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Chapter

Cytokine Gene Polymorphism and Cancer Risk: A Promising Tool for Individual Susceptibility and Prognostic Implications

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Abstract

Cytokines are potent molecules produced mainly by specific activated immune cells to control inflammatory responses besides other biologic processes. Although active participation of cytokines provides defense against carcinogenesis on the other hand, deregulation at the genetic level influences their activity to promote tumor development. Among many aspects, constitutional polymorphic sequence variations are key factors that derange the cytokine expression to lead an individual's propensity to risk for different cancers. Cytokine polymorphisms are now believed to alter these critical molecules that have a dual face in carcinogenesis as, when implicated in the activation of the immune response, these molecules check the cancer development while their persistent inflammatory reaction can envisage the development of malignancy and tumor growth. We have given ample evidence of case-control studies in a range of cancers where substantial evidence, as reported in this chapter, links polymorphism of cytokine gene susceptibility with numerous cancers. Cytokine gene polymorphism is vital to be significant bimolecular genetic determinants of susceptibility and prognosis of cancer. A strong need is felt for more case-control association studies in cytokine candidate genes involved in specific pathways for particular cancer in bigger powered sample sizes involving additional variables to disclose their factual risk for cancer.

Keywords: cytokines, polymorphism, malignancy, tumor, immune response, case-control, inflammatory reaction

1. Introduction

Cancer is the world's second leading cause of death and accounts for around 1 in 6 deaths worldwide. A projected 18.1 million new cancer-related cases and 9.6 million cancer-related deaths were recorded in 2018, according to the 2018 GLOBOCAN study. Lung cancer is the most frequently diagnosed cancer for both sexes with 11.6% of the total cases of cancer and is also the leading cause of cancer death with 18.4% of the total cancer deaths. Cancer, a cellular overgrowth disorder,

involves cellular transformation, apoptotic dysregulation, uncontrolled proliferation, invasion, angiogenesis, and metastasis [1]. A significant correlation between chronic infection, inflammation, and certain forms of cancer have been suggested in clinical and epidemiological research, with inflammation frequently occurring in and around tumors [2].

Recent studies have shown that chronic inflammation that regulates the microenvironment of the tumor is involved in the initiation of the tumor and is a critical component of tumor promotion and progression [3]. The insistent inflammatory microenvironment contributes to increased promotion of the tumor, accelerated progression, invasion of the surrounding tissues, angiogenesis, and eventually metastasis [4]. The tumor microenvironment has a vast abundance of cytokines as well as other inflammatory mediators which impact immunosuppression, cancer growth, tissue remodeling, and angiogenesis [5]. Cytokines are a heterogeneous group of glycoproteins or small soluble polypeptides (secreted or membrane-bound) chiefly produced by the immune cells which under normal conditions are produced in response to specific stimuli exerting pleiotropic and redundant effects thereby altering the behavior of the identical or different cells by regulating the growth, differentiation, and activation of normal cells especially immune cells [6]. Depending on the microenvironment, cytokines may either have pro- or anti-inflammatory or may even have immunosuppressive activity [7]. In response to both antigen-specific and nonspecific stimuli, the development of multiple cytokines by immune cells plays a crucial role in the outcome of inflammatory immune responses [8]. They are either released in response to a variety of cellular stresses, including carcinogen-induced injury, infection, inflammation, and immunity that inhibits tumor growth and progression, or are host-derived cytokines that cause cancer cells to promote growth, reduce apoptosis, aid invasion and metastasis. The role of cytokines in subsequent settings is to cause a host response aimed at controlling cellular stress and reducing cell damage. Although critical insult control encourages tissue repair, failure to control the injury can lead to the insistent development of cytokines, leading to further aggravation of tissue damage. Depending on several stages of cancer development and progression, host responses to cellular stress may influence it inherently [9]. Therefore, the cytokine mixture produced in the tumor microenvironment plays an important role in the pathogenesis of cancer [10]. The molecular and cellular changes that eventually lead to cancer stimulate changes in the local cytokine environment, stimulate immune cell intrusions, and release additional cytokines that function in an autocrine or paracrine manner [11]. In addition, pro-inflammatory cytokines are associated with anorectic and cachectic disease in patients with progressive cancer, pain in the form of both algia and dynia, toxicity, and resistance to treatment. Physical exercise can, however, alter cytokine levels and decrease fatigue in cancer patients, and may also increase their prognosis [7].

Cytokines provide a key molecular link between inflammation, tumor promotion, and progression which mainly include the interferons (IFNs), the interleukins (ILs), the tumor necrosis factor super family (TNFs), the transforming growth factor super family (TGFs), and Colony Stimulating Factors (CSFs) [12].

Genetic variations in the human genome can govern the risk of cancer development, symptoms, treatment, and its outcome [7]. In recent years, within cytokine gene sequences, many single nucleotide polymorphisms (SNPs) and a small number of microsatellite polymorphisms have been reported, mainly within their promoter regions [13] Indeed the most common variations in the genome are the SNPs [14]. Some suggest that the differences in SNPs may also help explain cancer disparities among the various ethnic groups [15]. Differential levels of gene transcription, including TNF -308 and IL-10-10822 can be associated with

some of these polymorphisms [16]. Several genetic studies have attempted to associate these cytokine polymorphisms with cancers; however, the studies are still limited, but increasingly evolving. The link between TNF alpha-SNPs and specific cancers, including oral carcinoma, has been documented in several studies [17] and non-Hodgkin's lymphoma [18], but most of these associations are refuted by others. IL-1 gene polymorphisms that provide increased expression of this pro-inflammatory cytokine are associated with an increased risk of cancers, mainly of gastric origin [19]. The association between IL-1B/IL-1RN polymorphisms and the development of gastric adenocarcinoma following *Helicobacter pylori* infection is also well known [20]. In relation to cancer, IL-10 polymorphisms are of particular concern since IL-10 has immunosuppressive and anti-angiogenic properties [8]. In view of this, this chapter highlights the essential role of genetic polymorphisms with respect to a host of cancers and their susceptibility in different geographical regions.

2. Pro-inflammatory cytokine gene polymprphisms

2.1 Solid tumors

2.1.1 Breast cancer

2.1.1.1 Interleukin 6

IL-6 is a major inflammatory pleiotropic cytokine that is considered a main growth-promoting factor [21]. Several IL-6 target genes are involved in the progression of the cell cycle and apoptosis suppression, which emphasizes the significance of IL-6 in tumorigenesis [22]. Many polymorphic IL-6 studies have shown that it is associated with breast cancer risk and prognosis. A study indicates that IL-6 is a predisposing genetic factor that contributes to the prognosis of breast cancer, with a G/C polymorphism associated with high levels of IL-6 production within the promoter region of the IL-6 gene correlating with a worse prognosis. While few studies have been published to date on polymorphisms within the IL-6 gene cluster and breast cancer [23], there is still controversy about the evidence on 174 G/C IL-6 polymorphism in breast cancer. The presence of IL-6 polymorphism was associated with an improved outcome in high-risk breast cancer, reported by DeMichele et al. [24]. Iacopetta et al. [25] found that the IL-6 polymorphism was predictive of the phenotype of aggressive breast cancer

2.1.1.2 Interleukin 10

IL-10 is an immunosuppressive and anti-angiogenic multifunctional cytokine that can have both tumor-promoting and inhibiting properties [26]. The IL-10 gene promoter has been recognized to have a significant number of polymorphisms (primarily SNPs) [27]. As a consequence, promoter polymorphisms have been the most scrutinized, particularly with regard to possible gene transcription and protein production influences. Many studies on the interactions between genotypes of IL-10 and breast cancer have been published. One small breast cancer study confirmed that the low-expression 21082 AA genotype was associated with a high risk of disease [28]. In comparison, a larger case-control study found a correlation between the 2592 AA genotype and the reduced risk of breast cancers [29] but did not associate with any clinical parameters.

