Clinics in Medicine

ISSN: 2688-6731

Review Article

Single Nucleotide Polymorphisms in MMPGenes and Susceptibility to Growth, Invasion, Progression, and Metastasis of Cancer

Taghvaei Somayye[1], Saremi Leila[2] and Motovalibashi Majid[3*]*

[1]*Department of Medical Biotechnology, National Institute of Genetic Engineering and Biotechnology, Iran*

[2]*Department of Biology, Islamic Azad University, Iran*

[3]*Department of Biology, Isfahan University, Iran*

Abstract

The growth and progression of cancer are complex multi step processes that require transformed cells are colonized to distant locations. Degradation of Extracellular Matrix (ECM) and basement membrane by Matrix Metalloproteinases (MMPs) are key steps in these processes. Invasion and metastasis are symptoms of cancer malignancy.

A family of enzymes called MMPs involves in cancer initiation and progression. Because, their main function is digestion of the ECM, as well as they are participating in physiological processes such as wound healing, bone absorption, and the development of mammary glands in various pathological conditions such as cancer. Tumor cells can use the digestive ability of MMPs. MMPs also are stimulating the growth of the metastatic tumor cells after the occurrence of the metastasis. Therefore, MMPs can act as an oncogene. Increasing evidence suggests natural Single Nucleotide Polymorphisms (SNPs) in MMP genes especially in the promoter are leading to their variant expression, in different individuals by changing susceptibility to diseases including acute myocardial infarction, rheumatoid arthritis, multiple sclerosis, and cancer. In this review, the role of MMPs in cancer (invasion, metastasis, angiogenesis) will be discussed and the many studies of the relation of SNPs in MMP genes will be illustrated.

Keywords: MMPs; Cancer; SNPs; Oncogene; Metastasis

Introduction

Cancer is a mechanism of cell destruction that is necessary for the growth and maintenance of a multicellular organism. Number of cancer mortalities and new cases in Iran and worldwide in 2020 showed in Figure 1. Indefinite proliferation, failure in response to growth inhibitory signals, and resistance to apoptosis and immune system are the main features of tumor cells. Some other attributes of these cells include separation from the base membranes, lack of gap and tight junctions with neighboring cells, migration through extracellular matrix, entry, and survival in blood or lymph circulation, and proliferation within vessel walls or after the exit of a vessel in the secondary site(s) [1].

The tumor environmental factors that inhibit tumor progression are components of ECM, basement membranes, oxygenactive species, limited availability of oxygen and nutrients, and immune system [2]. The tumor environment can be affected by stimulation of angiogenesis using active stromal fibroblasts, production of proteolytic enzymes, and change of extracellular matrix, and eventually, leads to tumor progression [3].

The Matrix Metalloproteinase (MMP) family is common in several characteristics: ability of decomposition at least a component of the basement membrane, action in the physiologic pH, activation with two Zn^{++} ions, inactivation by metal chelators and tissue metalloproteinase, and secretion as zymogene, and activation [4,5]. Since the role of the MMPs in invasion and metastasis of tumors is important, then very much attention has been attracted to them as one of the cancer therapeutic targets. MMP inhibitors have also evolved able to inhibit angiogenesis and tumor development. However, due to side effects, the use of these inhibitors was prevented [6]. The multistep process of carcinogenes is is suggested to be relying on the release of matrix-degrading enzymes, such as MMPs. MMPs can cleave most of the ECM components, for example, some native collagen types, gelatin, aggrecan, tenascin, entactin, proteoglycan, perlecan, fibronectin, vitronectin, and others. The spectrum of many MMP substrates is fairly similar, but some substrates can degrade more effectively than others [7,8]. Because identification of all genetic changes in MMPs genes by the Human Genome Project have been

Citation: Somayye T, Leila S, Majid M. Single Nucleotide Polymorphisms in MMPGenes and Susceptibility to Growth, Invasion, Progression, and Metastasis of Cancer. Clin Med. 2022; 4(1): 1040.

