese Han	GC
5	Gao, et al., 2015	Chinese	GC
6	Hou, et al., 2015	Chinese	GC
7	Li, et ql., 2015	Chinese	CC
8	Lv, et al., 2015	Chinese	CC
9	Qinghai, et al., 2014	Chines	GC
10	Wang, et al., 2014	Chinese	GC

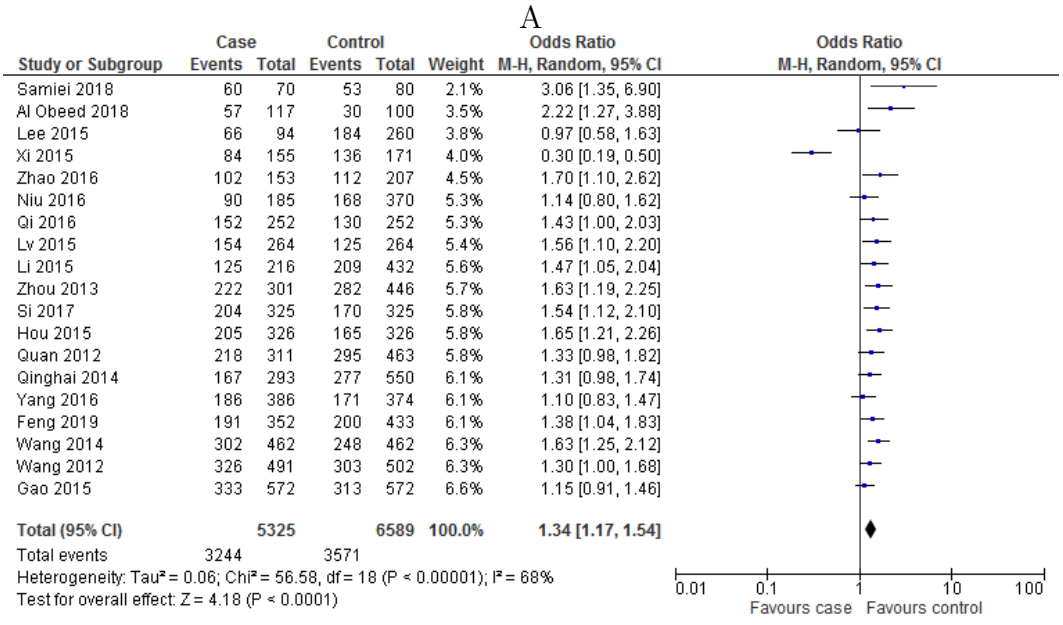
Sr No.	**Patient Number**	**CC**	**CT**	**TT**
1	325	19	33	273
2	185	145	23	17
3	252	16	25	211
4	386	308	52	26
5	572	42	70	460
6	326	18	34	274

7	216	83	95	38
8	264	196	53	15
9	239	220	25	48
10	462	39	138	285

Sr No.	**Control Number**	**CC**	**CT**	**TT**
1	325	9	31	285
2	370	332	42	6
3	252	9	22	221
4	374	323	45	6
5	572	47	66	458
6	326	10	30	286
7	432	179	188	65
8	264	209	48	7
9	550	466	51	33
10	462	19	118	325

Abbreviations: GC: Gastric Cancer; LC: Laryngeal Cancer; CC: Cervical Cancer; GC: Gastric Cancer.

A



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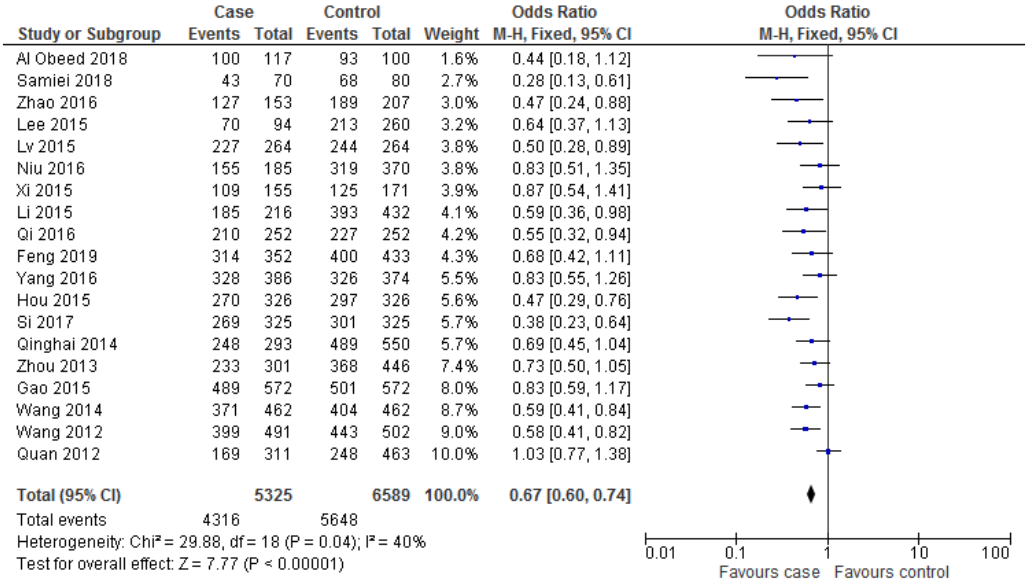
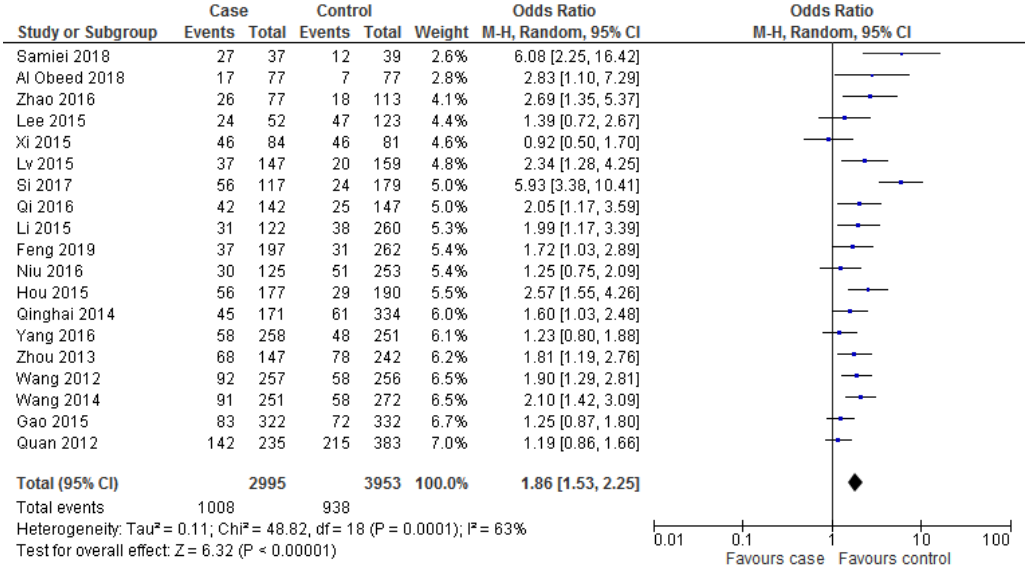


