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Review

Genetic Association Studies in Digestive System Malignancies

CHRISTOS TSIGRIS, AGAPE CHATZITHEOFYLAKTOU, CONSTANTINOS XIROMERITIS, NIKOLAOS NIKITEAS and ATHANASIOS YANNOPOULOS

First Department of Surgery, University of Athens Medical School, "Laikon" General Hospital, Mikras Asias 75, Athens GR-11527, Greece

Abstract. *The multifactorial process of carcinogenesis in the digestive system involves mutations in oncogenes or tumor suppressor genes, as well as influence of environmental etiological factors. In recent years, common DNA polymorphisms in low penetrance genes emerged as genetic factors that seem to modulate an individual's susceptibility to malignancy, through interaction with environmental factors, such as diet or smoking. The increasing number of publications of genetic association studies on digestive system neoplasias has produced both important true association results and negative or controversial results. Here, we review the findings of genetic association studies of gene polymorphisms in regard to cancers of the digestive tract (oral, esophageal, nasopharyngeal, gastric and colorectal). We discuss the association of several DNA polymorphisms in genes of cytokines, matrix metalloproteinases, signal transduction proteins, diet-, and coagulation-related factors with specific types of cancer in the digestive tract. Genetic studies, which lead to a true association, are expected to increase understanding of the pathogenesis of each malignancy and to be a powerful tool of prevention and prognosis in the future.*

Despite recent advances in oncology and genetics and their contribution to disease diagnosis and treatment, cancer still remains a major global health problem. Cancers in the digestive tract, in particular, appear to have a relatively poor prognosis and are placed among the most common cancers worldwide (1).

Correspondence to: Professor Christos Tsigris, First Department of Surgery, University of Athens Medical School, "Laikon" General Hospital, Mikras Asias 75, Athens GR-11527, Greece. Tel: +30 210 7713158, Fax: +30 210 7713158, e-mail: ctsigkri@med.uoa.gr

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Colorectal carcinomas appear to be third in frequency in women and fourth in men and they accounted for about 9.4% of the world total in 2002 (1). Gastric carcinoma ranks as the fourth most common cancer (8.6% of new cases) and the second most frequent cause of cancer deaths, although it shows wide international variation (1). Esophageal cancer is in the eighth place worldwide, with an impressive geographic variability and ranks as the sixth most common cause of death from cancer (1). Oral cancer constitutes another common malignancy, with higher frequency in men and low survival rates (1, 2). Among other cancers of the digestive tract, nasopharyngeal cancer appears relatively rare worldwide (0.7% of total cases), but it shows a characteristic geographic distribution with most cases found in Southeast Asia, North Africa and in Eskimo populations (1).

Genetic factors, such as alterations in oncogenes or tumor suppressor genes, have been linked as etiological factors in the multifactorial process of carcinogenesis (3). In recent years, a considerable interest has arisen in genetic factors that seem to modulate individual susceptibility to multifactorial diseases, such as common polymorphisms in low penetrance genes and their interaction with environmental factors, such as poor hygiene, drug, diet or smoking (4). These different forms of genes appear in high frequencies in the population and can be associated with a predisposition to and a high risk for development of carcinogenesis (5). The aim of this review is to focus on the role of genetic polymorphisms as important determinants of susceptibility in the pathogenesis of different types of cancer in the digestive tract.

Inherited Cancers of the Digestive Tract

Among cancers of the digestive tract, gastric and colorectal are known to have a hereditary basis (6, 7). Several studies have focused on the identification of causative genes for the hereditary types of cancer in order to provide the opportunity of an early diagnosis and prevention to family

members who are at risk through genetic screening (6, 7). Gastric cancer cases, with a familial association, range between 5-10%. Hereditary diffuse gastric cancer (HDGC) refers to a diffuse-type gastric cancer syndrome which follows an autosomal dominant inheritance pattern (6). Germ-line mutations in the E-cadherin gene (*CDHI*) have been identified and they account for approximately 30% of HDGC cases (6). Mutations in *MET* and *BRCA2* genes have also been reported, but generally there is little knowledge on the mechanisms underlying the genetic predisposition to this type of cancer and further studies are required (6).