Publisher Name: Medtext Publications LLC

Manuscript compiled: Jan 05th, 2022

***Corresponding author:** Somayye Taghvaei, Department of Medical Biotechnology, National Institute of Genetic Engineering and Biotechnology, Tehran, Iran, Tel: 44787301-10; Fax: 44787399; E-mail: somayyetaghvaei@gmail.com

Majid Motovalibashi, Genetic Division, Department of Biology, Faculty of Sciences, Isfahan University, Isfahan, Iran, Tel: 37932288; Fax: 36688302; E-mail: mbashi@sci.ui.ac.ir

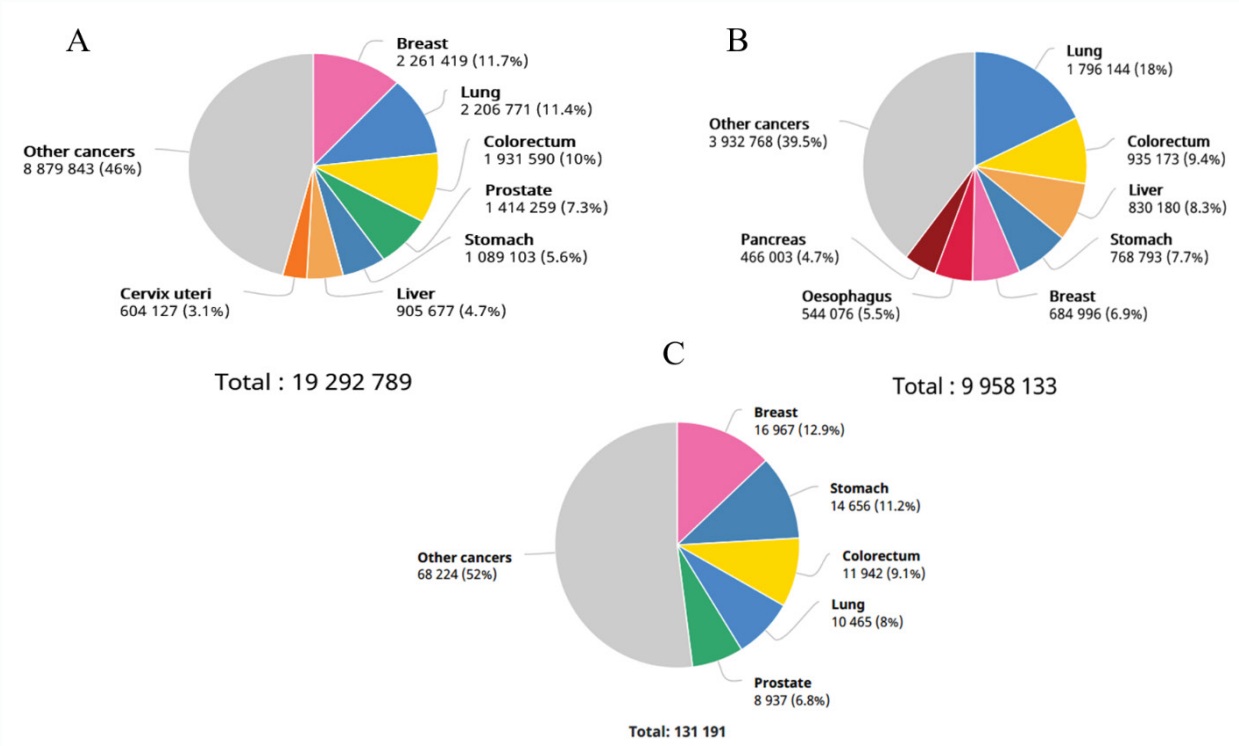

Figure 1: A) Number of new cases in 2020 in Iran, B) Number of mortalitiesin 2020 in worldwide, C) Number of new cases in 2020 in Iran.

led to the identification of MMP genes, therefore this review is an overview of concepts of cancer, the role of MMPs, and their Single Nucleotide Polymorphisms (SNPs) in the stages of cancer including angiogenesis, invasion, and metastasis. As those results of researches were approved. It should be noted that this review tries to recapitulate the most genetic variations in MMP genes.

MMPs

MMPs are a family of calcium and Zinc dependent endopeptidases and were produced from the reproduction of an ancestral gene and evolutionary branching [9]. Most of the MMP genes are placed on various chromosomes, but the MMP1-3-7-8-10-12-13-20, and 27 are located at position 11q22.2-22.3. The MMP family is classified into gelatinases (MMP-2 and MMP-9), collagenases (MMP-1, MMP-8, MMP-13, and MMP-18), matrilysins (MMP-7, and MMP-26), stromelysins (MMP-3, MMP-10, and MMP-11), membrane-type MMPs (MMP-14, MMP-15, MMP-16, MMP-24, MMP-17, and MMP-25), and others (MMP-12, MMP-19, MMP-20, MMP-21, MMP-23, MMP-27, and MMP-28) [10].