Study or Subgroup	Case Events	Case Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Al Obeed 2018	100	117	93	100	1.6%	0.44 [0.18, 1.12]
Samiei 2018	43	70	68	80	2.7%	0.28 [0.13, 0.61]
Zhao 2016	127	153	189	207	3.0%	0.47 [0.24, 0.88]
Lee 2015	70	94	213	260	3.2%	0.64 [0.37, 1.13]
Lv 2015	227	264	244	264	3.8%	0.50 [0.28, 0.89]
Niu 2016	155	185	319	370	3.8%	0.83 [0.51, 1.35]
Xi 2015	109	155	125	171	3.9%	0.87 [0.54, 1.41]
Li 2015	185	216	393	432	4.1%	0.59 [0.36, 0.98]
Qi 2016	210	252	227	252	4.2%	0.55 [0.32, 0.94]
Feng 2019	314	352	400	433	4.3%	0.68 [0.42, 1.11]
Yang 2016	328	386	326	374	5.5%	0.83 [0.55, 1.26]
Hou 2015	270	326	297	326	5.6%	0.47 [0.29, 0.76]
Si 2017	269	325	301	325	5.7%	0.38 [0.23, 0.64]
Qinghai 2014	248	293	489	550	5.7%	0.69 [0.45, 1.04]
Zhou 2013	233	301	368	446	7.4%	0.73 [0.50, 1.05]
Gao 2015	489	572	501	572	8.0%	0.83 [0.59, 1.17]
Wang 2014	371	462	404	462	8.7%	0.59 [0.41, 0.84]
Wang 2012	399	491	443	502	9.0%	0.58 [0.41, 0.82]
Quan 2012	169	311	248	463	10.0%	1.03 [0.77, 1.38]
Total (95% CI)		**5325**		**6589**	**100.0%**	**0.67 [0.60, 0.74]**
Total events	4316		5648			

Heterogeneity: Chi² = 29.88, df = 18 (P = 0.04); I² = 40%
Test for overall effect: Z = 7.77 (P < 0.00001)

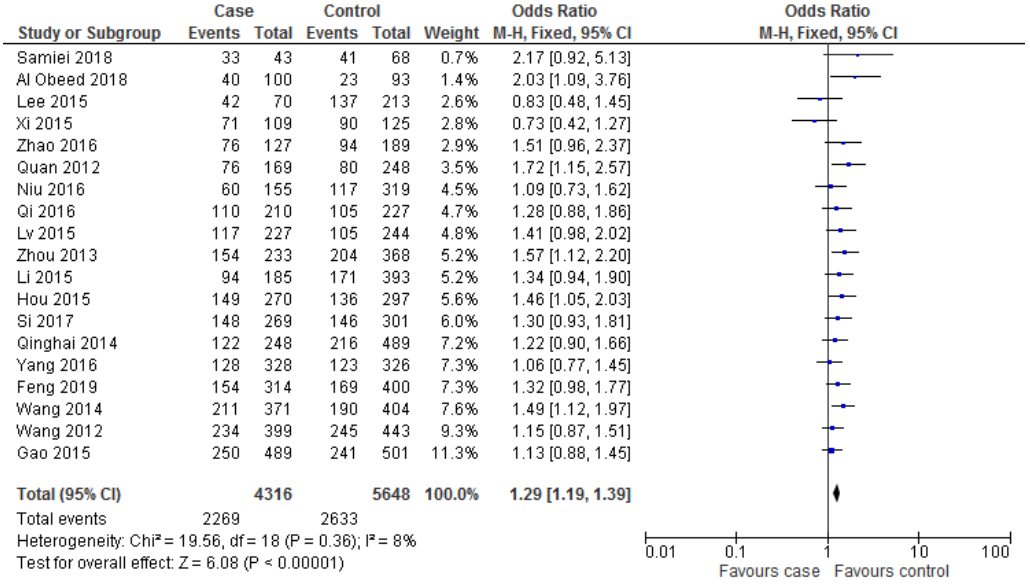
C



Study or Subgroup	Case Events	Case Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
Samiei 2018	27	37	12	39	2.6%	6.08 [2.25, 16.42]
Al Obeed 2018	17	77	7	77	2.8%	2.83 [1.10, 7.29]
Zhao 2016	26	77	18	113	4.1%	2.69 [1.35, 5.37]
Lee 2015	24	52	47	123	4.4%	1.39 [0.72, 2.67]
Xi 2015	46	84	46	81	4.6%	0.92 [0.50, 1.70]
Lv 2015	37	147	20	159	4.8%	2.34 [1.28, 4.25]
Si 2017	56	117	24	179	5.0%	5.93 [3.38, 10.41]
Qi 2016	42	142	25	147	5.0%	2.05 [1.17, 3.59]
Li 2015	31	122	38	260	5.3%	1.99 [1.17, 3.39]
Feng 2019	37	197	31	262	5.4%	1.72 [1.03, 2.89]
Niu 2016	30	125	51	253	5.4%	1.25 [0.75, 2.09]
Hou 2015	56	177	29	190	5.5%	2.57 [1.55, 4.26]
Qinghai 2014	45	171	61	334	6.0%	1.60 [1.03, 2.48]
Yang 2016	58	258	48	251	6.1%	1.23 [0.80, 1.88]
Zhou 2013	68	147	78	242	6.2%	1.81 [1.19, 2.76]
Wang 2012	92	257	58	256	6.5%	1.90 [1.29, 2.81]
Wang 2014	91	251	58	272	6.5%	2.10 [1.42, 3.09]
Gao 2015	83	322	72	332	6.7%	1.25 [0.87, 1.80]
Quan 2012	142	235	215	383	7.0%	1.19 [0.86, 1.66]
Total (95% CI)		**2995**		**3953**	**100.0%**	**1.86 [1.53, 2.25]**
Total events	1008		938			

Heterogeneity: Tau² = 0.11; Chi² = 48.82, df = 18 (P = 0.0001); I² = 63%
Test for overall effect: Z = 6.32 (P < 0.00001)

D



Study or Subgroup	Case Events	Case Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Samiei 2018	33	43	41	68	0.7%	2.17 [0.92, 5.13]
Al Obeed 2018	40	100	23	93	1.4%	2.03 [1.09, 3.76]
Lee 2015	42	70	137	213	2.6%	0.83 [0.48, 1.45]
Xi 2015	71	109	90	125	2.8%	0.73 [0.42, 1.27]
Zhao 2016	76	127	94	189	2.9%	1.51 [0.96, 2.37]
Quan 2012	76	169	80	248	3.5%	1.72 [1.15, 2.57]
Niu 2016	60	155	117	319	4.5%	1.09 [0.73, 1.62]
Qi 2016	110	210	105	227	4.7%	1.28 [0.88, 1.86]
Lv 2015	117	227	105	244	4.8%	1.41 [0.98, 2.02]
Zhou 2013	154	233	204	368	5.2%	1.57 [1.12, 2.20]
Li 2015	94	185	171	393	5.2%	1.34 [0.94, 1.90]
Hou 2015	149	270	136	297	5.6%	1.46 [1.05, 2.03]
Si 2017	148	269	146	301	6.0%	1.30 [0.93, 1.81]
Qinghai 2014	122	248	216	489	7.2%	1.22 [0.90, 1.66]
Yang 2016	128	328	123	326	7.3%	1.06 [0.77, 1.45]
Feng 2019	154	314	169	400	7.3%	1.32 [0.98, 1.77]
Wang 2014	211	371	190	404	7.6%	1.49 [1.12, 1.97]
Wang 2012	234	399	245	443	9.3%	1.15 [0.87, 1.51]
Gao 2015	250	489	241	501	11.3%	1.13 [0.88, 1.45]
Total (95% CI)		**4316**		**5648**	**100.0%**	**1.29 [1.19, 1.39]**
Total events	2269		2633			

Heterogeneity: Chi² = 19.56, df = 18 (P = 0.36); I² = 8%
Test for overall effect: Z = 6.08 (P < 0.00001)