2.1.1.3 Interferon-γ

Interferon-γ (IFN-γ) is the cytokine that likely has a vital role in carcinogenesis. Several combined epidemiological studies have shown that IFN-γ can function as a major risk factor for breast cancer development and progression, primarily due to genetic polymorphisms of IFN-γ [30]. Interestingly, genetic polymorphisms in the IFN-γ gene are likely to affect the degree of IFN-γ expression, leading to impaired function or decreased IFN-γ activity; subsequent low IFN-γ expression levels would encourage tumor development, which can contribute to can susceptibility to breast cancer [31]. In order to be more precise, many common IFN-γ gene polymorphisms have been found to increase the risk of breast cancer, such as rs20697 (−1615C/T) and rs2430561 (+874T/A) [30, 32, 33]. Contradictory findings have also been reported recently, although several studies have also suggested that IFN-γ genetic polymorphisms can play a critical role in breast cancer pathogenesis [30, 31]. Gene polymorphisms, with low levels of IFN-γ, can alter the function and expressions of IFN-γ. The rs2430561 A>T polymorphism was revealed by Liu et al. in intron 1 of IFN-γ [34]. The gene can transform its transcription functionally and lead to susceptibility to breast cancer [35]. Another meta-analysis shows that genetic polymorphisms within the IFN-γ gene were significantly associated with an increased risk of breast cancer, especially the polymorphism of 2430561 T>A. No connection was, however, identified between rs2069705 C>T polymorphism and breast cancer susceptibility. Genetic polymorphisms and the risk of breast cancer in Asians, but not among Caucasians, suggest that ethnic differences may affect the susceptibility of individuals to breast cancer [36].

2.1.1.4 Tumor necrosis factor-alpha (TNF-α)

TNF-α is an essential pro-inflammatory cytokine for human cancer growth and progression [37] by stimulating the development of genotoxic molecules (NO, ROS) that can lead to DNA damage and mutations, TNF-α can promote tumor initiation and progression. The increased risk of many cancers, including breast cancer, is associated with genetic polymorphisms that boost TNF-α development [33].

Increasing evidence has shown that a SNP in the promoter region of the TNF-α gene (−308G>A, rs1800629) induces genetic susceptibility in many forms of tumors like BC [38]. The TNF-α-308A allele tends to have a higher constitutive and inducible expression, as the −308G>A mutation affects the AP-22020 consensus binding site [39]. The results on the association of –308 (G/A) TNF-α polymorphism with breast cancer development are rather contradictory [40]. A rise in homozygous (−308AA) TNF-α genotype frequency was significantly associated with the development of breast cancer and poor prognosis in Tunisian women [40]. No link between the homozygous (−308AA) TNF-α genotype and breast cancer risk was identified in Holland. The association of allele (−308A) TNF-α with tumor vascularization has, however, been shown to be [41]. Where the majority of studies found no link between-308 (G/A) TNF-α polymorphism and the occurrence of breast cancer [42, 43]. Two recent meta-analyses have confirmed that the genotypes TNF-α-308GA and AA were significantly associated with a reduced risk of breast cancer in Caucasians [14, 16, 44, 45]. The allele frequencies in the controls of some studies [42, 46] did not show compliance with Hardy-Weinberg (HW) in the meta-analyses. In addition, Yang et al meta-analysis included one study comparing the frequencies of various genotypes of TNF-α-308 polymorphism in patients with benign breast disease and controls, and another study that did not have frequencies for each genotype [14, 16, 44, 45]

2.1.2 Hepato-celllular carcinoma

2.1.2.1 Interleukin-1

IL-1 α and IL-1β are pro-inflammatory and potent cytokines. It has been stated that the genes of this family are highly polymorphic that modulate the expression of IL-1β. IL-1β −511T/C, −31C/T, and +3593C/T are the most studied SNPs of the IL-1 gene family, in addition to 86bp of VNTR in intron 2 of the IL-1RN gene with 5 different alleles [47]. IL-1β-31C/T is associated with increased transcription initiation factor binding that has been shown to participate in hepatic carcinogenesis [48]. In the presence of IL-1β (−511CC and −31TT) genotypes, allele 2 was known to be a risk for HBV-related hepatocellular carcinoma (HCC). The IL-1β-511C allele was found to be an IL-1RN risk with no HCCC risk [49]. On the other hand, there was no connection between the IL-1β-511C allele and HCC in several studies. In the Wang et al. analysis [50], the IL-1β-31TT genotype and the IL-1β-511/−31CT haplotype were associated with an increased risk of HCC-related HCC and the risk factor was not the IL-1RN VNTR polymorphism.

2.1.2.2 Tumor necrosis factor-α

Polymorphisms of TNF-α (−1031T/C, −863C/A, −857C/T, −308G/A and −238G/A) are found to alter TNF-α development [51]. A critical risk factor for HCCC is regarded as TNF-α −308G/A [45], but TNF-α-238G/A is engineered to play a passive role in the risk of HCC [52]. On the other hand, several other studies indicated an increased risk of HCC for the allele TNF-α-308A [51]. The association between TNF-α promoter alleles such as TNF-α-308A and TNF-α-238A and various TNF-α-238A expressions is indicated in several studies [39].

2.1.2.3 Interleukin-6

In order to counteract inflammatory reactions, IL-6 is a key factor in viral infections. In the promoter area, the most studied genetic polymorphisms in the IL-6 gene are located downstream (−597G/A, −572G/C, −174G/C, and −373A/T), and have an effect on IL-6 development levels at the transcriptional stage [52]. These are reported to be associated with chronic hepatitis, where IL-6-572G/C was found to be associated with the risk of HCC-related HBV [53].

2.1.3 Gastric cancer (GC)

2.1.3.1 Interleukin-1Beta

There are three associated genes in the IL1 cluster: IL1-A, IL-1B, and IL-1RA that encode the signal proteins IL-1, IL-1, and their receptor, IL-1RA, respectively. The association between IL-1B and IL-1RA gene polymorphisms and the development of gastric cancer (GC) has been identified in numerous studies [47]. Polymorphisms of IL-1 are located in positions-511 (CT, rs16944), -31 (TC, rs1143627), and 3954 (CT, rs1143634) that affect the expression of IL-1. The majority of studies classify the IL1β-511 polymorphism T allele as normal among Caucasian individuals with non-cardiac GC but preferably for cancer of the intestinal subtype. It is, therefore, feasible to propose this SNP as a possible GC predictive marker. Even after numerous meta-analyses have been carried out, investigations of the IL1B-31 TATA-box polymorphism appear to be controversial. Around 14 studies [54] reported a slight non-significant correlation between the C variant allele and GC risk in comparison

with TT homozygotes. Again, in contrast with Hispanic or Caucasian cultures, there was no correlation between Asian groups. A modest increase in the intestinal GC subtype among C allele carriers in Caucasian populations was suggested by histologic stratification, but this statement was not true for the diffuse GC subtype. Wang et al. also found that the +3954 gene polymorphism T allele contributes to the GC risk. A lack of interaction between the +3954 polymorphism and GC was stated by Xue et al. [55]. A limited number of studies were conducted on the IL-1β-+3954 C/T polymorphism [55].

2.1.3.2 Interleukin-2

In the differentiation of CD41-positive T cells into Th1 and Th2 effector subsets, IL-2 effectively controls the immune response and plays an important role. IL-2 leads to the activation and transmission of immune responses that are inflammatory, including *H. pylori*-induced gastric inflammation. In the promoter region, IL-2, IL-2-330, and -384 have two types of SNPs that affect IL-2 development [56, 57]. Wu et al. [57], reported that the T allele significantly reduced the risk of gastric cardiac cancer with IL-2-330 polymorphism. Another research, on failed to show a significant association with IL-2-330, while Togawa et al. [58] on the other hand, stated in 2005 that the IL-2-330 T/T genotype in Japan increased the risk of gastric atrophy associated with GC. The IL-2-330 polymorphism yields contradictory findings. In addition, for IL-2-384 and +11.4 polymorphisms and GC growth, no significant association has been seen [59].

2.1.3.3 Interleukin-6

IL-6 appears to be involved in gastric oncogenesis, as serum IL-6 levels show an increase in the gastrointestinal cells and mucosa of patients suffering from GC [60]. The data collected indicated that the polymorphism of IL6-174G/C was related to the risk of GC in the West. The suppression of tumor necrosis factor-α and IL-11 could explain the carcinogenic properties of IL-6 [61]. In 2009, Kang et al. showed a strong negative association among HP-positive cases and controls between the IL6-572G/C polymorphism GG genotype and duodenal ulcer risk. The effect of the G allele on the rate of synthesis of proteins has not been determined to date, and the role of this SNP remains unclear.