The MMP substrates include growth factors, binding proteins, their receptors, cell adhesion molecules, chemokines, cytokines, apoptotic ligands, angiogenic factors, chemokine molecules, proteinase inhibitors, and clotting factors [11,12]. The MMPs are involved in the physiological and pathological processes including embryonic development, ovulation, wound healing, heartfailure, arthritis, atherosclerosis, periodontal disease, bonechanges, and especially cancer [13,14]. Most MMPs expression in tissues is often low and induces during ECM changes, which may increase cell proliferation, invasion, and metastasis by stimulating angiogenesis or cancer progression. Therefore, it is not surprising that increased MMPs levels were observed in numerous cancers [15,16]. Membrane tissue 1-matrix metalloproteinase (MT1-MMP) is involved in the physiological and pathological changes of the ECM, cell migration, invasion, activation of MMP-2, MMP-13, and MT4-MMP, and activation of growth factors particularly Vessel Endothelial Growth Factor (VEGF), tumor growth, enlargement of blood vessels, and lung metastasis. Expression of MT4-MMP in breast cancer, prostate cancer, and gliomas cancer has been identified. Initial studies have shown the role of MT1-MMP and MT4-MMP in the initial growth and the metastasis of cancer (lung) [17].

Several *in vitro* studies have been demonstrated that cleavage of particular substrates by MMPs can directly affect tumor growth. These substrates contain pro-forms of growth factors as Transforming Growth Factor (TGF)-β and inhibitory proteins of growth factor as Insulin-like Growth Factor Binding Proteins (IGFBPs) which one of those has been indicated *in vivo* to have a relationship with tumor growth [18]. Different research results are showing single nucleotide polymorphisms in MMP genes especially, MMP-1, 2, 3, 7, 8, 9, 12, 13, 14, 15, 17, 20 relate to susceptibility, invasion, and metastasis of different cancers such as breast, gastric, lung, ovarian, stomach, gallbladder, ovarian, colorectal, oral, renal, salivary, prostate, tongue, endometrial, esophageal, nasopharyngeal, melanoma, thyroid, pancreatic cancers, and etc. that is indicating a striking role of MMPs in cancer.

Structure of MMPs: MMP proteins consists of at least three homologous domains. The first domain is a signal peptide required for protein secretion. The second domain is propeptidase domain that comprises a consensus cysteine-switch sequence and is responsible for the activation of MMP enzymes. The third domain is the catalytic domain containing the consensus sequence of zinc-binding and is needed for the proteolytic action. The amino-terminal signal peptide is composed of 17-29 amino acids which is necessary for targeting the enzyme to the endoplasmic reticulum and Golgi complex for the later

excretion out of the cell [19].

Regulation of MMPs: The catalytic activity of MMPs is controlled at four main levels, including gene expression through transcriptional and post-transcriptional mechanisms, extracellular localization and cell or tissue type of MMP release, zymogen activation by pro-domain removal, and inhibition by specific and non-specific inhibitors, e.g. Tissue Inhibitors of Matrix metalloproteinases (TIMPs) and a 2-macroglobulin, respectively [20]. Active MMPs can regulate the global proteolytic potential by degradation of inhibitors or inactivation of other proteases and activation of zymogen [21].

MMP-7 is capable cleavage of the cell surface non-matrix substrates such as F as ligand, E-cadherin, and Tumor Necrosis Factor (TNF), which are key players in signal transduction, cell-cell adhesion, and apoptosis [22]. MMP-7 also cleavages IGFBP and Heparin Binding-Epidermal Growth Factor (HB-EGF) which their effects result inmitogenic increase and cell disorganization and cause epithelial to mesenchymal change and cancer progression [23].

At transcriptional level, the MMP expression is performed by multiple mechanisms [24]. While its regulation is carried out by transcription factors, including basic Fibroblast Growth Factor (bFGF), Epidermal Growth Factor (EGF), Tumor Growth Factor (TGF), cytokines (IL-4,and IL-10), steroid hormones, the cell-cell, cell-matrix interactions, oncogenes, and tumor promoters [25].

MMPs are involved in the early stages of tumor growth, regulating the of cell growth, apoptosis, and the vessel formation through a diverse group of receptors other than components of the ECM including growth factors binding proteins, pro-growth factors, tyrosine kinase receptors, cell attachment molecules, and other proteinases [26-29]. MMPs in cancer tissues unlike normal tissues are increased and, in most cases, they are associated with poor survival. The role of MMPs in invasion and metastasis first reported in melanoma, and the tumor cells have been recognized as source of MMPs. However, increasing evidences has been indicated that most of the normal cells express detectable levels of MMPs [30]. Tumor inflammatory cells and stromal fibroblasts in tumor tissue induce the production of MMPs from the surrounding cells by producing of cytokines and proteins [31]. Stromal cells have also been suggested to express MMPs [32].