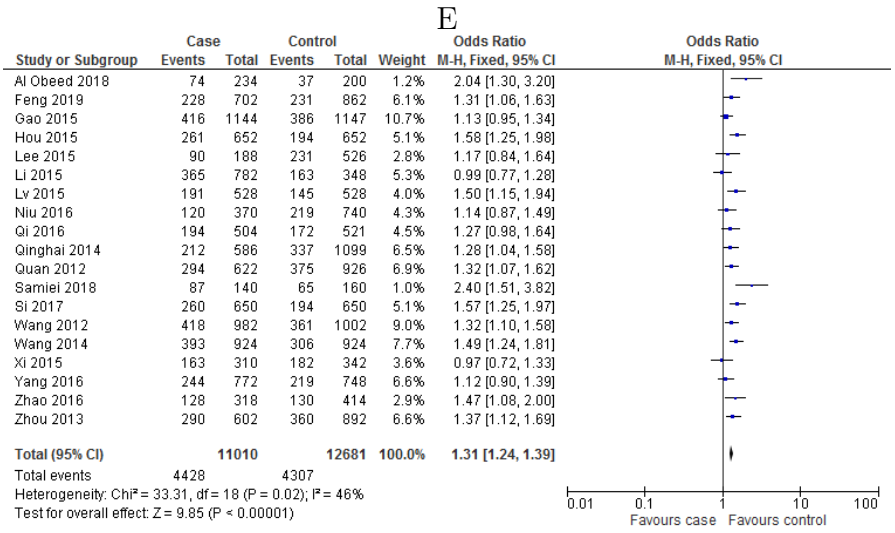


FIGURE 4.2: Analysis of the Association Between IL-17A rs2275913 G/A and Susceptibility to Cancer. A) Dominant (AA+AG vs GG). B) Recessive (GG+AG vs AA). C) Homogeneous (AA vs GG). D) Heterogeneous (AG vs GG). E) Allelic (A vs G).

On the basis of heterogeneity for dominant and homogeneous comparison, random effect model used. Fixed effect model used for recessive, heterogeneous and allelic model because these have $I^2 < 50\%$. (Figure: 4.2).

4.2.1 IL-17A rs2275913 G/A and Gastric Cancer (GC) Risk

Out of nineteen, seven papers involving 2444 cases and 2743 controls were based on association of rs2275913 and gastric cancer. Almost same results were found as in overall analysis. Considerable relation with gastric cancer risk was observed in all genetic models; dominant model (AA+AG vs GG; OR =1.36, 95% CI =1.22-1.52, P<0.00001), homogeneous model (AA vs GG; OR =1.71, 95% CI =1.44-2.03, P<0.00001), heterogeneous model (AG vs GG; OR =1.27, 95% CI =1.13-1.43, P<0.00001) and allelic model (A vs G; OR =1.30, 95% CI =1.20-1.41, P<0.00001). While recessive model (GG+AG vs AA; OR =0.65, 95% CI =0.56-0.77, P<0.00001) showed association with reduced risk of gastric cancer because diamond position favoured control group. Fixed or Random effect model used based on heterogeneity (Figure: 4.3).

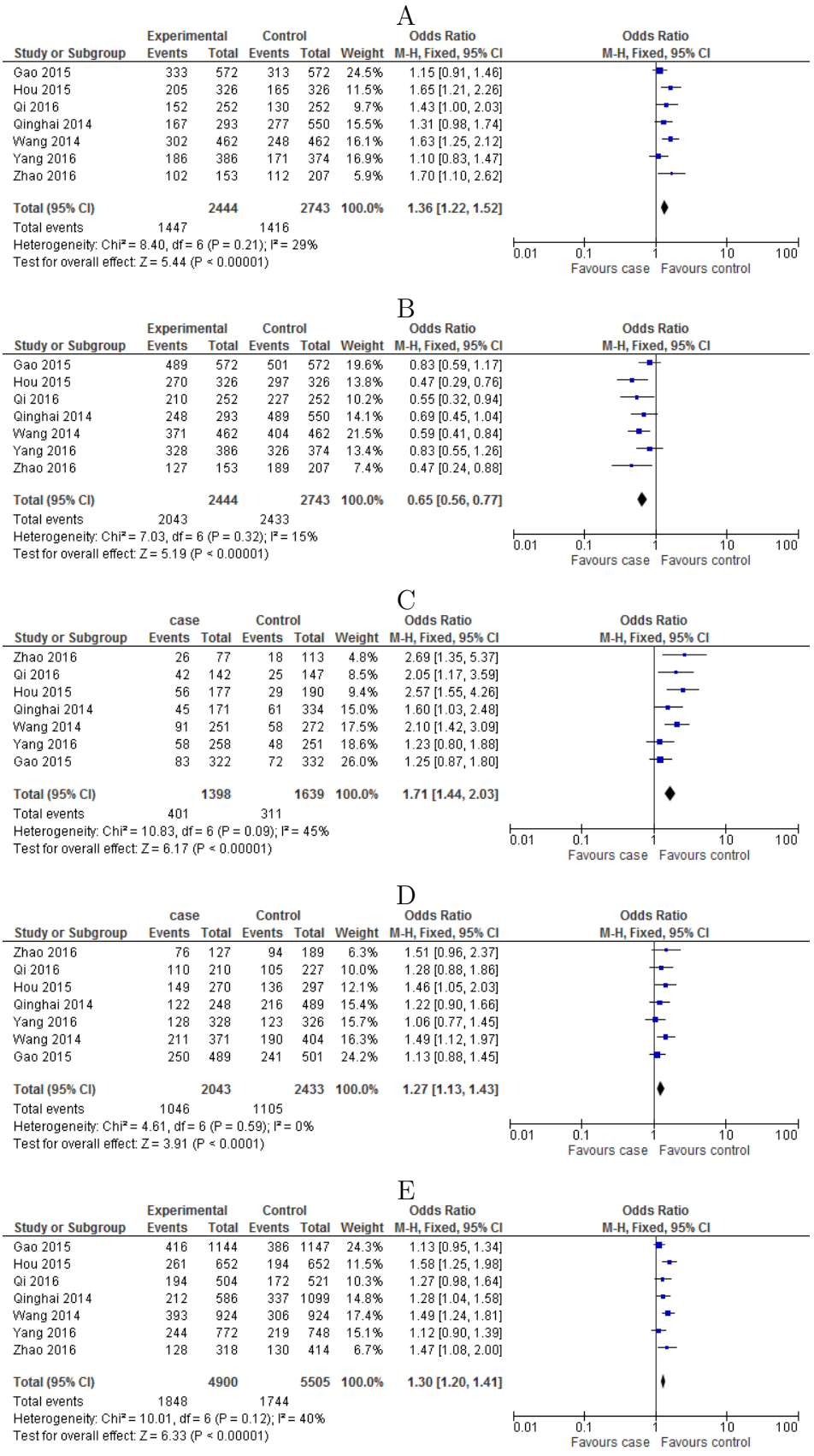


FIGURE 4.3: Analysis of the Association Between IL-17A rs2275913 G/A and Gastric Cancer. A) Dominant (AA+AG vs GG). B) Recessive (GG+AG vs AA). C) Homogeneous (AA vs GG). D) Heterogeneous (AG vs GG). E) Allelic (A vs G).

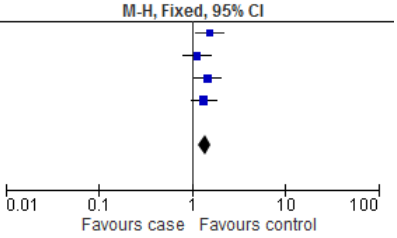
4.2.2 IL-17A rs2275913 G/A and Cervical Cancer (CC) Risk

Four papers containing 976 cases and 1529 healthy controls information were used to conducted meta analysis to find relation/association between rs2275913 and cervical cancer. According to analysis results and diamond position dominant, homogeneous, heterogeneous and allelic were found associated with increased risk of cervical cancer. While no association observed in recessive model. Random effect model used for only recessive model that have 56% heterogeneity and fixed effect model used for remaining models during analysis (Figure: 4.4).