2.1.3.4 Interleukin-8

IL-8 improves the proliferation and migration of cells and serves as a chemical attractor and mediates chronic inflammatory processes [62]. In contrast, mucosal levels of IL-8 were found to be elevated in GC patients, and the prognosis was significantly lower in patients with high expression of IL-8 compared to patients with moderate levels of this protein [63]. IL-8 can induce Reg protein expression in stomach cells, which intensifies gastric mucosal cell proliferation and may indirectly promote the initiation of GC [64]. In the IL-8 gene locus, fifteen functional polymorphisms occur, and some can alter gene expression [65]. Several IL8- case-control studies on 251A/T (rs4073), IL8 +396T/G (rs2227307), and IL8+ 781C/T (rs2227306) were conducted in which IL8-251A/T, A allele was associated with increased GCC [66]. Kang et al. [67] also found that higher GC risk is correlated with the AA genotype of HP-positive individuals. Due to conflicting findings, the role of IL-8 gene polymorphisms in GC remains unclear. The −251 polymorphism of

the gene, however, seems to play a major role in the development of GC and needs further study. In this region, the +396 and +781 SNPs are almost unexplored.

2.1.3.5 Interleukin-17A and 17F

IL-17A and IL-17F, synthesized by activated T cells, are characterized as pro-inflammatory. Five variants of this cytokine are known which differ in properties and sites of expression from the founding member IL-17A. Several studies have shown that IL-17 leads to gastric carcinoma growth and progression [68]. It has recently been suggested that a low IL-17 tumor expression rate can imply a poor prognosis in GC patients. Wu et al. reported that in comparison with the mutant AA genotype, the GA and GG genotypes of +7488 SNP were correlated with an increased GC risk and also reported the absence of a link between IL17-197G/A polymorphism and GC risk [69].

2.1.3.6 Tumor necrosis factor-α

One of the pro-inflammatory cytokines strongly expressed in *H. pylori*-induced gastritis is TNF-α, a potent gastric acid secretion inhibitor [70, 71]. While the TNF-α promoter has recorded several polymorphisms, most studies have concentrated on the G/A polymorphism at position 307 since most of the other polymorphisms are functionally silent. In patients with polymorphism at position 307 with malignant tumors, multiple studies find a higher concentration of TNF-α [72]. TNF-α is a pro-inflammatory cytokine, which is a mediator of the immune response in *H. pylori* and shares many biological behaviors with IL-1 [73]. It doubles the risk of gastric cancer without any correlation with the risk of gastric cancer of the esophagus or cardium [74, 75]. Studies done on the effect of TNF-α 307 polymorphisms on the expression of mucosal cytokine and showed no substantial differences in TNF-α level between different allele carriers that indicate that this polymorphism does not affect the development of cytokine. Some race-specific associations have been proposed by another meta-analysis summarizing data on TNF-α, 308 variants, with an increased risk of gastric cancer in various ethnic populations. TNF-α 238 polymorphisms were not substantially associated with the risk of gastric cancer, consistent with previous results [76]. Another research showed that a possible risk factor for gastric cancers is TNF-α 857 T allele.

2.1.4 Prostate cancer

2.1.4.1 Interleukin-1

The relation between the risk of IL-1 family polymorphisms, including IL-1A, IL-1B, and IL-1RN and prostate Cancer (PCa), has been less studied. There was no important correlation between PCa risk and IL-1B/IL-1RN polymorphism in several studies. In a recent meta-analysis, IL-1A, IL-1RN (rs315951 and rs3087263), and IL-1B+3953 (rs1143634) polymorphisms were not significantly correlated with the risk of PCa. In homozygote and recessive models, IL-1B-511 (rs16944) polymorphism was significantly associated with PCa risk, and in the heterozygote model, the allele comparison IL-1B-31 (rs1143627) polymorphism was also marginally significantly associated with PCa risk. Therefore, the meta-analysis indicated that IL-1B-511 (rs16944) and IL-1B-31 (rs1143627) sequence variants were significantly associated with PCa risk. This result presents more new evidence that pro-inflammatory cytokines and inflammation play an important role in the etiology of PCa [77].

2.1.4.2 Interleukin-6

Interleukin 6 (IL 6) plays a crucial role in the inflammatory phase among the cytokines involved in inflammation. Mandić et al., found that IL-6-174 SNP differs between ethnicities and that single polymorphic cytokine variants most likely have little effect on the susceptibility of PCa [78]. The study by Pierce et al. showed that circulating IL- 6 and its gene polymorphism did not affect the risk of PCa [79]. Whereas Mandal et al. had a contrary view [80]. Another meta-analysis of 11 independent studies, including 10,745 cases and 13,473 controls based on several recently published studies which indicated an inconsistent conflicting and incon-sistent trends of association between IL- 6 (174 G/C) and PCa. IL- 6 (174 G/C) polymorphism has been found not to be a risk factor for prostate cancer in the general population [81].

2.1.5 Esophageal cancer

2.1.5.1 Interleukin 6

IL-6 (interleukin-6) is a pro-inflammatory peptide that is actively involved in tumorigenesis [82]. The effect of IL-6 and IL-6 receptors (IL-6R) on the prognosis of esophageal cancer (EC) has been identified [83]. Systemic and/or local IL-6 therefore appears to be a central molecule in the stimulation of ESCC progression. Different studies have shown an association between various IL-6 polymorphisms and cancers. Polymorphism of IL-6-634G>C and prognosis after EC esophagectomy revealed that when EC patients were treated surgically, those with the IL-6-634G/G or G/C genotype had a 3-fold poorer prognosis than those with the C/C genotype. In comparison, IL-6R polymorphism and IL-6 tumor expression are not associated with prognosis [84]. With respect to EC, Oka et al. [85] stated that poor survival was associated with high serum IL-6 levels. Buraczyn et al., on the other hand, stated that in the presence of inflammatory stimulation, patients carrying the G allele and to an even greater extent the G/G genotype showed higher IL-6 output at position −634 in the IL-6 promoter region than patients carrying the C allele [86]. Kitamura et al. also reported that the 634 G allele is associated in vitro with increased IL-6 production in peripheral mononuclear blood cells [87]. While IL-6 levels are associated with different cancers, the rela-tionship between IL-6 and EC polymorphisms requires further evaluation because less studies are available [88].

2.1.5.2 Interleukin 12

The pro-inflammatory cytokine family is the Interleukin 12 (IL-12) family, which is essential for host tumor resistance [89]. A few studies have determined whether polymorphisms and serum levels of the IL-12 family (IL-12A gene rs568408, IL-12Bgene rs3212227, IL-27 gene rs153109, rs17855750, rs181206) and its family receptor (IL-12Rb1, 378 C/G) gene are correlated with EC. Studies that revealed polymorphisms of IL-12 rs568408, rs3212227, and IL-12Rb1 gene 378 C/G and serum levels of IL-12p40 and IL-27p28 were significantly associated with the risk of EC [90]. IL-12Rb1 gene Codon 378 C to G causes a transition in amino acid (glycine to arginine), which may further weaken the transcript's subsequent biological activity and is linked to many malignancies such as leiomyoma [91].

2.1.5.3 Interleukin-18

Interleukin-18 (IL-18) is another cytokine that is mainly involved in the inflammatory immune response and is a potent factor triggering IFN-γ. Genetic IL-18 gene polymorphisms have recently been observed to have a significant effect on the vulnerability of a number of inflammatory diseases and various malignancies, including EC [92]. Different SNPs have been identified in the promoter region of the IL-18 gene and are likely to influence gene activity [93]. In the promoter region of the same gene, three SNPs were found at distinct positions −137, 607, and 656 relatives to the transcriptional start site. A study conducted by Ye et al. in the Chinese population investigated 137 G/C and 607 C/A polymorphisms of the IL-18 gene in EC patients. The 137 GC and CC genotypes were associated with a significantly increased risk of ESCC as compared with the −137 GG genotypes as G to C substitution at position 137 abolishes a histone4 transcription factor-1(H4TF-1) nuclear factor-binding site and hence has an impact on IL-18 activity. Nevertheless, in EC patients, the genotype and allele frequencies of IL-18 promoter 607 C/A polymorphism were not substantially different from those in healthy controls. The results, therefore, indicate that IL-18 137 G/C polymorphism could be used as an ESCCC genetic susceptibility marker [94].