Angiogenesis

Angiogenesis includes the growth of endothelial cells and digestion of vascular endothelial old basement membrane, the formation of a cavity, penetration and migration, proliferation, and maturation of endothelial cells for formation of a capillary bed. Studies have established the expression of MMPs in this capillary network. Several growth factors can promote MMPs, which are containing cytokines and growth factors, with the activation of zymogen forms, and VEGF, through stimulation of neovascularization [33-35].

Angiogenesis is beginning with the releasing of factors eg VEGF, bFGF, and TNF from inflammatory cells, mast cells, macrophages, and tumor cells. After binding to specific receptors on cell surfaces and endothelial cell activation are leading to the induction of cell proliferation, enhanced expression of cell adhesion molecules (e.g. integrin), MMPs secretion, and enhanced migration and invasion. It has also observed an imbalance between proangiogenic and antiangiogenic factors in some early malignant cancers, even before the malignant status [36].

VEGF, akey angiogenic driver, not only stimulates proliferation and migration of endothelial cells but also activates passive MMPs. VEGF also activates MMPs and affects the activity of TIMPs, for instance, the activation of MMP-2 and MMP-9 by MMP-7 [27] and the activation of MMP-1, 8, 9, 13 by MMP-3 [37].

Tumor metastasis is essential to angiogenesis, and without this process, the tumor can grow only 1 mm^3 to 2 mm^3. Besides, tumors with higher angiogenic cells have higher ability of metastasis and invasion. MMP-13 also increases the bioavailability of VEGF. MMP-3, and MMP-7 increase cell proliferation and angiogenesis by separation of HB-EGF. MMP-9 also enhances invasion and angiogenesis with the activation of TGF-β. MMP-9 and MMP-13, because of the release of VEGF from the ECM, are the main factors in the promotion of tumor angiogenesis. With the production of inhibitors such as endostatin, angiostatin, and neostatin, MMPs can prevent angiogenesis and most MMPs have opposite functions in tumorigenesis [38,39].

Invasion

Degradation of the ECM and the basement membranes by cancer cells are main processes in the invasion. Three types of enzymes namely MMPs, serine proteinases, and cysteine proteinases degrade efficiently the ECM. MMPs with malignant phenotypes are joined because invitro evidences have shown that malignant tumors can degrade collagen and MMPs have this character [36].

Invasion allows cancer cells to enter the blood stream or lymph system, to reach distant organs and form secondary tumors. Invasion and metastasis not only occur in cancer but also happen during fetal development and in non-cancerous diseases [40]. The ability of tumor cells for detachment from tumor and migration depends on the differentiation degree and lack of adhesion of cell-cell is a characteristic of malignant tumors. Obstruction of differentiation and lack of cell-cell adhesion by E-cadherin lead to releasing tumor cells to invasion and metastasis and the inhibition of tumor migration is the main stage in the inhibiting metastasis [41]. Tumor invasion is regulated by specific chemokines and many cancers, including, breast, ovarian, prostate, kidney, brain, lung, and thyroid cancers are expressing chemokine receptors to stimulate tumor cell adhesion and to increase endothelial cell growth understress [42]. As well as chemokine scan cause to the secretion of MMPs. Invasion is also increased by separation of E-cadherin by MMP-3 and MMP-7 (MMP-3, 7, 9, and 19) and MMPs are digesting each of the six IGFBP and are increasing their bio-availability and tumor growth [22]. The decreased invasive capacity of tumor cells was observed when the endogenous inhibitors of MMPs known as TIMPs were expressed [18].

Metastasis

Metastasis is the final step in the progression of metastatic tumors from normal to a malignant state. The limiting step of the metastasis rate is being called growth in the organ [43]. Metastasis is in charge of 90% of human cancer mortality [44]. Clinical observations have been shown that distant metastasis can occur many years after primary tumor resection [45].

Each step of metastasis is necessary, and by an interaction between the tumor cells, the host, and environment is regulated. The formation of the metastasis depends on the invasion of the tumor cells to the surrounding tissues and the formation of the metastatic tumors in the distant organs. Although a large number of cells isolate from the primary tumor and enter to vessel system, their small percentage succeed in making metastasis and the number of metastatic colonies depends on the number of cells that entered blood or lymph circulation

[46]. Moreover, some cells enter tumor dormancy therefore, the number of metastatic colonies is lower than expected. The exit of tumor dormancy requires changes in proliferation and angiogenesis [47].