In colorectal carcinoma (CRC), hereditary syndromes account only for ~2-6% of the cases (7). There exists a number of syndromes with Mendelian dominant inheritance, such as familial adenomatous polyposis (FAP), hereditary non-polyposis colon cancer (HNPCC), the Peutz-Jeghers syndrome (PJS) and juvenile polyposis (JPS) with mutations in the *APC* gene, defects in DNA mismatch repair genes (*MLH1, MSH2, PMS2* and *MSH6*), germline mutations of the *LKB1*/*STK11* genes and mutation of *SMAD4* or *ALK3* gene, respectively (7, 8). *MYH*-associated polyposis (MAP) syndrome follows the autosomal recessive inheritance pattern and occurs from bi-allelic mutations in the *MYH* gene (7, 8).

In light of the above, the majority of digestive tract cancer cases are not inherited in a clear Mendelian fashion. Low penetrance genes may influence susceptibility for malignancy in addition to certain environmental factors. Such subtle genetic contributions may be identified only by genetic association studies (5).

Genetic Polymorphisms and Multifactorial Diseases

The interaction between host genetic factors and the environment constitutes the basis of the understanding of pathogenesis of complex human diseases, such as cancers (5). In recent years, and after the completion of the human genome project, population-based association studies have emerged as a useful examination tool for genes involved in common multifactorial diseases (including malignancies) with an evident environmental component (5, 9). Such studies estimate the risk for developing a certain malignant disease by comparing the frequency of polymorphic genotypes in cases and controls (5). The increasing number of single nucleotide polymorphisms (SNPs) has stimulated scientific interest, so that they have become amenable to the majority of genetic association studies (5). SNPs differ from mutations in the fact that they occur in the general population with a frequency of at least 1%, while mutations occur in less than 1%. It is estimated that up to 10 million SNPs exist in the human genome and there are more to be identified (9).

Despite their modest effect at an individual level, SNPs can be associated with an increased risk for developing a multifactorial disease, such as a carcinoma, because of their high frequencies in the population (4, 5). Environmental factors, such as diet or smoking, can reveal the phenotypic expression of susceptibility genes, in cases where a polymorphism affects metabolic pathways, or it modifies the gene expression, which is induced by the external environment (4).

In recent years, the number of publications based on the genetic association studies of cancer has rapidly increased. However, the existence of several studies with negative or controversial results raises the demand for certain basic criteria to be defined and properly followed, so as false positive and negative results are avoided (5, 8, 10). Nevertheless, such studies, which lead to a true association, are expected to contribute to the understanding of complex traits and could be a powerful tool for prognosis and prevention of malignancies (10).

Association of Gene Polymorphisms with Digestive Cancers

Common gene polymorphisms, mainly SNPs, have emerged as important determinants of susceptibility to cancer (5). In recent years, an impressive number of common SNPs in candidate genes has been associated with the different forms of cancer in the digestive tract. Among the most studied genes are those that are cogently linked to the pathophysiology of the particular cancer. Such genes encode for cytokines, as mediators of the adaptive and innate immune response, factors of the human leucocyte antigen system (HLA), matrix metalloproteinases (MMPs) and their inhibitors, diet-related factors and other genes encoding coagulation-related factors or signal transduction proteins (5, 11-14). Table I shows a detailed list of SNPs in candidate genes associated with carcinomas in the digestive tract.

Immune System Gene Polymorphisms

The impact of the immune response on the potential for malignancy is well-established, highlighting a straightforward association between chronic inflammation and subsequent malignant transformation of the inflamed tissue (15). Genes encoding for products with a key role in regulation of the immune response include the human leukocyte antigen (HLA) and cytokine gene families (16).