A

Study or Subgroup	Case Events	Case Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Lv 2015	154	264	125	264	21.8%	1.56 [1.10, 2.20]
Niu 2016	90	185	168	370	24.0%	1.14 [0.80, 1.62]
Li 2015	125	216	209	432	24.5%	1.47 [1.05, 2.04]
Quan 2012	218	311	295	463	29.6%	1.33 [0.98, 1.82]
Total (95% CI)		**976**		**1529**	**100.0%**	**1.37 [1.16, 1.62]**
Total events	587		797			

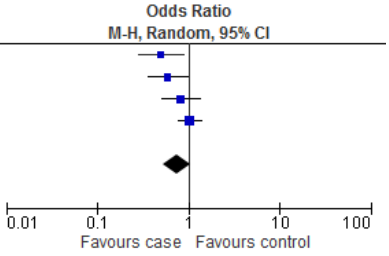
Heterogeneity: Chi² = 1.77, df = 3 (P = 0.62); I² = 0%
Test for overall effect: Z = 3.70 (P = 0.0002)



B

Study or Subgroup	Case Events	Case Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
Lv 2015	227	264	244	264	19.8%	0.50 [0.28, 0.89]
Li 2015	185	216	393	432	22.7%	0.59 [0.36, 0.98]
Niu 2016	155	185	319	370	23.3%	0.83 [0.51, 1.35]
Quan 2012	169	311	248	463	34.2%	1.03 [0.77, 1.38]
Total (95% CI)		**976**		**1529**	**100.0%**	**0.75 [0.53, 1.05]**
Total events	736		1204			

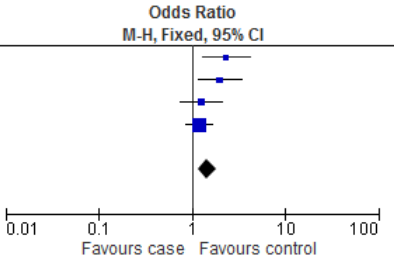
Heterogeneity: Tau² = 0.07; Chi² = 6.84, df = 3 (P = 0.08); I² = 56%
Test for overall effect: Z = 1.67 (P = 0.10)



C

Study or Subgroup	Case Events	Case Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Lv 2015	37	147	20	159	11.7%	2.34 [1.28, 4.25]
Li 2015	31	122	38	260	14.7%	1.99 [1.17, 3.39]
Niu 2016	30	125	51	253	20.9%	1.25 [0.75, 2.09]
Quan 2012	142	235	215	383	52.7%	1.19 [0.86, 1.66]
Total (95% CI)		**629**		**1055**	**100.0%**	**1.46 [1.16, 1.83]**
Total events	240		324			

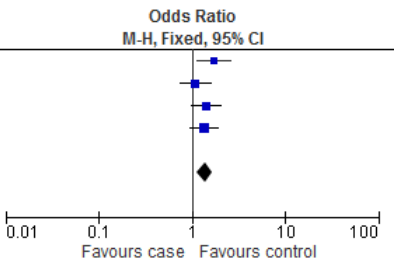
Heterogeneity: Chi² = 5.46, df = 3 (P = 0.14); I² = 45%
Test for overall effect: Z = 3.25 (P = 0.001)



D

Study or Subgroup	Case Events	Case Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Quan 2012	76	169	80	248	19.2%	1.72 [1.15, 2.57]
Niu 2016	60	155	117	319	25.3%	1.09 [0.73, 1.62]
Lv 2015	117	227	105	244	26.4%	1.41 [0.98, 2.02]
Li 2015	94	185	171	393	29.0%	1.34 [0.94, 1.90]
Total (95% CI)		**736**		**1204**	**100.0%**	**1.37 [1.13, 1.65]**
Total events	347		473			

Heterogeneity: Chi² = 2.51, df = 3 (P = 0.47); I² = 0%
Test for overall effect: Z = 3.27 (P = 0.001)



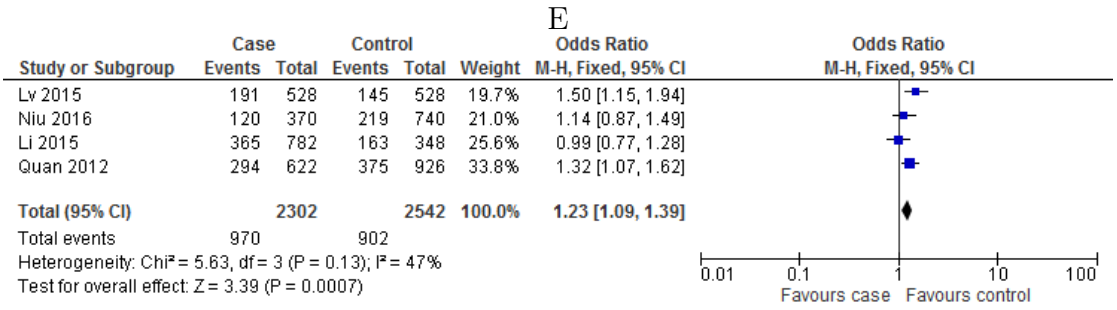
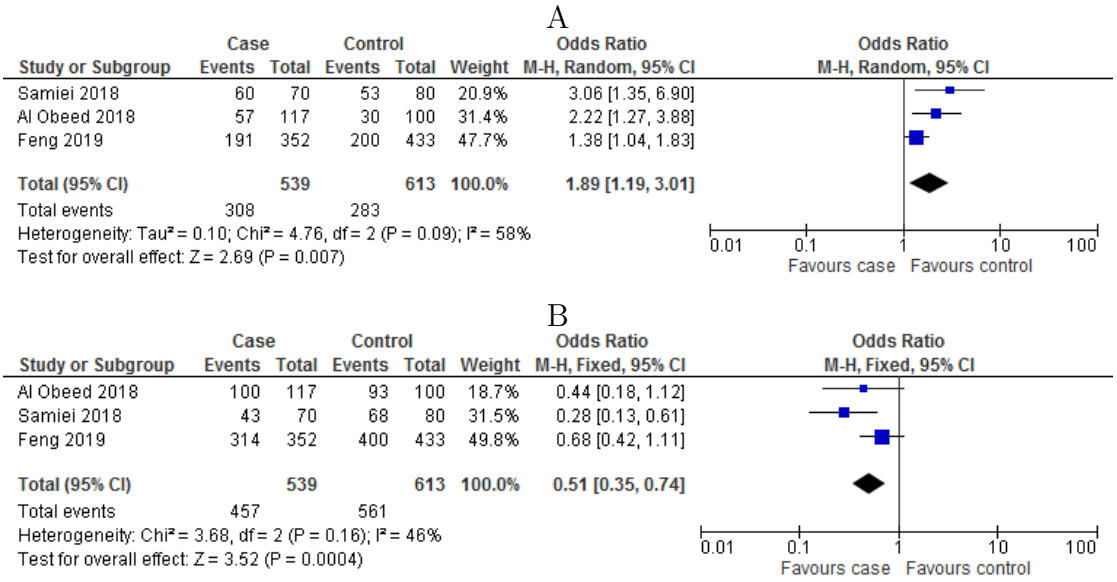


FIGURE 4.4: Analysis of the Association Between IL-17A rs2275913 G/A and Cervical Cancer. A) Dominant (AA+AG vs GG). B) Recessive (GG+AG vs AA). C) Homogeneous (AA vs GG). D) Heterogeneous (AG vs GG). E) Allelic (A vs G).