Degradation of the ECM by the MMPs not only may facilitate the metastasis but also may cause the cell growth by releasing the growth factors. Many genes participate in the metastasis and seem the regulation of the expression of these genes that functionally participate in the metastasis can occur in a tissue-specific method with different regulatory genes such as oncogenes and tumor suppressor genes that multiple stages of the specific metastatic phenotype are inducing [48]. Several reports have shown the high expression of MMPs in many cancers compared with normal tissues.

MMP8 reduces metastasis by increasing the cellular adhesion, and the relation of its expression with the reduction of incidence of breast cancer was observed [49]. The high expression of anti-apoptotic effectors such as BCL2, and BCL-XL, and the lack of initial factors of apoptosis path way result in resistance to apoptosis and elevation of metastatic potential. When expressing, metastasis inhibitor genes can inhibit exclusively metastasis but have no effect on other processes, and reduction of their expression through transcription inactivation and Loss of Heterozygosity (LOH) in the tumor cells have been found [2].

Anti-cancer therapies targeting MMPs

TIMPs indicated ability to prevent the function of MMPs and represented selectivity for anti-cancer therapies. TIMP-1 can prevent angiogenesis by the destructive action of MMPs. However, these biological molecules have a restricted half-life when experimented *in vivo* to validate their act as a pharmaceutical factor. Establishing this fact, studies are now centralized ongaining an alternative solution to minimize the role of MMPs in cancerprogression [36].

SNPs ofMMP genes and cancer

Sequence variations including SNPs in the promoter region and the coding region of MMP genes result in their variable expression in different people. SNPs are variations in DNA which were observed in more than one percent of the population of the world. SNPs may change the structure and function of protein through single nucleotide substitution in the coding region of the gene and also the gene expression through changes in the coding and regulatory regions [50]. The study of polymorphisms helps to identify people at risk of disease and to define medical purposes.

The relation of MMP-1 (collagenase-1) with different cancers has been investigated and displayed. A link was shown between 1G/2G (-1607) polymorphism and Colorectal Cancer (CRC) by Kouhkan et al. in Iran and Hinoda et al. in Japan [51,52], hematogenous metastasis of CRC by Sunami et al. in Japan [53], lung cancer by Zhu et al. in United States, Liu et al. and Ma et al. in China, and Scherf et al. in Germany [30,54-56], and breast cancer by Przy by Lowska et al. in Poland, Padala et al. in India, Hughes et al. in United Kingdom, Hojati et al. and Balkhi et al. in Iran [57-61]. Zhou et al. and Hsiao et al. did not also find any relation for breast cancer in China and Taiwan, respectively [62,63]. The positive relation of 1G/2G (-1607) polymorphism with cancer has also been demonstrated in melanoma by Ye et al. in United Kingdom, glioma by Kawal et al. in India, and ovarian cancer by Li et al. in China and Kanamori et al. in Japan [64-67]. No relation was shown in ovarian cancer by Ju et al. in Korea [68]. Other cancers include gastric cancer by Devulapalli et al. in India [69], gall bladder cancer by Yan et al. in China [70], oral cancer by Li et al. in China [71], tongue cancer by Shimizu et al. in Japan [72], Prostate cancer by Liao et al. in Taiwan [73], and no relation with prostate cancer by Weng et al. in China [74]. The study by Nikfarjam et al. also found no relation with gallbladder cancer in Iran [75], and the study by Tao et al. Found protective effect of this polymorphism with gall bladder cancer in China [76]. Bialkowska et al. [77], also demonstrated no relation of this polymorphism with lung, colon, and breast cancers in Polish population. Other studies include the carcinogenesis effect of 1G/2G (-1607) polymorphism in endometrial cancer by Nishioka et al. in Japan [78], nasopharyngeal cancer by Nasr et al. in Tunisia and Kondo et al. in Taiwan [79,80], Esophageal cancer by Bradbury et al. in United States [81], and renal cell carcinoma by Hirata et al. in Japan [82].