2.1.5.4 Tumor necrosis factor-α

Tumor necrosis factor-alpha (TNF-α) is a pro-inflammatory cytokine that plays a major role in host defense and inflammatory responses but also induces cell death and tissue degradation in some instances [95]. There have been reports of dysregulated expression of TNF-α associated with a number of tumors, including EC, [96]. A number of SNPs of TNF-α gene have been found, which include TNF-α-238 G/A (rs361525), TNF-α-308G/A (rs1800629), TNF-α-857C/T (rs179972), TNF-α-863C/A (rs1800630), TNF-α-509C/T (rs1800469) and TNF-α-1031T/C (rs1799964) [83]. Among these, the most common TNF-α polymorphisms occur at position 308 in the promoter region and are extensively studied, showing a strong association with increased TNF-α production [97]. Many studies have focused on the association between TNF-α-308 G>A (rs1800629) and EC risk [98]. Deans et al. have found that the genotype AA TNF-α 308 is associated with an adverse prognosis of gastroesophageal cancer [99]. In contrast, the results of the Cui et al. study found that TNF-α-308G/A polymorphism was not associated with EC risk [100]. In addition, Guo et al. did not find a significant difference between EC patients and controls in the overall genotypic distribution of TNF-α-308G/A polymorphism [101]. In addition, few meta-analyzed studies report that TNF-α-308 G>A (rs1800629) is poorly associated with an increased risk of EC [102]. Conclusions on the role of TNF-α -308G/A gene polymorphism in the risk of EC have, therefore, been inconsistent.

2.1.5.5 Interferon-γ

The cytokine produced against viral and intracellular bacterial infections in the human body is Interferon-gamma (IF-γ). Many polymorphisms have been investigated mostly in IFN-gamma, which are significantly associated with many complications such as susceptibility to many infections [103]. It has been stated that a risk factor for EC may be the IFN-γ + 874AT genotype. The study by Du et al. has shown that IFN-γ + 874, T allele may predispose for EC [104]. Another research found that an important association existed between the genetic polymorphism of

INF-γ 874A>T and infectious complications following esophagectomy in a cohort of EC patients [105].

2.1.6 Pancreatic cancer

2.1.6.1 Interleukin-1 beta

Interleukin 1b (IL1b), a central IL-1b gene-encoded pro-inflammatory cytokine, has been associated with chronic inflammation and plays an important role in inflammatory pancreatic diseases, including pancreatic cancer [106]. In the production of pNETs, the functions of IL-1b −511C/T and +3954 C/T genotypes remain unclear. PNETs are a heterogeneous group with different biology and prognosis of tumors; they can occur as solitary tumors, and up to 15% of pNETS are part of hereditary syndromes. The findings of Maja et al. [107] showed a significant correlation between the IL-1b −511C/T genotype and CTCT −511/+3954 genotype combination and susceptibility to functional pNET growth, and the risk of non-functional pNET development were associated with patients with CTCC −511/+3954 genotype combination. All of these findings indicate IL-1b participation in the growth of pNET [107].

2.1.6.2 Interleukin-2

In T cell-dependent immunity, IL-2 is a potent pro-inflammatory cytokine and a central regulatory cytokine. Several SNPs) have been found to alter IL-2 production in the promoter region and to be associated with inflammation-based cancer [58]. The G-allele in the IL-2 promoter at the −330 position seems to correlate with higher IL-2 output [108]. It has been shown that during the cell cycle, dividing cancer cells release IL-2 in various concentrations and that IL-2 promotes cancer development [109]. Hofsli and collaborators found that GEP-NET carcinogenesis growth factors downregulate the IL-2 receptor, presenting proof of an additional mechanism through which neuroendocrine cancer cell growth is promoted [110]. It was found that G-allele raises the expression of IL-2 at the −330 position and that individuals homozygous for the G-allele have three times higher IL-2 values [108].

2.1.6.3 TNF-α

In the inflammatory etiology of pancreatic cancer, TNF-α plays a very crucial role. The risk factor for various forms of cancer, such as hepatocellular carcinoma, gastric cancer, and breast cancer, has been identified as TNF-α-308 polymorphism [111–113], while previous studies have reported that polymorphisms in the TNF-A-308 A/G gene are not linked to pancreatic cancer [78].

2.1.7 Bladder cancer

2.1.7.1 Interleukin-6

IL6 is an inflammatory pleiotropic cytokine released by different types of lymphoid/non-lymphoid cells [114]. Immune response, cell survival, proliferation, and apoptosis are critical for [113]. In the IL-6 promoter region, numerous polymorphic variants have been identified that are associated with IL-6 transcription activity [115] which indicates a connection to cancer [116].

IL-6 polymorphism has been shown to modulate changes in its expression to cause cancer risk, including bladder cancer. Association studies of IL-6 gene

polymorphisms conducted in India and globally confirm the risk of several CC genotype and C allele cancers, especially BCC allele cancers [117, 118]. Fishman et al. have stated that IL-6-174 G/C polymorphic variation affects transcription and IL-6 protein expression [119]. Conversely, several studies from other parts of the Indian and Caucasian population indicated that conflicting findings were present [120, 121]. The variant genotype IL-6-174 G/C was shown to be significantly associated with an increased risk of BC [122] but no BC risk association was found by other authors [123]. In addition, there was no proven association between IL-6-572 G/C, -596 A/G polymorphisms, and BC risk [118].

2.1.7.2 TNF-α gene polymorphisms

A major inflammatory cytokine is the tumor necrosis factor-alpha (TNF-α) gene, which mediates a connection to all steps involved in tumor growth and development. TNF-α gene polymorphisms and their receptors have conceptualized the understanding of the genetic effects of inflammatory consequences [124]. Polymorphic sequence differences are mainly documented in association studies of various cancers like BC, with some studies refuting and other studies showing the association for cancer risk, mostly single nucleotide changes in TNF-α promoter [125, 126]. This contentious link between TNF-α polymorphisms and UBC is due to the race, sample size, and technical aspects involved. Of the 7 variants of the TNF-α gene studied by Marsh et al., 859T and +488A polymorphisms were significantly linked to BC risk [127]. Another research investigates 3 TNF-al-1031 T>C polymorphism SNPs where high risk was identified for controls of BC cases [128]. Similarly, experiments on TNF-al-308 G>A polymorphism have also reported controversial results [129, 130]. Although TNF-α-308 A variant alleles with a major risk relationship to BC risk were observed by Lima et al. [131].

2.1.8 Gliomas

2.1.8.1 IL-4 gene polymorphism

Research by Brenner et al. found that the polymorphism of IL-4 (rs2243248, −1098T>G) was substantially correlated with the overall risk of glioma [132]. Another study showed that IL-4 induced aberrant Stat3 activation in glioblastoma cells but not in normal human astrocytes, and hypothesized that aberrant Stat3 activation induced by IL-4 could contribute to the pathogenesis of GBM cells [133].

IL4R encodes the interleukin-4 receptor alpha chain that can connect interleukin 4 and interleukin 13 to regulate the development of IgE [134]. In 2013, TianboJin et al. reported that rs1801275 in the IL-4R gene can predict the over-dominant model of Glioma susceptibility by 2.29-fold [135]. Furthermore, another article also stated that rs1801275 could increase the risk of studying glioblastoma [136]. However, an important link between mutant IL-4R alpha rs1801275 and gliomas was not found by Ruan et al. [137].

2.1.8.2 IL-12gene polymorphism

Many SNPS, like 1188A/C, in the IL-12 gene will affect its levels of expression and are associated with several tumors such as nasopharyngeal carcinoma [138] and breast cancer [139]. This SNP might influence the susceptibility of individuals to glioma. Haidar et al. stated that neither mutant (hetero or homozygous) genotypes nor mutant IL-12p40 1188A/C variant allele appears to be associated with gliomas

[140]. In line with a meta-analysis review, this outcome [141]. The stratification by cancer type showed that the variant only represents a risk factor for cervical and nasopharyngeal cancer, although these authors found a substantial association of the variant with overall cancer.