4.2.3 IL-17A rs2275913 G/A and Colorectal Cancer (CRC) Risk

From nineteen studies, three studies involving 539 cases and 613 healthy controls were based on rs2275913 association with CRC. All genetic model found strongly associated with colorectal cancer. Because all have significant P value. Recessive model (GG+AG vs AA; OR =0.51, 95% CI =0.35-0.74, P=0.0004) showed association with reduced colorectal cancer risk and remaining four was associated with increased cancer risk. Random effect model used in dominant, homogeneous and allelic while in other three fixed effect model used (Figure: 4.5).



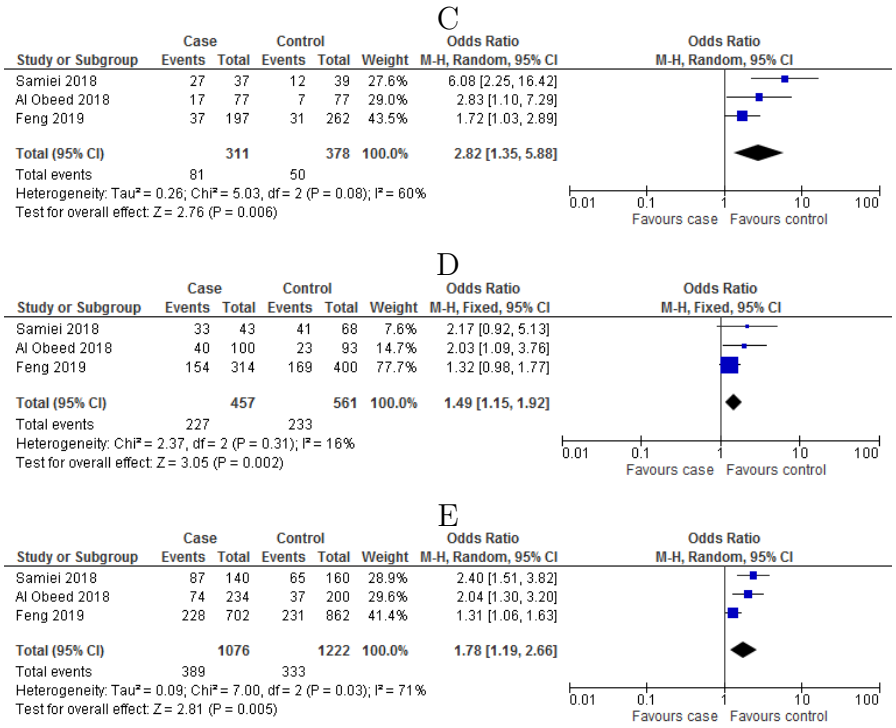
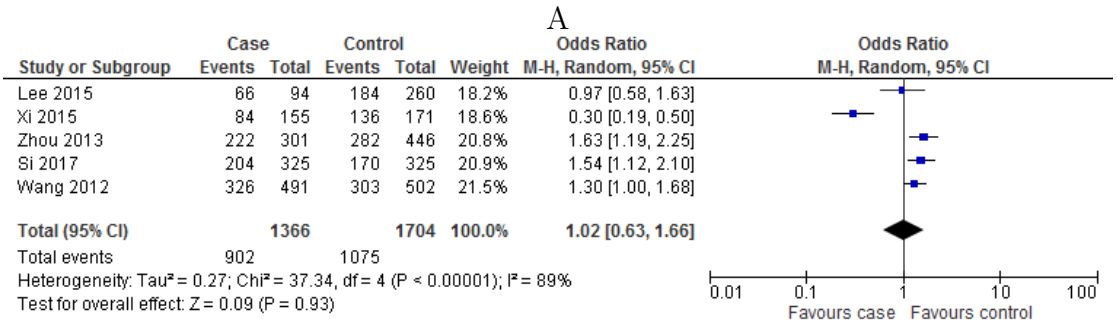


FIGURE 4.5: Analysis of the Association Between IL-17A rs2275913 G/A and Colorectal Cancer. A) Dominant (AA+AG vs GG). B) Recessive (GG+AG vs AA). C) Homogeneous (AA vs GG). D) Heterogeneous (AG vs GG). E) Allelic (A vs G).

4.2.4 IL-17A rs2275913 G/A and Other Cancer Risk

Five papers one for each papillary thyroid cancer, breast cancer, lung cancer, hepatocellular carcinoma and bladder cancer were included in this analysis. All the individual paper combined then referred and analyzed as other cancer. According to analysis results association was not observed in dominant model. While, homogeneous, heterogeneous and allele model showed association with increase cancer risk. Recessive model showed association with decreased cancer risk. Random or fixed effect model followed based on heterogeneity (Figure: 4.6).



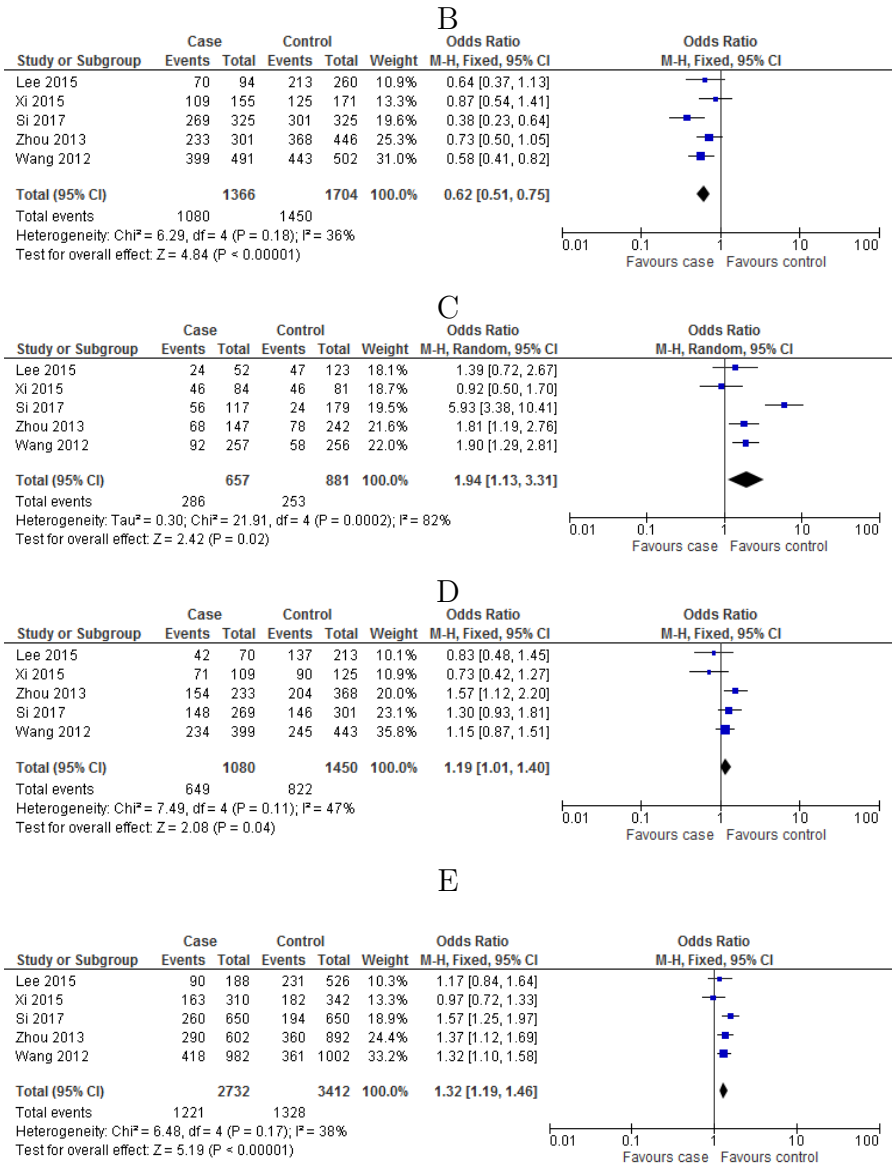


FIGURE 4.6: Analysis of the Association Between IL-17A rs2275913 G/A and Other Cancer. A) Dominant (AA+AG vs GG). B) Recessive (GG+AG vs AA). C) Homogeneous (AA vs GG). D) Heterogeneous (AG vs GG). E) Allelic (A vs G).