Positive relations of MMP2-1306 C/T polymorphism were also showed in cancers: head and neck by Fang et al. in China [83], prostate by Srivastava et al. in India [84], breast by Habel et al. in Tunisia, Slattery et al. in United States, and Grieu et al. in Australia [85-87], ovarian by Zhu et al. in China [88], prostate by Weng et al. in China [74], Gastric cardia adenocarcinoma by Miao et al. in China [89], hepatocellular carcinoma recurrence by Wu et al. in China [90], Progression and invasion of CRC by Banday et al. in Kashmiri population, Xu et al. in China, Hesham Mahmoud et al. in Saudi population, Kang et al. in Korea [20,27,91-93], susceptibility to lung cancer by Yu et al. in China [94], Salivary gland cancer by Radunovic et al. in Serbia [95], T-cell Acute Lymphoblastic Leukemia by Lin et al. in China [96], Esophageal cancer by Yu et al. in China [97], and gall bladder cancer by Yan et al. in China and Srivastava et al. in India [70,98]. In the while, Tao et al. [76], showed protection in Asian population (China) for MMP-2. -1306 C/T did not show relation in cancers: oral (by Li et al. in China) [71], colorectal (by Kang et al. in Korea) [93], gastric (by Kubben et al. in Netherlands) [99], prostate(by Adabi et al. in Iran) [100], laryngeal carcinoma (by Liutkevicius et al. in Lithuania) [101], and breast (by Zhou et al. in China) [62]. This polymorphism also significantly protective showed effect in breast cancer by Zhou et al. in China [102].

The carcinogenesis effect of MMP2-735 C/T polymorphism was seen in head and neck carcinoma by Hojihoseini et al. in Iran [103], cardia adenocarcinoma, esophageal squamous cell carcinoma by Li et al. in North China [8], and cervical cancer by Zhang et al. in China [104]. C-1306-C-735 haplotype in the MMP-2 promoter contributes to the risk of the occurrence and metastasis of esophageal squamous cell carcinoma through increasing expression of MMP-2 which was indicated by Yu et al. in China [97]. Also, Zhou et al. [105], showed that C-1306 or C-735 containing haplotypes increase lung cancer risk in China. In the study by Dofara et al. [106], T-1306 and T -735 polymorphisms associated with reduced risk of breast cancer in China, Mexico, and Tunisia. Radunovic et al. [95], also showed MMP-2-1575 G/Apolymorphism has minor importance for salivary cancer in Serbia, and Habel et al. [107], showed which MMP2 (promoter) variants: rs243864(-790 G/A), rs243865 (-1306 C/T), rs243866(-1575 G/A), and rs2285053 (-735 C/T) also have protective effect in Tunisian women. Kiani et al. [9], also showed MMP-2-1575 G/A polymorphism increases prostate cancer risk in patients with diabetes or in individual smokers in Iran.

Results of the various researches in the world wide have shown -1171 5A/6A MMP-3 polymorphism significantly associates with esophageal squamous cell carcinoma in China [37], lung cancer

in Lebanon and China [108,109], breast cancer risk in Italy [110], growth and metastasis of breast cancerin South India, Italy, Egypt, and Iran [58, 110-112], CRC in Japan and Iran [52,112], and lymphatic metastasis in esophageal squamous cell carcinoma in China [37]. No association was also found in the studies in other worldwide regions in gastric cardiac adenocarcinoma (China) [37], Ovarian (China) [66], Gallbladder (North India) [113], Breast cancer (China) [62], laryngeal carcinoma (Lithuania) [101], and oral (China) cancers [71].

The studies also reported the relationship ofthe-181 A/GMMP7 polymorphism with susceptibility to metastasis of breast cancer by Beeghly-Fadiel et al. in China [114], Prostate cancer by Białkowska et al. in Poland [115], Ovarian cancer by Li et al. and Zhu et al. in China [66,88], Gastric cancer by Kubben et al. in Netherlands and Alakus et al. in Germany [99,116], and glioma by Kawal et al. in India [65]. But this polymorphism protected gallbladder cancer in the Asian population (China) [76], and had no association with bladder cancer in the polish population [117], and with breast, lung, and colon cancers in the Polish population [77]. Other studies include association of -181 A/GMMP7 polymorphism with CRC in Kashmiri and Taiwanese populations [20,118], no association with CRC in a Chinese population [83], and association with CRC in the study by Motovali-Bashiet al. in Iran [119]. MMP-7 rs11225297 is in high linkage disequilibrium with MMP-8 rs11225395 and was significantly associated with breast cancer survival in a large two-stage survival study among Chinese women [120].

These four SNPs of MMP-8 including rs11225395, rs1940475, rs1892886, and rs1276284 have been shown a positive relationship with lymphatic metastasis of breast cancer in Chinese population [121]. Despite these positive reports of MMPs in cancer, the protective effect of +17C/GMMP8 polymorphism displayed in cancer such as lung cancer by González-Arriaga et al. in Northern Spain [122] and no relation in bladder cancer in the Polish population were found by Wieczorek et al. [117]. MMP-8 -799 C/T polymorphism increased ovarian cancer risk in China [88], cancer risk in non-Asian populations [123], and had inhibitory effect on breast cancer metastasis by in Belgiumet al. [124].