2.1.8.3 IL-13 gene polymorphism

IL-13 plays an important role in allergies and is essential for the suppression of tumor immune surveillance through an immune regulatory pathway [142]. SNPs, including rs25041, rs1800925, and rs1295686, found in the IL-13 gene, are closely linked to IL-13 expression. In human malignant glioma cell lines and in primary tumor cell cultures, IL-13 has been shown to be over-expressed [143]. The serum immunoglobulin E (IgE) level could be significantly increased by the rs20541 A allele (glutamine (Gln, Q) form) in different populations [144]. Evidence has also been established by previous research that IgE levels in patients with glioma were lower than in people without glioma [136]. It is very fair to expect the IL-13 gene rs20541 polymorphism to exert some effect on glioma susceptibility due to its important roles in immune surveillance and serum IgE level modulation. A recent meta-analysis review, however, indicates that the IL-13+rs1800925 genotype could be a risk factor for gliomas and that IL-13+rs20541 contributes to cancer [145] (**Table 1**).

2.2 Hematological malignancies

2.2.1 Lymphomas

2.2.1.1 IL-4 and IL-5 gene polymorphisms

In the proliferation of T cells, Il-4 and Il-5 play a key role. The study of the relationship between SNPs was chosen from the main immunological genes of cytokines and NHL in several studies. This represents a pathway-based approach to the investigation of common genetic variants in the cytokine network of Th1 and Th2. Common genetic variants of the Th2 cytokine genes have been observed and are associated with NHL risk. SNPS has been shown to be substantially associated with an increased risk of NHL in the TH2 genes IL-4 ($-1098T>G$) and IL-5 ($-745C>T$) [165].

2.2.1.2 IL-6 gene polymorphism

While monocytes are the main source of IL-6, many cells, including dendritic cells, lymphocytes, neutrophils, mast cells, mesenchymal cells, and tumor cells, may produce it. IL-6 rs1800797 (IL-6 rs1800795G>C, rs1800796G>C, rs1800797G>A) was the only SNP to demonstrate substantial survival outcomes, with DLBCL co-dominant model (GG/AG/AA) and recessive model (AA genotype versus combined GG/GA genotype) subjects having worse overall survival. The correlation between polymorphism of the IL-6 gene promoter and the risk of lymphomas, however, shows inconsistent results. A common case-control study conducted by the International Lymphoma Epidemiology (Inter Lymph) consortium in 2006 to examine the relationship between gene polymorphisms and the risk of lymphoma showed that there is no correlation between IL-6 promoter polymorphism (174G>C rs1800795) and the risk of NHL [166].

Activity	Cancer type		Cytokines	Polymorphisms	Association	Allele	References
Pro-inflammatory	Solid tumors	Breast	IL-6	−174 G/C	High grade tumor	−174 CC	[25]
			IL-10	21082 G>A	Worst prognosis	−21082 AA	[28]
					High risk	−21082 AA	[29]
			IFN-γ	+874T/A	Increased risk	+874 AA	[36]
				−1615C/T	No	—	[36]
			TNF-α	−308G/A	Poor prognosis	−table308GA, AA	[40]
					No	—	[43]
		HCC	TNF-α	1031T>C	No	1031T>C	[146]
				863C>A	Yes	863C>A	[146]
				857C>T	No	857C>T	[146]
				308G>A	Yes	308G>A	[146]
			IFN- γ	+874T>A	Risk factor	+874T>A	[147]
			IL-18	607A>C	Risk factor	607A>C	[148]
				137C>G	Risk factor	137C>G	[149]
				148G>C	Risk factor	148G>C	[150]
			IL-16	rs11556218T>G	Risk factor	rs11556218T>G	[151]
				rs4072111C>T	Risk factor	rs4072111C>T	[151]
				rs4778889	Risk factor	rs4778889	[152]
			IL-12A	rs3212227A>C	Risk factor	rs3212227A>C	[153]
			IL-12B	rs2243115T>G	Risk factor	rs2243115T>G	[147]

Activity	Cancer type	Cytokines	Polymorphisms	Association	Allele	References
	Gastric	TNF-α	TNF-α 307	Race sp. asso.		[150]
			TNF-α 307, 1031, 863, 857, and 238	Not favoring		[154]
						[75]
			TNF-α 307	Not favoring		[155]
		IL-1β	IL1β –31 T/C	Slight non sig	C allele	[155]
			IL1β –511C/T	Significant association	TT	[94]
				Association	T allele	[156]
				Association	T allele	[55]
			IL1β +3954 C/T	Lack of association	T allele	[55]
				Association	T allele	[156]
		IL-6	Il-6 −174 G/C	Association	GG	[157]
			IL-6 −572 G/C	Negative association	GG	
			IL-6 −597 G/A	Lack of association	G allele	[158]
		IL-8	IL8 –251A/T,	Lack of association	TA	[158]
			IL8 +396T/G,	Lack of association	GG	[158]
			IL8+781C/T	Lack of association	CT	[157]
		IL-2	IL-2 -330	Sig reduced risk	T allele	[57]
				Non-sig association	T allele	[159]
				Sig association	TT genotype	[58]
			IL-2 −384G/T, +114G/T	Non-sig association		[59]
		IL17A and IL17F	–197G/A	Lack of association	AG	[4]
			+7488A/G	Association	GG	[4]

Activity	Cancer type	Cytokines	Polymorphisms	Association	Allele	References
	Prostate	IL-6	IL-6 −174	Least association		[78]
		IL-1	IL-6	No. assoc.		[79]
			IL-6	Association		[80]
			IL-6 −174 G/C	No association		[81]
			IL-1α/IL-1RN/ILβ +3953	No association		[77]
			IL-1β-511/IL-1β-31	Association		[77]
	Esophageal	IL-6	−634	Poor prognosis	−634GG	[84]
		IL-12A	rs568408 G>A	Susceptibility	rs568408 GA,GG	[160]
		IL-12B	rs3212227A>C	Significant risk	rs3212227AC,CC	[160]
		IL-12Rb1	−378	Susceptibility	−378 GG	[160]
		IL-18	−137 G/C	Increased risk	−137 CC,	[94]
			−607 C/A	No	−607 C/A	[94]
		TNF-α	−308	Adverse prognosis	−308 A/A	[99]
		IFN-γ	+874A>T	Protective	+874AT,TT	[104]
	Pancreatic	IL-1β	−511C/T, −511/+3954	Favouring	CT genotype	[106]
		IL-2		Favouring	CT genotype	[107]
		TNF-α-308	IL-2 −330	Favouring	G allele	[108]
		A/G	TNF-α-308 A/G	Not favouring	AG	[69]
	Bladder cancer	TNF-α	1031T>C	No	1031T>C	[161]
			−857C>T	Yes	−857C>T	[161]
			−308G>A	Yes	−308G>A	[161]
		IFN-γ	IFN-γ +874	Yes	IFN-γ +874	[162]

Activity	Cancer type	Cytokines	Polymorphisms	Association	Allele	References
		IL-1β	−511C>T	No	−511C>T	[123]
		IL1-RN	VNTR	Yes	—	[163]
	Glioma	IL-4	−588C>T	Suggestive association	−588TT	[132]
			−1098T>G		−1098GT,GG	[132]
		IL-4R	+828A>G	Overall risk	+828A>G	[164]
				Overall risk	—	[137]
		IL-12	−1188A>C	No	—	[140]
		IL-13	+2044A>G	No susceptibility	+2044AA,AG	[136]

Table 1.
A meta-data of different pro-inflammatory cytokine polymorphisms and their association in various solid tumors.

2.2.1.3 IL-10 gene polymorphism

A number of studies have evaluated the association between specific polymorphisms of IL-10 genes and the risk of non-Hodgkin lymphoma but fewer studies analyzed the impact of IL-10 polymorphisms on the prognosis of patients with DLBCL. There is clear evidence that in hematologic malignancies, immune-regulatory cytokines play a major role. The relationship of seven single nucleotide polymorphisms (SNPs) in two selected cytokines (IL-6 rs1800795 G C, rs1800796 G>C, rs1800797 G>A, IL-10 rs1800871 G A, rs1800872 G>T, rs1800890 A>T, rs1800896 T>C) to risk and overall survival was examined in different studies [167].