HLA peptides, encoded by the genes of human histocompatibility system, are widely expressed cell surface molecules which present antigenic peptides to T-lymphocytes in order to secrete cytokine mediators, among other molecules, and thus modulate the immune response (16). The HLA-encoding loci constitute the most polymorphic genetic system in humans and this contributes to genetic diversity and to differences in susceptibility to diseases (16).

Table I. *Accumulated data of genetic association studies between gene polymorphisms and cancers of the digestive tract with respective references in parentheses. (–) No association; (+) minor association requiring further study; (++) strong association.*

	Oral	Nasopharyngeal	Esophageal	Gastric	Colorectal
HLA					
*HLA-DQAI *0102*				++ (6, 9, 17, 18)	
*HLA-DQBI *0301*				+ (9, 19)	
*HLA-DRBI *1601*				++ (9, 19)	
Cytokines					
IL-1B (–31,–511)	– (22, 23)		– (9)	++ (6, 9, 48)	– (24)
*IL-1RN (*2/*2)*			– (9)	++ (6, 9, 48)	
IL-2 (–384T/G,+114G/T T330G)			– (25)	– (25)	
				++ (26)	
IL-4 (–168G/A,–588C/T, –590C/T)	+ (23), ++ (27)				– (28)
IL-6 (–174G/C)	++ (29)		– (25)	– (25)	++ (14, 30, 31)
IL-8 (–251T/A)	++ (32)		– (33)	++ (9, 23, 32, 33)	++ (34), + (30), – (31)
IL-10 (–592			– (25)	++ (9 ATA), – (25)	– (24, 36)
819C/T		– (35)	– (25)	–(25)	+ (34)
–1082A/G)	++ (40)		– (25,37)	+EBV (38, 39)	– (24, 36)
				– (25, 37)	
IL-18 (–137,–607)	– (50)	+ (35)			
TGF-B1					
(–509C/T		++ (41)		+ (42)	– (24)
+896C/T)		++ (41)			+ (36)
TNF-A (–308G/A)	++ (43-45)	– (46)	+ (47)	++ (9, 6, 37, 38, 48)	– (24, 31, 49)
TNF-B (+252G/A)	– (45)		+ (47)	+ (47)	++ (15)
MMPs					
MMP-1 (1607 ins/delG)	++ (53, 54, 56, 57)	++ (54, 57)	– (58)	– (58, 59)	+ (60), – (61)
MMP2 (–1306 C/T)	++ (62, 63)	++ (62)	++ (62)	++ (62, 64)	++ (65, 66)
MMP-3					
(–1171 ins/delA)	++ (55)		++ (67)	– (67)	– (61)
(–1612 ins/delA)					+ (60), – (61)
MMP-9 (–1562 C/T)	++ (68)			++ (60, 64)	– (69, 70)
TIMP-2 (–418 G/C)	++ (62, 71)	++ (62)		– (72)	
Diet-related factors					
CYP1A1					++ (14)
CYP1A2					++ (14)
CYP2E1	– (76)		+ (77)	+ (78)	+ (79, 80)
GSTA1					
(*B/*B, A*/B*)					++ (79, 81)
GSTM1	+ (76, 82)		+ (77, 83, 84)	+ (85), – (78)	++ (79, 86, 87)
GSTT1	– (76, 82), + (88)		+ (83), – (84)	+ (78, 87), – (89)	+ (79, 87, 90)
GSTM1, GSTT1				+ (87)	++ (79, 87, 91)
MTHFR				++ (92–94),	
(C677T)	+ (95)		++ (92, 96)	– (97, 98)	++ (99, 100)
Coagulation-related factors					
ACE (I/D)	+ (101, 102)			+ (103, 104), – (105)	
Factor V (G1691A)	+ (106)		+ (107)	+ (107), – (108)	+ (108), –(109)
GPIa (C807T)	+ (110)				
PAI-1 (4G/4G)	++ (111)				++ (14, 111)
Prothrombin (G20210A)	– (106)			– (108)	– (109)
Signal transduction proteins					
COX-1 (L15-L16del)					+ (14)
COX-2 (V511A)					+ (14)
E-cadherin (–160 C/A)				++ (112), – (113)	
EGF (61 A/G)				++ (59)	
HER-2/c-erbB2 (Ile655Val)				++ (59)	
ICAM-1 (R241G, K469E)					+ (31)
PPARγ (GAla12)				+ (114)	+ (14, 31)
VEGF (+936C/T)	++ (119)			+ (120)	– (121)