The relation of the (-1562) C/TMMP9 polymorphism in different studies were showed especially with susceptibility and metastasis of breast cancer in Iran, Invasion and development of breast cancer in Iran [125], and breast cancer development in Iran [125-127]. MMP-9C-1562T polymorphism al one and in combination with MMP-2 C-735T polymorphism increased the risk of breast cancerin Taiwanese population [128] and in other world regions were reported that presence of T allele is in relation with CRC metastasis (Kashmiri, Korean, Taiwanese and North Chinese populations) [20,93,128-130], Tumor progression and malignant phenotype of gastric cancer (Japanese and Chinese populations) [131-133], Susceptibility to prostate cancer (Tunisian population) [134], Invasion and metastasis of breast cancer (North East London population) [59], Breast cancer risk (British population) [135,136], and tumor growth and breast malignancy (Polish population) [57]. Other cancers with positive association with C-1562T polymorphism included salivary gland cancer in Serbia [95], Cervical cancer in China [104], and no association with lung cancer in China and France [137,138], Breast cancer [139] and CRC in Sweden [140], NSCLCin China [141], Papillary thyroid carcinoma in Serbia [142], and T-cell Acute Lymphoblastic Leukemia in China [96]. While, the relation did not find by Roehe et al. in South Brazil and Beeghly-Fadiel et al. [143,144], in China in breast cancer. MMP-9 rs3918242 (-1562 C/T), but not rs3787268 (A/G, intron) and rs17576(Q279R) polymorphisms may be risk factor for breast cancer in China [145]. Also, the Q279R and the R574PMMP-9 coding polymorphisms were associated to metastasis of lung cancer in China [146]. 279Q, 574R, and 668R alleles of MMP-9 were related to metastasis of melanoma in United States [147] and CA microsatellite polymorphism was associated to the invasion of bladder cancer in China [70]. While, Yang et al. [148], have been shown that P574R and R668Q polymorphisms did not associate with CRC in Chinese population.

The relation of -82A/GMMP12 polymorphism was showed with the invasion of the gallbladder by Kader et al. in United States [149], Ovarian cancer risk by Zhu et al. and Liu et al. in China [88,150], and CRC by Van Nguyen et al. in Southeastern Sweden [151]. As well as, the association of -1082A/GMMP-12 polymorphism with NSCLC was showed in United States [50].

In a few studies, the effect of haplotype was surveyed, Bradbury et al. [81], showed which 82G-5A-2G haplotype cause to increased risk of esophageal cancer in United States and Su et al. [50], showed which 1G-5A- 82A-1082A (MMP-1-MMP-3-MMP-12-MMP-12) haplotype may be associated with a higher risk of lung cancer in United States.

-77 A/G MMP-13 was associated with NSCLC by Li et al. in China [141] but, it was not associated with CRC by Van Nguyen et al. in Southeastern Sweden [151], and also with breast, colon, and lung cancers in the Polish population [77]. As well as, -82A/GMMP-12 and -77 A/G MMP-13 associations with developing ESCC and GCA were found in the North China by Li et al. [8].

The +6767 and +7096 polymorphic genotypes and haplotype -165 T: +221 T: +6727 C: +6767 G:+7096 T: +8153 G of MMP-14 gene contributed in the risk and pathological development of hepatocellular carcinoma in Taiwan [152].

MMP-20 rs2292730, rs12278250, 9787933 showed the positive relations with ovarian cancer in China [88], but rs738791, rs738792, rs2267029, rs28382575, and rs131451 did not show associations with uterine cervical cancer in Taiwanese population [153].

Conclusion

The tumor progression is a multi step process that involves complex molecular events such as separation of the tumor cells from a primary tumor, invasion to surrounding tissues, and formation of metastatic tumors [26]. Collagentype IV is a major component of the basement membrane and the first barrier that is decomposed by the tumor cells with the expression of MMP-2 and MMP-9 [154]. The tumor and the stromal cells can produce MMP-9. MMPs with the initiation of carcinogenes is and an increase in angiogenesis in the primary site and the metastatic site can stimulate tumor progression. Since angiogenes is requires to the progression of the primary tumor and invasion to the surrounding tissues, therefore MMPs with the formation of the hole in the ECM and creation of progression pathway of de novo capillaries have an important role in the development of angiogenesis. Several studies have shown, MMPs expression is increasing in endothelial cells adjacent to tumor cells [155].