2.2.2 Leukemias

2.2.2.1 IL-15, -18 and-1β gene polymorphism in acute lymphoblastic leukemia (ALL)

The proliferation of T, B, and NK cells is encouraged by IL-15, a pro-inflammatory cytokine. Some studies have previously shown that IL-15 can protect hematologic tumors from drug-induced in vitro apoptosis, and high expression of IL-15 is associated with childhood ALL CNS disease. Several minimal residual diseases (MRD)-related IL-15 SNPs have been shown to have a link to increased in vitro transcription/translation efficiency of IL-15. As found by the GWAS scan, there are 5 SNPs in the IL-15 locus that are significantly correlated with childhood ALL therapy response. In the most recent study, polymorphisms of the IL-15 rs10519612 CC genotype have been shown to be associated with adult ALL1 [69]. Polymorphisms of IL-1β (rs16944) and IL-18 (rs1946518) have been shown to predict the prognostic consequences and manage ALL. The impact of the rs1884444 sequence variant on relapse rate and connection of rs10889677 AA genotype with favorable prognostic factors recommend the influence of the investigated SNPs on ALL response to treatment and outcome.

2.2.2.2 Other gene polymorphisms in acute and chronic leukemia (AML and CML) and chronic lymphocytic leukemia

Polymorphisms of IL-1β (rs16944) and IL-18 (rs1946518) have been shown to predict the prognostic consequences and manage ALL care. In cytokine genes, several SNPs have been identified, indicating that certain alleles may lead to alterations in cytokine production [168]. It is, therefore, hypothesized that variants of the cytokine gene can influence the expression of genes and may be associated with leukemia pathogenesis.

The relation between the polymorphism of IFNγ +874T>A (rs2430561) and the risk of CML [169] or earlier, CLL was assessed. Various studies have suggested that the IFNγ+874T>A polymorphism leads to the susceptibility of CML and CLL [168]. No association between TGFβ1 rs1800470 polymorphism and leukemia was identified in earlier studies. Nursal et al., on the other hand, found that variants of the genes TNF-α rs361525, IL-10 (−1082G>A rs1800896, −819C>T rs1800871, −592C>A rs1800872) and TGF-β1 (codon 25) may have a significant association with AML etiopathogenesis [170]. The relation between TNF-α 308G>A, IL-10 (−592T>G, −819T>C, −1082T>C), IFN-γ +874T>A and TGF-β1 (codons 10 and 25) was not identified to confer any risk to CML [169].

2.2.3 Myelomas

2.2.3.1 IL-1gene polymorphism

IL-1 is a potent cytokine that is pro-inflammatory and functions as an endogenous pyrogen. IL-1 has two cytokines formed by two diverse genes, IL-1 alpha, and IL-1β. Cytokine plays a crucial role in the development, differentiation, and function of different immune cells in cells. An important interaction between IL-1 alpha-889C>T and IL-1β-3737C>T and the risk of MM was shown to have an association with polymorphisms of IL-1 [171].

2.2.3.2 IL-6 gene polymorphism

As a proliferative factor for multiple myeloma (MM), IL-6, a cytokine with broad inflammation and immunity functions, is identified. Some myeloma cells and bone marrow stromal cells may produce IL-6 and can restrain apoptosis in myeloma [172]. Previous studies have shown that IL-6 expression can be partly genetically modulated in the promoter region of IL-6 by polymorphisms located at the rs1800795 location. Recent studies have shown that the association of IL-6 rs1800795 polymorphism with MM risk is negligible.

2.2.3.3 TNF-α gene polymorphism

Gene polymorphisms of TNF-α may also be essential for its functional variation. Research has shown that a TNF-α allele (−308) has been expressed at lower levels in MM subjects, indicating that an allele can have a protective effect against disease [173]. However, the GG genotype of TNF-α (−238) was shown to be correlated to early progression in MM in another study [174].

2.2.3.4 IL -12 gene polymorphism

IL-12 is a cytokine that stimulates immunity that is both innate and adaptive. This induces cytotoxicity of Th1 cells and has been shown to have effective immunomodulatory and anti-tumor activities [175]. However, while IL-12 is an inflammatory cytokine, protection from neoplastic disease appears to be the prevalent activity of the cytokine in this case. There is no clear link between IL-12 (rs1801131) (A>C), polymorphism, and the risk of MM in recent studies [176] (**Table 2**).

3. Anti-inflammatory cytokine gene polymprphisms

3.1 Solid tumors

3.1.1 Breast cancer

3.1.1.1 IL-1β gene polymorphism

A variety of cell types, including monocytes, macrophages, and epithelial cells, are formed by interleukin-1β (IL-1β) belonging to the IL-1 family and have multiple biological effects [190]. IL-1β induces the expression of pro-inflammatory genes that may play a key role in the early stages of carcinogenesis, such as cyclooxygenase type 2, inducible nitric oxide synthase, and other cytokines/chemokines. A number of studies have documented the association of IL-1β polymorphisms with

Activity	Cancers type			Cytokines	Polymorphisms	Association	Allele	References
Pro-inflammatory	Hematological cancers	Lymphomas	HL	IL-1	+4345 T>G	Significant	−TG	—
				IL-6	−174 G>C	Significant	174 GC	[177]
				TNF-α	−863/308 C>A/G>A	Not significant	−863/308 CA,GA	[177]
			NHL	IL-6	rs1800795 G> C	Not significant	−174GC	[166]
					rs1800796 G>C	Significant	−598GA	
				TNF-α	rs1800629 G>C	Significant	−308GA	[157]
				TNF-β	rs909253 A>G	Significant	−252AG	[178]
				IL-4	rs2243250T>G	Significant	−1098TG	[178]
				IL-5	rs2069812 C>T	Not significant	−745CT	
		Leukemias	ALL	IL-1β	rs16944 G>A	Significant	TT	[179]
				IL-18	rs1946518	Significant	TT	[180]
				IL-15	rs10519612	Significant	CC	[181]
				IL-6	174G/C	Significant	rs1800795 GC	[182]
				IL-4	590C/T	Not significant	rs2243250 CT	[170, 183]
			AML, CML, CLL	IL-1α	889C>T-	Significant	889CT	
				IL-1β	3737C>T	Significant	3737CT	[184]
				IL-2	rs1800795 G>C	Significant	174/52GC	[185]
				IL-6	rs1801131C>G rs361525G>A	Not Significant	CG	[184]
				TNF-α	rs2430561T>A	Significant	-308/238 GA	[186]
				IFN-γ	889C>T-	Significant	+874T TA	

Activity	Cancers type	Cytokines	Polymorphisms	Association	Allele	References
	Myelomas	IL-1 α	889C>T	Highly significant	CT	[187]
		IL-1β	3737C>T	Highly significant	CT	[187]
		IL-6	174/52G>C	Significant	rs1800795 GC	[188]
		IL-12	rs1801131 A>C	Not significant	rs1801131AC	[185]
		TNF-α	−308/238 G>A	Significant	rs1800629-308/238 GG	[189]

Table 2.
A meta-data of different pro-inflammatory cytokine polymorphisms and their association in various liquid cancers.

the risk of breast cancer, establishing the important role of IL-1β in its development. The findings are contradictory due to the relatively small sample size of the study. Ito et al. [191] first recorded that rs1143627 is significantly correlated with the risk of breast cancer (CC vs. TT: OR = 1.82). The correlation in the Chinese population was followed by another case-control analysis by Liu et al. (CC vs. TT: adjusted OR=1.72). All the studies for rs1143627 included in the meta-analysis were conducted in Asian populations, suggesting that rs1143627 could contribute to the risk of breast cancer, especially in Asians [34].

3.1.1.2 TGFβ -1 gene polymorphism

A multifunctional cytokine that is important for maintaining homeostasis involving bone and muscle differentiation, immune response, and tumor suppression is the transforming growth factor beta-1(TGFβ-1). Increased TGFβ-1 development occurs in different tumor types and is associated with tumor grade severity [192]. There is evidence that when the proliferative inhibition effect of the TGFβ-1 signaling pathway has been overridden by other oncogenic mutations, TGFβ-1 functions as a suppressor of tumor initiation but as a promoter of tumor progression [193]. The 29T/C transformation that generates a Leu10Pro replacement in the TGFβ-1 precursor signal peptide has been reported to be associated with TGFβ-1 secretion of the protein and thus may have altered the risk of breast cancer. In the published clinical trials, Dunning et al. [194] concluded that in studies (20,837 patients and 22,879 controls) from European countries, TGFβ-129T/C T polymorphism was strongly correlated with breast cancer risk (C/C versus T-carrier, 1.21; 95% CI 1.05–1.37); Hishida et al. [195] found that the C/C genotype was substantially correlated with a decreased risk of breast cancer relative to the T/T genotype (OR = 0.45, 0.20–0.98); polymorphisms are not likely to be associated with major increases in the overall risk of breast cancer among Caucasian women in the promoter region of TGFβ-1. Another meta-analysis review indicated that the 29T/C polymorphism did not contribute to breast cancer risk in both recessive, dominant, and other genetic models [196].