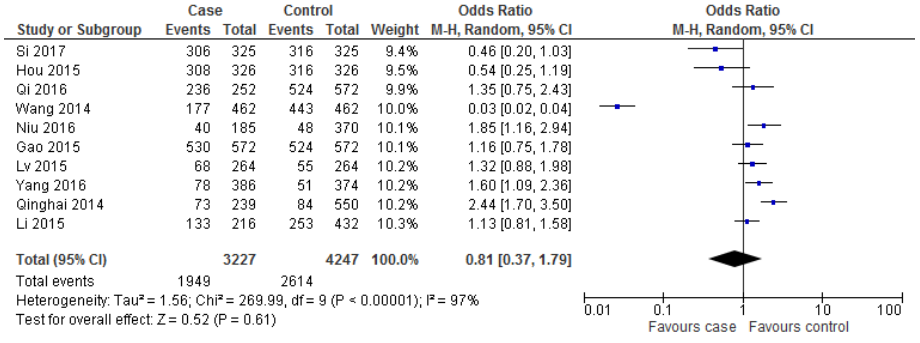
4.3 Association Between IL-17A rs3748067 T/C Polymorphism and Cancer Risk

Ten studies selected to find association of IL-17A rs3748067 C/T and cancer risk. Detailed information in Table 4.2. Included studies containing 3,227 cases and 4,247 healthy controls for analysis. To find association meta-analysis performed for five genetic models; Dominant model (TT+CT vs CC), Recessive model (CC+CT

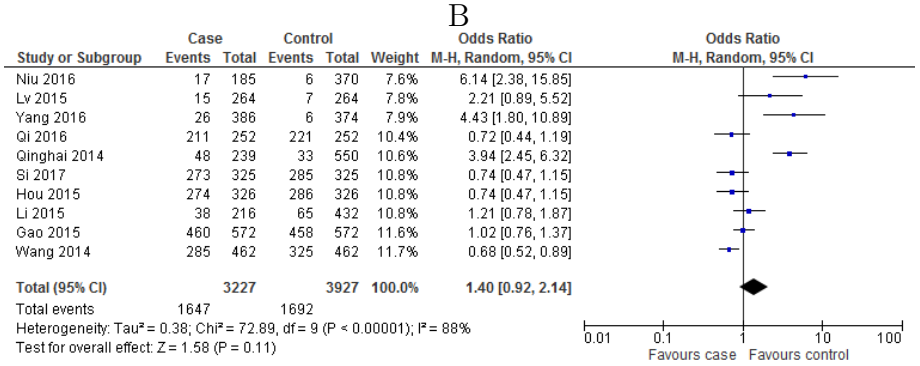
vs TT), Homogeneous Model (TT vs CC), Heterogeneous Model (CT vs CC), Allelic Model (T vs C).

Analysis result for all genetic model; dominant (TT+CT vs CC; OR =0.81, 95% CI =0.37-1.79, P=0.61), recessive (CC+CT vs TT; OR =1.40, 95% CI =0.92-2.14, P=0.11), homogeneous (TT vs CC; OR =1.29, 95% CI = 0.75-2.24, P=0.36), heterogeneous (CT vs CC; OR =0.77, 95% CI =0.55-1.08, P=0.13) and allele model (T vs C; OR =1.14, 95% CI =0.84-1.55, P=0.39) were shown that IL-17A SNP rs3748067 was not associated with under study cancer forms. Because in all genetic models P value is greater than 0.05 and diamond also touch the null line effect. Random effect model applied in all genetic models because of I^2 >50% (Figure: 4.7).