Recently, the importance of polymorphisms within HLA-encoding loci has emerged in the development of malignancy in the digestive tract. In particular, several HLA class II alleles have been linked to increased risk for gastric cancer, as shown in Table I (6, 9, 17-19).

Cytokines are small secreted or membrane-bound proteins produced by cells in response to specific stimuli which alter the behavior of the same or other cells, generally within the hematopoietic system (16, 20). Interleukins (ILs), tumor necrosis factors (TNFs), transforming growth factors (TGFs) and interferons (IFNs) are members of the gene family of cytokines and they are further divided into pro- and antiinflammatory molecules (20). They are part of a highly complex and coordinated network and they modulate their own synthesis or that of other cytokines or cytokine receptors (16, 20). They act by binding to specific receptors in order to initiate signal transduction and subsequently to regulate the growth, differentiation and activation of immune cells (12, 20). Deregulation of cytokine production has an indirect influence on the development of diseases such as cancer by provoking angiogenesis and tumor growth and facilitating invasion and metastasis (20, 21).

In recent years, an increasing number of SNPs was detected within cytokine gene sequences and particularly within the promoter regions. Several of these polymorphisms may be associated with different levels of transcription, although cell type and stimulus seem to be important (12). Through genetic association studies, common SNPs in cytokines and their interaction with environmental factors have been linked to susceptibility to malignancy in the digestive tract, as shown in Table I.

Oral cancer has been associated with common polymorphisms in inflammation-related genes (29). Several studies have introduced strong association between SNPs in interleukins 6, 8, 10 and TNF-A with susceptibility for oral cancer (29, 32, 40, 43, 45). As for an SNP (-590C/T) in the *IL-4* gene, a strong association with increased risk for oral cancer has been found in Europeans, but unclear association was found from a previous report in a Chinese population (23, 27). Furthermore, there seems to be no association between *IL-1B* gene polymorphisms and risk for oral cancer (22, 23).

Nasopharyngeal carcinoma (NPC) appears attributable to environmental factors, such as smoking, salted foods and Epstein-Barr virus (EBV) infection (46). Recently, it was proposed that the variability of cytokine production may influence the outcome of viral infections (51). However, recent studies on polymorphisms in *IL-10, IL-18* and *TNF-A* as candidate genes found no association with susceptibility to the disease, but further studies are required (35, 46). In the case of *IL-18* polymorphisms (–137C/G, –607C/A), they may represent a risk factor for tumor aggressiveness (35).

Several genes from different pathways, critical for the inflammatory response, have been associated with esophageal cancer (52). Despite this fact, genetic association studies of common SNPs in various interleukin genes (Table I) failed to show any association between these polymorphisms and esophageal cancer (9, 25, 33, 37). However, a study in North China, did find some association between SNPs in *TNF-A* and *TNF-B* genes and risk for esophageal cancer in that population (47).