3.1.2 Hepato-cellular carcinoma

3.1.2.1 IL-10 gene polymorphism

During chronic viral infections, IL-10, an immune suppressor cytokine, plays a vital role in the weakened host immune response, where its secretion is stated to be genetically regulated [197]. The most studied SNPs that have an influence on IL-10.1 development are IL-10 (−1082G/A, −819T/C, and −592A/C). The reports suggested that −1082 G allele and GCC haplotype are correlated with high IL-10 expression, where less expression association is shown by ATA haplotype. On the other hand, studies have shown that IL-10GCC and IL-10 haplotype AAGCC (−3575, −2763, −1082, −819, and −592) are associated with lower IL-10 haplotype concentration [198].

3.1.2.2 TGF-β1 gene polymorphism

In addition to +869T/C (Codon 10), +915G/C (Codon 25) and +788C/T (codon 263), TGF-β1 polymorphisms are identified in TGF-β1-988C/A, -800G/A, -509C/T and in insertion/deletion [199, 200]. Several SNPs are identified in TGF-β1 (+869T/C and +915G/C) [201] while TGF-β1 +869T allele was found to be correlated with high TGF-β11 expression [202].

3.1.3 Gastric cancer

3.1.3.1 IL-4 gene polymorphism

IL-4 is also recognized as a pro-inflammatory cytokine suppressor and an enhancer of anti-inflammatory cytokine synthesis [203]. The polymorphism of the promoter IL4-590C/T (rs2243250) is widely studied because the mutant T allele has been documented to increase IL-4 expansion compared to the C allele [204]. In contrast with the TT genotype, Wu et al. found an increased risk of developing diffuse form and cardiac GC for the CT/CC genotype in 2003. It is also proposed that lower IL-4 levels in the gastric mucosa favor the growth of GC. The genetic polymorphism IL4-168T/C (rs2070874) tested by Wu et al. [205] stated that a reduced GC risk among the Chinese population was correlated with mutant C allele.

3.1.3.2 IL-10 gene polymorphism

As an immune suppressor and anti-inflammatory mediator, IL-10 typically acts. From the transcriptional start site, there are 3 functional promoters SNPs at-1082 (A to G, rs1800896), -819 (C to T, rs1800871), and -592 (A to C, rs1800872) pairs in the IL10 locus. Studies of IL10-1082A/G, IL10-592A/C, and IL10-819C/T polymorphisms indicate the absence of major discrepancies in the distribution of genotypes between GC patients and healthy controls [206–208].

3.1.4 Prostate cancer (PCa)

3.1.4.1 IL-10 gene polymorphism

The most studied cytokine for PCa risk is IL-10. Controversial findings have emerged in this regard, where various studies show conflicting results and the latest meta-analysis showed that IL-10 (rs1800871) polymorphism was not correlated with PCa danger [209]. On the contrary, another meta-analysis indicated that polymorphic variants of IL-10 (rs1800871) and IL-10 (rs1800872) reinforce the idea that these may be moderately correlated with advanced PCa and thus affect disease progression [210]. The 2011 study by Shao et al found no substantial evidence suggesting variations in allele frequency or genotype distribution between PCa patients and control subjects for any of the three SNPs IL-10-1082 A>G, -819 C>T and -592 C>A.

3.1.5 Esophageal cancer

3.1.5.1 IL-1β gene polymorphism

In cell proliferation and apoptosis, interleukin 1β (IL1β) is involved which is an essential mediator of inflammatory response. IL1β induces COX-2 expression, inducible synthase nitric oxide, and other cytokines/chemokines, which can function significantly in the early stages of carcinogenesis. Many cancers such as gastric cancer and inflammatory bowel disease are associated with IL1β polymorphisms [211]. One of the polymorphisms associated with IL1β levels in the promoter area is rs16944 G>A [212]. According to Liang et al., IL1ß rs16944 GA variant heterozygotes had a substantially decreased chance of ESCC rather than IL1ß rs16944 AA homozygotes, in line with the Thai population study showing that IL1ß rs16944 GG genotype was found to be more common in patients with gastric cancer [213, 214]. However, minimal studies have been performed that can provide us with

clear proof of the functionality in the risk of ESCC of IL1ß rs16944 G>A polymorphism.

3.1.5.2 TGF-β1 gene polymorphism

Two main components of TGF-β signaling that play an important role in carcinogenesis are the transforming growth factor β1 (TGF-β1) and its TGF-β1RII receptor. Several functional polymorphisms were observed in TGF β1 and TGF β1 RII and were correlated with elevated TGF-β1 serum or plasma levels and increased TGFβ1RIII transcription activity. Epidemiological evidence has shown that two transforming growth factor-beta 1 (TGF-β1) gene polymorphisms (namely rs1800468G>A and rs1800471G>C) could be involved in the production of cancer. Their function in the carcinogenic process of esophageal squamous cell carcinoma (ESCC) has, however, been less well described. In recent studies, two polymorphisms of this gene (namely rs1800468G>A and rs1800471G>C) have been shown to be associated with TGF-β1 dysfunction and increased tumor risk [215, 216]. Several evidence indicates that ESCC risk may be increased by the genotypes with rs1800471 C alleles and rs1800471G>C polymorphism may play an important role in ESCCC tumorigenesis [217]. There were some drawbacks to this analysis, however. In contrast to the above findings, several studies have shown that RS#1800468 polymorphism is not associated with an increased risk of ESCC, but with a reduction in the survival of this tumor, consistent with other studies of various cancers [216, 218].

3.1.6 Pancreatic cancer

3.1.6.1 TGF-β1 gene polymorphism

TGF-β functions not only as a powerful epithelial, endothelial and hematopoietic cell proliferation inhibitor but also acts as an effective pro-inflammatory cytokinetic cell proliferator. In cellular proliferation, angiogenesis, differentiation, migration, and apoptosis, TGF-β pathway has important roles. TGF-β expression levels have been reported to correlate with the period of postoperative survival in various malignancies [219]. A study by Zhang et al. [220] showed the TT genotype to be more common in patients with leakage of pancreatic anastomosis in TGF-β. In addition, TT genotype cases had an increased level of bilio-digestive anastomosis leakage.

3.1.7 Bladder cancer

3.1.7.1 IL-6 gene polymorphism

Interleukin-6 (IL6), a pleiotropic inflammatory cytokine released by different types of lymphoid/non-lymphoid cells, is important for immune response, survival of cells, proliferation, and apoptosis [113]. In the IL-6 promoter region, different polymorphic variants have been identified that are associated with IL-6 transcription activity [115], IL-6 influences the release of acute-phase proteins in the acute inflammatory response and regulates the anti-inflammatory cytokines, thereby influencing the strength of inflammatory response. IL-6 is active in multiple cancer growth pathways and promotes neo-angiogenesis. IL-6 polymorphism has been shown to modulate changes in its expression to induce cancer risk, like bladder cancer. Association studies of IL-6 gene polymorphisms conducted in India and globally support the risk of CC genotype and C allele in many cancers, especially

BC. Fishman et al. have stated that IL-6-174 G/C polymorphic heterogeneity affects transcription and IL-6 protein expression. The variant genotype of IL-6-174 G/C has been shown to be substantially associated with an increased risk of BC but other authors have not identified any risk association. In addition, there was no proven association between IL-6-572 G/C, -596 A/G polymorphisms, and BC susceptibility [117].

3.1.7.2 IL-4 gene polymorphism

Interleukin-4 (IL-4), an anti-inflammatory cytokine produced mainly by activated CD4+T cells, plays a significant role in the production of Th2 to examine and destroy distorted cells and eradicate extracellular pathogens [221]. The risk conferred by IL-4-590 C/T polymorphism in different cancers has been substantiated by studies from different quarters [222]. In order to modulate the incidence of BC, a polymorphic variance of IL-4-590 C/T was found and another analysis similarly observed a substantial difference in variant allele distribution between cases and controls [223].