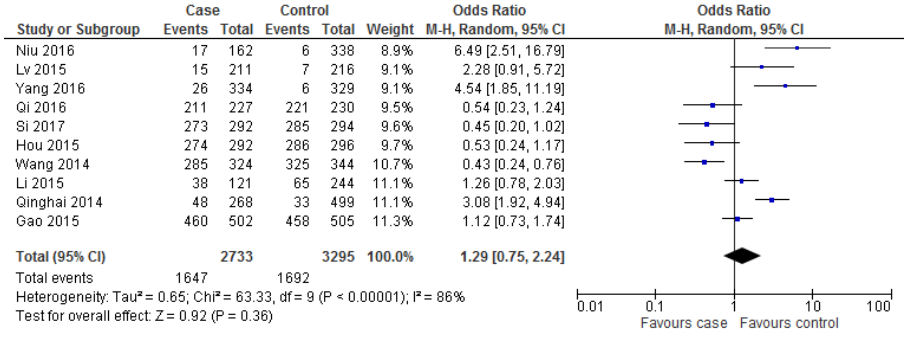
A



B



C



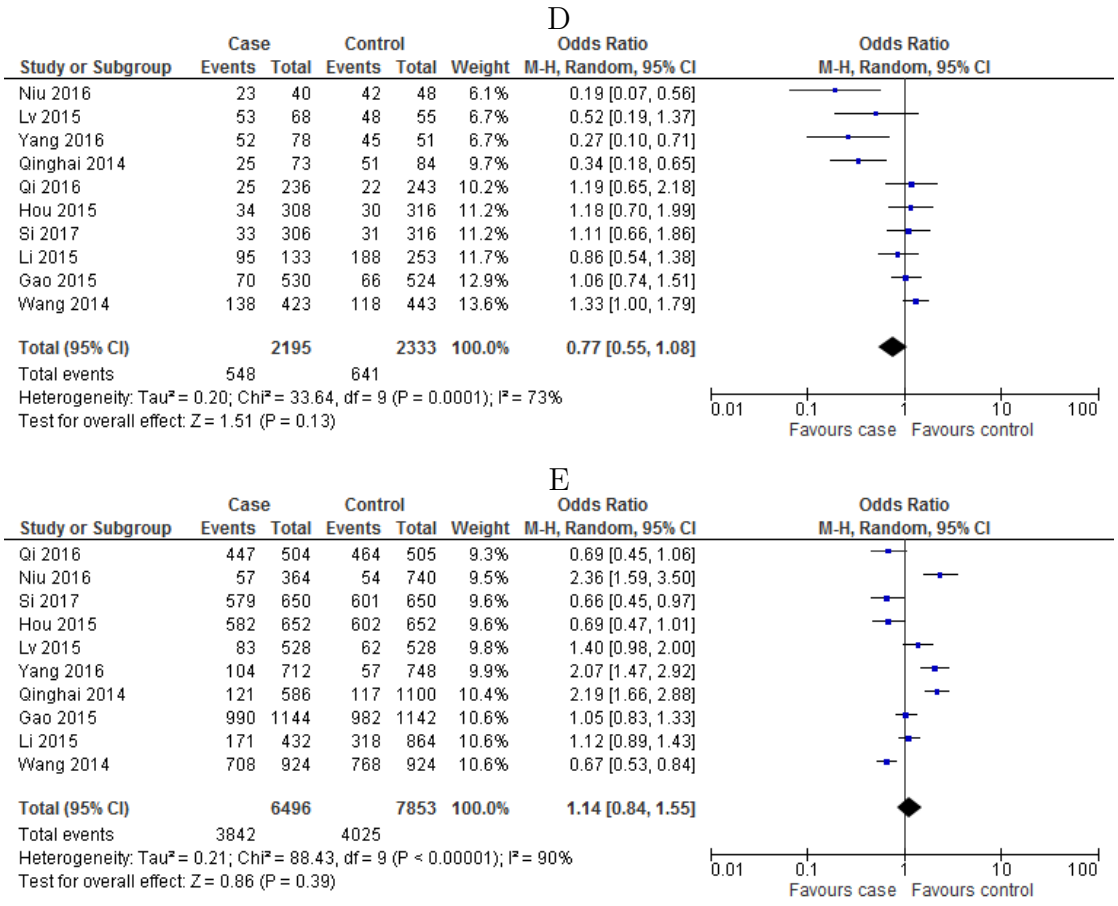


FIGURE 4.7: Analysis of the Association Between IL-17F rs3748067 C/T and Risk of Cancer. A) Dominant Model (TT+CT vs CC). B) Recessive Model (CC+CT vs TT). C) Homogeneous Model (TT vs CC). D) Heterogeneous Model (CT vs CC). E) Allelic Model (T vs C).

4.3.1 IL-17A rs3748067 C/T and Gastric Cancer (GC) Risk

Out of ten 6 papers based on rs3748067 association with gastric cancer involving 2,237 cases and 2,536 healthy controls. Overall, our statistical analysis did not find a significant relationship between the rs3748067 polymorphism and progression of cancer disease.

As shown in (Figure 4.8) all genetic models P value is greater than 0.05, So that suggested no relation between rs3748067 and gastric cancer risk. Heterogeneity was more than 50% in all genetic models so, random effect model applied during analysis. All statistical analysis results shown in summary tables (Table 4.3 & 4.4).

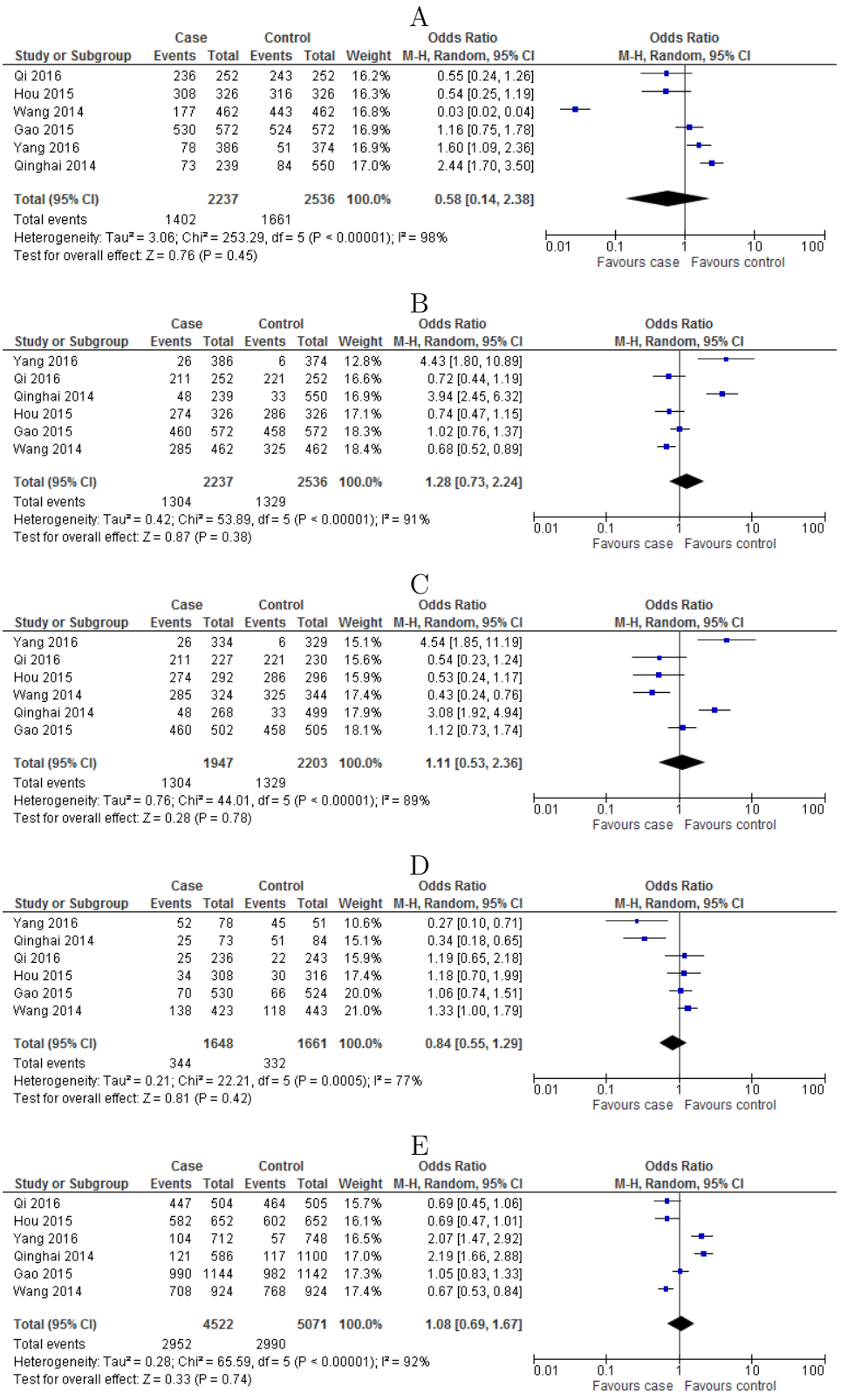


FIGURE 4.8: Analysis of the Association Between IL-17F rs3748067 C/T and Risk of Gastric Cancer. A) Dominant Model (TT+CT vs CC). B) Recessive Model (CC+CT vs TT). C) Homogeneous Model (TT vs CC). D) Heterogeneous Model (CT vs CC). E) Allelic Model (T vs C).

TABLE 4.3: Summary Table for Meta-Analysis of the IL-17A rs2275913 Polymorphism with Risk of Cancer

Polymorphisms	**Cancer type**	**No. Of Studies**
rs2275913		
Dominant Model	Overall	19
	GC	7
	CC	4
	CRC	3
	Other cancer	5
Recessive Model	Overall	19
	GC	7
	CC	4
	CRC	3
	Other cancer	5
Homogeneous Model	Overall	19
	GC	7
	CC	4
	CRC	3
	Other cancer	5
Heterogeneous Model	Overall	19
	GC	7
	CC	4
	CRC	3
	Other cancer	5
Allelic Model	Overall	19
	GC	7
	CC	4
	CRC	3
	Other cancer	5

Association test			**Heterogeneity test**		
OR	**CI 95%**	**P-value**	**Model**	**P-value**	**I_2 test**
1.34	1.17-1.54	0.0001	RE	0.00001	68
1.36	1.22-1.52	0.00001	FE	0.21	29
1.37	1.16-1.62	0.0002	FE	0.62	0
1.89	1.19-3.01	0.007	RE	0.09	58
1.02	0.63-1.66	0.93	RE	0.00001	89
0.67	0.6-0.74	0.00001	FE	0.04	40
0.65	0.56-0.77	0.00001	FE	0.32	15
0.75	0.53-1.05	0.1	RE	0.08	56
0.51	0.35-0.74	0.0004	FE	0.16	46
0.62	0.49-0.80	0.0002	FE	0.18	36
1.86	1.53-2.25	0.00001	RE	0.0001	63
1.71	1.44-2.03	0.00001	FE	0.09	45
1.46	1.16-1.83	0.001	FE	0.14	45
2.82	1.35-5.88	0.006	RE	0.08	60
1.94	1.13-3.31	0.02	RE	0.0002	82
1.29	1.19-1.39	0.00001	FE	0.36	8
1.27	1.13-1.43	0.0001	FE	0.59	0
1.37	1.13-1.65	0.001	FE	0.47	0
1.49	1.15-1.92	0.002	FE	0.31	16
1.19	1.01-1.4	0.04	FE	0.11	47
1.31	1.24-1.39	0.00001	FE	0.02	46
1.3	1.20-1.41	0.00001	FE	0.12	40
1.23	1.04-1.45	0.02	FE	0.13	47
1.78	1.19-2.66	0.005	RE	0.03	71
1.32	1.19-1.46	0.00001	FE	0.17	38

Abbreviations: OR = Odd Ratio; CI = Confidence Interval; RE = Random-Effect.