Various etiological factors have been linked with gastric cancer, with the gram-negative bacterium *Helicobacter pylori* being the most recognized risk factor for this malignancy (9, 15). Moreover, EBV infection is present in about 10% of gastric cancers worldwide (6). Pro- and antiinflammatory cytokines have been associated with gastric cancer, since *H. pylori* causes the initiation of chronic inflammation in the gastric mucosa (9). SNPs in various cytokines, such as *IL-1B, IL-1RN, IL-2* (T330G), *IL-8, TNF-A* and *TNF-B*, are highly associated with an increased risk for gastric cancer (6, 9, 23, 26, 33, 38, 47, 48). The data on the *IL-10* polymorphisms appear more controversial. No association was found between these polymorphisms and cardiac gastric cancer (25, 37), whereas homozygosity for the low IL-10 *ATA* haplotype (based on three promoter polymorphisms at positions –592, –819 and –1082) increased the risk for non-cardia gastric cancer (9). Furthermore, there has been unclear association between the A→G polymorphism at position –1082 of the *IL-10* promoter and EBV-associated gastric cancer (38, 39).

Precursor lesions to colorectal carcinoma (CRC) have been associated with inflammatory biological features (14, 15). Furthermore, expression of NF-κB, which stimulates the secretion of inflammatory cytokines, among other molecules, has been identified in colorectal cancer (15). Strong association has been found between SNPs in *IL-6, IL-10* (–819C/T) and *TNF-B* and increased risk for colorectal cancer (14, 15, 30, 31, 34). Controversial data have been reported for the T→A polymorphism at position –251 of the *IL-8* gene. One group found an increased association with risk for colorectal adenoma (34), in another study it was associated with reduced risk of CRC (30) and in yet a third study it showed no association (31). Further studies are required to resolve this issue.

Matrix Metalloproteinase Gene Polymorphisms

The extracellular matrix (ECM) is essential for various physiological processes, such as growth, development and tissue repair (73). Matrix metalloproteinases (MMPs) are a family of at least 28 highly conserved metal-dependent proteolytic enzymes that mediate the degradation of different components of the ECM and basement membranes and regulate various cell behaviors (13, 55, 67). Increased expression of MMPs has been associated with tumor invasion and metastasis, since these steps require proteolysis of basal membranes and the ECM (74, 75). However, recent studies

suggested that MMPs also play an important role in almost every step in cancer development, by regulating tumor growth and apoptosis, promoting angiogenesis and affecting cell adhesion (60, 74, 75). Furthermore, it is held that MMPs have a key role in the production and preservation of a microenvironment essential for the early steps of carcinogenesis (55). Expression of MMPs is controlled mainly at the levels of transcription, pro-enzyme activation and activity inhibition by certain enzyme-specific inhibitors, which include a family of anti-proteinases known as tissue inhibitors of metalloproteinases (TIMPs) (13, 74, 75).

There have been several polymorphisms identified, especially in the promoter regions, that seem to modulate the transcription activity of these genes. Many of these polymorphisms have been studied for associations with increased risk for cancer in the digestive tract (Table I). The C→T SNP at the –1306 position of the MMP-2 gene promoter was found to have a strong association with most types of cancer in the digestive tract (62-66). Generally, oral cancer was found to be highly associated with polymorphisms in *MMP-1, MMP-2, MMP-3, MMP-9* and *TIMP-2* genes (53-57, 62, 63, 68, 71). These findings are similar to NPC, except for the *MMP-3* and *MMP-9* gene polymorphisms, where no data are available (54, 57, 62). In esophageal cancer, a strong association was found for SNPs in *MMP-2* and *MMP-3* genes (62, 67). Furthermore, *MMP-2* and *MMP-9* gene SNPs revealed strong association with gastric cancer, whereas in CRC, results have been more controversial, with a strong association with the *MMP-2* gene polymorphism (60, 62, 64-66). A combination of *MMP-1* and *MMP-3* gene polymorphisms was associated with risk for CRC in one study, but showed no association with a study conducted in a Chinese population (60, 61).

Polymorphisms in Diet-related Genes

Dietary factors have been reported to influence the development of various cancers, including those in the digestive tract (16). The multifactorial process of carcinogenesis involves environmental/dietary, genetic and epigenetic modulators, as well as gene-environment / gene-nutrient interactions. The diet, in addition to providing vital nutrients, is also a major source of carcinogens and mutagens and is related to about 35% of all cancer deaths (79). Epidemiological studies have shown that, apart from tobacco, three dietary constituents (alcoholic beverages, aflatoxins, salted foods) are mainly associated with the development of cancer and that vegetables, fruit, fibres and other antioxidants have a protective role against cancer (79).