3.1.7.3 TGF- β gene polymorphism

TGF-β1 is the most abundant type of TGF-β, which includes numerous polymorphic variants that regulate the expression of TGF-β1 proteins. The risk association of TGF-β1 polymorphisms in a number of cancers has been verified. TGF-β1 was shown to be associated with the possibility of BCC in 41 SNPs. In comparison, 3 polymorphisms in TGF-β1 and 4 in the TGFβR1 gene showed no correlation yet another study reported comparable outcomes of negligible interaction with BC [210]. Gautam et al., on the other hand, observed an important association between TGF-β1 c.29 C/T and the risk of BCF [118].

3.1.8 Gliomas

3.1.8.1 TGF-β gene polymorphism

TGF-β functions as an oncogenic factor that contributes to the growth and invasion of cells and lowers host tumor immune responses [224]. The −509C/T TGF-β1 gene polymorphism can theoretically control the transcription of TGF-β1. The 869T/C polymorphism may have decreased cancer survival in patients carrying the −509C/T T allele and in patients with the 869T/C C allele, as both of these alleles are associated with elevated levels of TGF-β1. In comparison, TT genotype-carrying glioma patients and CC genotype patients have longer average survival. Therefore, in patients with glioma, the TT genotype of the −509C/T polymorphism and the CC genotype of the 869T/C polymorphism have the ability to be used as predictors of improved survival.

3.1.8.2 IL-10 gene polymorphism

IL-10 has pleiotropic effects on inflammation and immunoregulation and can facilitate carcinogenesis [54]. In gliomas, several IL-10 gene polymorphisms have been shown to influence disease susceptibility and severity [134]. The association of the IL-10 rs1800871 C/T genotype with increased survival in low-grade glioma patients was confirmed by Mingjun et al. [225]. Another research found an important protective interaction of variant IL-10 (−1082A/G) G allele inst glioma whereby It has been shown to induce an increase in the development of

IL-10 In 2012, Tanikawa et al. [226] noted that high serum IL-10 levels increased tumor-specific immune response and decreased tumor growth. The exact role of IL-10 in glioma is unclear; further studies are needed to elucidate the mechanisms underlying the relationship between IL-10 polymorphisms and the prognosis of glioma patients (**Table 3**).

3.1.9 Lymphomas

Studies regarding the role of interleukin gene polymorphisms in Hodgkin's Lymphoma have revealed anti-inflammatory functions of IL-1R and IL-10 [240, 241].

3.1.10 Leukemias

3.1.10.1 IL-10 gene polymorphism in ALL

In cancer growth and progression, interleukin-10, a pleiotropic cytokine serves as an immune stimulant factor. In ALL IL-10 SNP rs1800896 was correlated with the progression of the disease and also affect the cytokine expression. Many experiments, however, studied IL-10 rs100896 T/C polymorphism to determine the relevant relationship with susceptibility and prognosis.

3.1.11 Myelomas

3.1.11.1 IL-1Ra gene polymorphism

In response to similar stimuli that induce IL-1 release, the IL1-Receptor Antagonist (IL-lRa) is developed and released. According to Liang Zheng et al., carriers of IL1B rs16944 GA variant heterozygotes had a slightly reduced chance of multiple myeloma compared to IL-1B rs16944 AA homozygotes, had a slightly reduced [213].

3.1.11.2 IL-10gene polymorphism

IL-10 suppresses immune responses as an immunosuppressive cytokine by functioning simultaneously on the innate and the adaptive immune system. IL-10 can also inhibit pro-inflammatory cytokine secretion, antigen presentation, and cell growth. In the pathogenesis of hematological disorders, both IL-10 and IL-10R SNPs are involved. IL-10-592G/A and IL-10-1,082G>A SNPs, -592(C) or -1,082(G) are considered to be correlated with a strong IL-10 expression and a low -592(A) or -1,082(G) expression (A). However, studies have shown, that the C allele of IL10-592 has no clear interaction with MM [242].

3.1.11.3 TGF-β gene polymorphism

TGF-β is an active regulatory cytokine with divergent hemopoietic cell effects. Usually, TGF-β serves to reduce the release of immunoglobulin by B cells. Studies have shown that TGFβ1 genotypes with rs1800471 C alleles may raise the risk of MM and rs1800471G>C polymorphism may play a significant role in MMM tumorigenesis [217].

Activity	Cancer type		Cytokines	Polymorphisms	Association	Allele	References
Anti-inflammatory	Solid tumors	Breast	IL-1β	−511C>T	High risk	−511 CC	[23]
			TGFβ1	Codon 29T>C	Significant risk	29TT	[194]
					No	—	[196]
		HCC	IL-1β	511T>C	Risk Factor	511T>C	[49]
			IL1-RN	Intron 286bp	Risk Factor	Intron 286bp	[47]
				Allele 2 VNTR		Allele 2 VNTR	[227]
			TGF-β1	509C>T	Risk Factor	509C>T	[228]
			IL-4	2590C>T	Risk Factor	2590C>T	[229]
				233C>T	Risk Factor	233C>T	[230]
			IL-6	−597G>A	No	−597G>A	[231, 232]
				−572G>C	Risk factor	−572G>C	[54]
				−174G>C	Risk factor	−174G>C	[233]
			IL-10	−1082G>A	Risk factor	−1082G>A	[156]
				−819T>C	Risk factor	−819T>C	[156]
		Gastric	IL-4	IL-4 −590C/T	Asso	T allele	[234]
				IL-4–168T/C	Neg assoc	C allele	[234]
			IL-10	IL-10–1082 A/G	Lack of assn	AA	[206]
				IL-10–819 C/T	Lack of assn	TC	[235]
				IL-10–592 A/C	Lack of assn	AC	[207]

Activity	Cancer type	Cytokines	Polymorphisms	Association	Allele	References
	Prostate	IL-10	IL-10 (rs1800871)	Not favouring		[209]
			IL-10rs1800871)/(rs1800872)	Favouring		[210]
			IL-10 −1082 A/G	No association		[210]
			−819 C/T	No association		
			−592 C/A	No association		
	Esophageal	IL-1β	rs16944 G>A	Protective	rs16944 GA	[213]
		TGFβ1	rs1800468G>A +915G>C	Significant risk	rs1800468AA	[216]
				Significant risk	+915 CC	[227, 236]
	Pancreatic	TGFβ	TGF-β	Association	TT genotype	[237]
	Glioma	TGFβ1	−509C/T,869T/C	Better prognosis	−509TT,869CC	[238]
		IL-10	−819 C>T	Improved survival	−819 CC	[225]
			−1082A/G	Protective role	−1082GG	[239]

Table 3.
A meta-data of different anti-inflammatory cytokine polymorphisms and their association in various solid tumors.

4. Conclusion

Germline constitutional mutations or changes in the polymorphic sequence are key instruments used as molecular tools to predict the susceptibility of a person to risk numerous cancers. Cytokines are also thought to be essential molecules that have a dual face due to pro-inflammatory as well as anti-inflammatory mechanisms in carcinogenesis. These molecules regulate the development of cancer when involved in the activation of the immune response, while their recurrent inflammatory reaction will envisage the development of malignancy and tumor formation. Any differences in the polymorphic sequence of cytokine genes cause heterogeneity in their expression to deregulate genetic regulation, which eventually makes a person vulnerable to multiple cancers. As stated in the t segment, considerable evidence that links cytokine gene susceptibility polymorphism with various cancers has materialized their position as important bimolecular genetic cancer susceptibility and prognosis determinants. In studying candidate genes implicated in particular pathways for specific cancer; we conclude there is a desperate need for more case-control association studies involving additional variables haplotypic gene-gene associations and clinical-pathological features to unearth factual association for cancer. Because cytokine polymorphisms play a crucial role in immunological processes in which a rich supply of inflammatory cytokines are produced by various intensities of inflammation and cancer microenvironment, research into genetic polymorphisms in cytokine genes and their reaction to chemo-radiotherapy is believed to assist patients with cancer treatment and management.

Conflict of interest

The authors declare no conflict of interest.

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