TABLE 4.4: Summary Table for Meta-Analysis of the IL-17A rs3748067 Polymorphism with Risk of Cancer

Polymorphisms	**Cancer type**		**No. of studies**		
rs3948067					
Dominant Model	Overall		10		
	GC		6		
Recessive Model	Overall		10		
	GC		6		
Homogeneous Model	Overall		10		
	GC		6		
Heterogeneous Model	Overall		10		
	GC		6		
Allelic Model	Overall		10		
	GC		6		
Association test			**Heterogeneity test**		
OR	**CI 95%**	**P-value**	**Model**	**P-value**	**I_2 test**
0.81	0.37-1.79	0.61	RE	<0.00001	97
0.58	0.14-2.35	0.45	RE	<0.00001	98
1.4	0.9-2.14	0.11	RE	<0.00001	88
1.28	0.73-2.24	0.38	RE	<0.00001	91
1.29	0.75-2.25	0.36	RE	<0.00001	86
1.11	0.53-2.35	0.78	RE	<0.00001	89
0.77	0.55-1.08	0.13	RE	0.0001	73
0.84	0.55-1.29	0.42	RE	0.0005	77
1.14	0.84-1.55	0.39	RE	<0.00001	90
1.08	0.68-1.67	0.74	RE	<0.00001	92

Abbreviations: OR odd ratio; CI = confidence interval; RE = random-effect.

4.4 Discussion

IL-17 is a crucial family of cytokines, initially known to be produced by T helper 17 cells [131]. IL-17A and IL-17F show a remarkable function among the different family member in inflammation, autoimmune disorder and cancers [102, 132]. IL-17A rs22759133 polymorphism is present in close vicinity to two nuclear factors stimulated T cell binding motifs, and it enhance IL-17 production, which then up-regulates IL-17-related immune responses [133]. There were many studies performed to find association but the role of IL-17A in the pathogenecity of the carcinoma has not yet clear. In recent years, various studies have shown that SNPs of IL-17A can regulate transcription and translation, as well as carcinogens [32,134].

Published studies have showed relation between IL-17A polymorphisms and the cancer risk, mainly gastric cancer and cervical cancer. Some previous studies results discussed here. Wang, et al. found that individuals with IL-17A rs2275913 GA, AA genotype, and A allele were more susceptible to gastric cancer than the others [22]. However Gao, et al. Study suggest that rs2275913 have no affect on gastric cancer [23]. According to Wang, et al. individuals carrying CC genotype and C allele of rs3748067 are more susceptible to gastric cancer than the other one. While Gao, et al. study had not found association between rs3748067 polymorphisms and threat of developing gastric cancer [22, 23]. Quan, et al. analyses showed that the polymorphism of rs2275913 might be a risk factor for cervical cancer [18]. According to Lv,et al. genotype of rs2275913 have effect on cervical cancer, cases with minor (AA) genotype were more susceptible to cancer than the major (GG). Niu, et al. study observed that the variant TT enhance cervical cancer risk than genotype CC [19, 21]. This meta-analysis was performed to find out accuracy and precise results regarding this.

Meta-analysis purpose was to find out the association of two variants of the IL-17A (rs2275913, rs3748067) and susceptibility to cancers in Asian population. Nineteen studies were included, (19 for rs2275913, 10 for rs3748067) accounts 5325 cases and 6589 controls that focused on IL-17A rs2275913, while 3227 cases and 4247 controls

that used in study of IL-17A rs3748067. In overall analysis IL-17A rs2275913 showed a strong association with cancer disease or risk of cancer (understudy) in all genetic models dominant, homogeneous, heterogeneous and allelic. Recessive model showed deviation in results compared to other that it favoured the controls with significant P value. Cancer subgroup statistical analysis by cancer type also showed significant association as in overall analysis and recessive model as in overall analysis and subgroup analysis also showed association with control and might be used to decrease cancer risk. There were no significant association found between IL-17A rs3748067 and cancer (understudy types). All genetic models showed greater P value than compared to significant. Latest version 5.4 of Review Manager 2020 was used for meta-analysis.

Previously meta-analysis performed on the same question related to SNP rs2275913 suggested that the IL-17A (rs2275913) polymorphism was related with increase cancer risk for all genetic model [135]. According to Niu et al. IL-17A polymorphisms might be a risk factor for cancer, specially gastric cancer, in Asian populations [136] While An updated meta-analysis by Dai, et al. favoured previous studies results [137]. This meta-analysis results supported the previous meta-analysis studies. But in this meta-analysis the main difference is that recent papers were included and rs3748067 was not included in previous meta-analysis. To the best of our knowledge, rs3748067 association with cancer not studied previously. The main objective is that with the passage of time environmental and genetic factor change and their affects on any disease changed. However, this study contain the recent study and showed the same results as that of previous only recessive model showed deviation. So, this study recommended more research in this field to clear this confusion.

Chapter 5

Conclusions and Recommendations

Results concluded that the IL-17A rs2275913 might be a risk factor for cancer in Asian populations because four genetic model dominant model (AA+AG vs GG), homogeneous comparison (AA vs GG), heterogeneous comparison (AG vs GG) and allele comparison (A vs G) showed strong association of rs2275913 with cancer (used in study) and subgroup analysis like Gastric Cancer, Cervical Cancer, Colorectal Cancer.While recessive model (GG+AG vs AA), showed positive association with cancer and observed that genotype GG+AG might be protective against cancer risk. In case of IL-17A rs3748067, we had not found association in all genetic models; dominant model (TT+CT vs CC), recessive model (CC+CT vs TT), homogeneous model (TT vs CC), heterogeneous model (CT vs CC) and allelic Model (T vs C) during overall analysis with cancer disease and with gastric cancer.

This study and previous related to this showed that IL-17A rs2275913 have significant association and is a risk factor for cancer disease So, it can be used in therapeutic and drug designing. However, there are few limitations related to this study. First, the two polymorphisms were showed association with cancers risk, but included studies focused on Gastric cancer rather than other cancer types,

Thus, further studies are required for precise and authentic results. Second, all included studies assessed in Asian populations, almost more than 50% studies included performed in Chinese population while in case of IL-17A rs3748067 SNP all study performed in Chinese population. Analyses of other Asian countries are lacking. Therefore, more case-control studies are needed. Third, meta analysis focused cancer disease and its type without considering other factors that may influence the study results such as age, sex and tobacco use. Fourth, there is about more than 100 types of cancer and in this study we included only 8 cancer types. Thus, further studies on different types of cancer are required. These are some limitation that need to be solved in future studies.

Overall, results of current meta-analysis is satisfactory and supported previous published work. In-spite of described limitations, this meta-analysis give precise estimation of relationship between IL-17A polymorphisms and cancer risk in Asian population.

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