Despite the fact that direct genetic evidence is still lacking, molecular epidemiology studies indicate a cancer-related role of several polymorphic low penetrance genes that affect activation of metabolism as well as detoxification and DNA repair when xenobiotic substances are digested (84). The process of metabolism activation requires phase I enzymes and that of detoxification phase II enzymes, as well as several protective components of the diet (79). In the case of tobacco, most carcinogens are metabolized by multistep enzymatic mechanisms involving both activation and detoxification reactions (82).

Glutathione-*S*-transferases (GSTs) constitute an important family of xenobiotic-detoxifying phase II enzymes catalyzing the detoxification of active metabolites, such as polycyclic aromatic hydrocarbons (PAHs), present in the diet and tobacco (14, 82). Thus, variations in GST expression, due to genetic polymorphisms, may affect the process of carcinogenesis by altering the exposure levels to several carcinogens, such as tobacco-derived carcinogens (82). Most notably, a *GSTM1* polymorphism has been associated with most of the cancers of the digestive tract (Table I), and colorectal cancer in particular, in conjuction with increased consumption of poultry and fish (76, 77, 79, 82-84, 86, 87). However, controversial results appear for GSTT1, since in some studies an association with cancers of the digestive tract has been reported, while in others no such association has been found (76, 78, 79, 82-84, 87-90).

Cytochrome P-450 (CYP) phase I enzymes are involved in the oxidative metabolism of many substances, including mutagens, chemical carcinogens and other environmental constituents (14). CYP1A1 has a critical role in the metabolic activation of carcinogenic PAHs and its increased activity-related polymorphisms have been associated with risk for colorectal cancer (Table I) (14). CYP1A2 is responsible for the metabolism of PAHs, heterocyclic amines and aromatic amines (all of them formed during boiling or frying of meat). A high activity *CYP1A2* gene polymorphism has been associated with risk for colorectal carcinoma and several other cancers (Table I) (14). CYP2E1 is the key enzyme for the metabolic activation of nitrosamines before they can bind to DNA and cause carcinogenic mutations. *CYP2E1* gene polymorphisms have been mainly linked to esophageal, gastric and rectal rather than colon cancer (77-80).

Methylenetetrahydrofolate reductase (MTHFR) is a key enzyme in folate metabolism (100). Folate is essential in DNA synthesis, repair and methylation since it is the main methyl donor required for intracellular methylation reactions and *de novo* deoxynucleoside triphosphate synthesis (95, 99, 100). Thus, folate deficiency because of low dietary intake (for example low consumption of green vegetables) may be carcinogenic through disruption of the physiological processes above (95). *MTHFR* gene polymorphisms in conjunction with low folate intake have been associated with susceptibility to most cancers of the digestive tract (Table I), although some reports are still controversial (92-100).

Polymorphisms in Coagulation-related Factors

Angiotensin I-converting enzyme (ACE) is a cell surface zinc metallopeptidase, with a key role in the rennin-angiotensin system, which is important in the regulation of blood pressure and serum electrolytes (101, 104, 105). ACE converts angiotensin I to angiotensin II, inactivates bradykinin and may also contribute to the biological behavior of tumors, through growth stimulation and increased vascular permeability (101). A 287 bp insertion (I) or deletion (D) in the ACE gene leads to variances in ACE expression and has been associated with oral and gastric malignancies (Table I) (101-105).

Coagulation factor V Leiden and prothrombin G20210A mutations are common genetic defects which constitute thrombophilia-predisposing factors (106). *Factor V Leiden*, but not *prothrombin* polymorphism, has been associated with digestive tract malignancies (106-109).

Glycoprotein Ia (GPIa), also known as $\alpha_2\beta_1$ integrin, is an heterodimeric cell surface collagen receptor which regulates interaction between cells and adhesion of blood platelets to the extracellular matrix. A common silent polymorphism (C807T) in the coding region of the *GPIa* gene has been associated with increased risk for oral cancer (110).

Plasminogen activator inhibitor-1 (PAI-1) is responsible for the activation of plasmin by regulating the activities of tissue plasminogen activators. Furthermore, it has an important role in cellular adhesion and migration, through its binding to vibronectin and integrins (111). A deletion/insertion polymorphism (4G/5G) in the promoter region of the *PAI-1* gene affecting gene transcription has been associated with risk for oral and colorectal cancer (14, 111).

Polymorphisms Related to Signal Transduction Proteins

Cyclooxygenase (COX), also known as prostaglandin H synthase, catalyzes the formation of prostaglandins G_2 and H_2. There are two COX isoforms, COX-1 and COX-2, that share 60% homology and have critical roles in maintaining prostanoid levels and in inflammatory processes, respectively. Polymorphisms in *COX-1* and *COX-2* genes have been associated with colorectal cancer, with the *COX-2* gene polymorphism (V511A) having a protective effect (14).

Cell adhesion molecules may function as tumor suppressors. One of them, E-cadherin, has a key role in the regulation of morphogenesis and inhibition of cell infiltration in epithelial tissues (59). Intercellular adhesion molecule-1 (ICAM-1) is expressed on vascular endothelium and is involved in the transendothelial migration of neutrophils and T-cell activation (31). SNPs in *E-cadherin* and *ICAM-1* genes have been associated with risk for gastric and colorectal cancer, respectively, although there are controversial results for the *E-cadherin* gene polymorphism (31, 112, 113).

Growth factors and their receptors consist of molecules that, apart from cell growth, also induce extracellular matrix degradation and angiogenesis for tumor invasion and proliferation (59, 115-118). Polymorphisms in these factors, such as epidermal growth factor (EGF), vascular epithelial growth factor (VEGF) and human epidermal growth factor receptor-2 (HER2), have been associated with susceptibility to gastric cancer (59, 120). *VEGF* gene polymorphisms, in particular, have also been shown to have a strong association with risk for oral cancer (119).

Peroxisome proliferator-activated receptor γ (PPARγ) belongs to the family of PPARs, which are steroid hormone protein receptors, and is activated by fatty acid-like chemicals called peroxisome proliferators (PPs) (14). PPARγ plays a key role in gene expression as a ligand-activated nuclear transcription factor and is thought to be involved in immunological mechanisms and carcinogenesis (31). A single nucleotide polymorphism in the coding region (34C/G) that causes the amino acid change of Pro12Ala introduces an association with risk for gastric and colorectal cancer (14, 31).

Conclusion

Single nucleotide polymorphisms appear to be important determinants of susceptibility to the different types of cancer in the digestive tract, through genetic association studies. Polymorphisms in genes encoded by the human histocompatibility system and in particular, in several HLA class II alleles, have been associated with susceptibility to gastric cancer. Different cytokine gene polymorphisms have been related to different cancer risks, with *IL-8* and *TNF-A* gene polymorphisms being associated with most of the cancers in the digestive system. Furthermore, an increased association has been shown between polymorphisms in MMP genes and these cancers, with SNPs in the *MMP-2* gene being related with all cancers in the digestive tract that have been reviewed in the present study. SNPs in diet-related factors, as well as in genes that encode for signal transduction proteins, have been mainly linked with risk for gastric and colorectal cancer. Last but not least, polymorphisms in several coagulation-related factors have been mostly associated with susceptibility for oral carcinoma and less for gastric and colorectal cancer.

Genetic association studies have emerged as a powerful tool for the analysis of human cancers. Despite the fact that further studies are still required, this rapidly developing field of molecular biology seems promising in the prevention and prognosis of human malignancies in the future.

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