Invasion and metastasis by conversion epithelial cadherins to mesenchymal are regulated. So that, over expression of E-cad in epithelial carcinoma associates with cancer progression. But N-cad, which normally is expressing in neuronal and mesenchymal tissues, is increasing during tumor invasion that is indicating a change of

epithelial to mesenchymal. R-cad is another cadherin. The studies were demonstrated the reduction of R-cad and E-cad, but increased expression of N-cad in metastatic breast cancer [156]. Metastasis is defined by the endpoints, which are metastatic failures and have been discovered in the special organs away from the primary tumor. While sometimes the steps by which the formation of metastasis is inhibited other than those observed.

Invasion, the movement of tumor cells and their penetration to near tissues has the a central role in the metastasis, and destruction of adhesive joints are increasing the mobility and separation of the tumorcells, which are leading to metastasis [157]. Studies with MMPs synthetic inhibitors were showed a more protected role of MMPs in invasion, andmetastasis. So that, British biotech inhibitor batimastate (BB-94), (a synthetic MMP inhibitor) metastatic melanoma, breast carcinoma and colon and colorectal tumor cells and breast tumor cells reduced. Also, combinational therapy with specific inhibitors of gelatinase A and cytotoxic agentshas been decreased invasion and metastasisof lung carcinoma.

Also, transfection of gelatinase A CDNA in bladder cancer cells increased the region of lung metastasis, increased expression of MT-MMP, and increased survival of carcinoma cells of mice. Several degrading proteases of ECM in addition to its activators, inhibitors, and their receptors are increasing in cancer cells [41].

MMPIs are no directly killed cancer cells but angiogenesis, invasion, and metastasis processes are targeting. There are evidences that TIMPs in the cells having receptor have growth stimulatory effects. However, factors such as the relative concentration of MMPs and specific TIMPs and extracellular environment may affect the reply of the tumor cellsto change in TIMPs expression. However, the MMPs relate to metastasis and there is no doubt that they are the main participants of the metastasis process [158,159].

The Human Genome Project has been identified millions of SNP that are attractive biomarkers in diagnosis, treatment, screening, staging, or grading [109]. New evidences showed that sequence variations including SNP in the promoter and the coding region of the MMP genes result in variable expression in different people and change of their susceptibility to cancer. MMP1, 2, 3, 7, 8, 9, 12, 13, 14, and 20 were shown to contribute in cancer such as breast, lung, CRC, ovarian, gallbladder, gastric, renal, oral, head and neck, cervical, endometrial, esophageal, nasopharyngeal, laryngeal, leukemia, salivary, prostate, tongue, thyroid, pancreatic cancers, hepatocellular carcinoma, melanoma, glioma, and etc in different populations.

Viewed differences between stated risks are presumably due to the differences in genetic context, sample size of the studied population, and environment. The main features of cancer cells can include proliferation, invasion to surrounding tissues, and migration to distant organs, which are leading to sporadic metastasis, the main cause of cancer deaths. Then, MMPs are attractive targets for cancer therapy and the developmentof new inhibitors with, less toxic and more effective, accompanied by conventional combinational factors is the main focus of cancer therapy researches. As well, the study of clinicopathological may help to identify populations at high risk and provide attractive targets for targeted therapies because, in the majority of studies, the relation of SNPs of MMP genes with clinicopathological characters such as smoking status, age, gender, stage, and grade of tumor were showed.

References

1. Weber GF. Molecular mechanisms of metastasis. Cancer Lett. 2008;270(2):181-90.
2. Gupta GP, Massague J. Cancer metastasis: building a framework. Cell. 2006;127(4):679-95.
3. Engers R, Gabbert HE. Mechanisms of tumor metastasis: cell biological aspects and clinical implications. J Cancer Res Clin Oncol. 2000;126(12):682-92.
4. John A, Tuszynski G. The role of matrix metalloproteinases in tumor angiogenesis and tumor metastasis. Pathol Oncol Res. 2001;7(1):14-23.
5. Yao Z, Yuan T, Wang H, Yao S, Zhao Y, Liu Y, et al. MMP-2 together with MMP-9 overexpression correlated with lymph node metastasis and poor prognosis in early gastric carcinoma. Tumour Biol. 2017;39(6):1010428317700411.
6. Sauter W, Rosenberger A, Beckmann L, Kropp S, Mittelstrass K, Timofeeva M, et al. Matrix metalloproteinase 1 (MMP1) is associated with early-onset lung cancer. Cancer Epidemiology Biomarkers Prev. 2008;17(5):1127-35.
7. Wieczorek E, Wasowicz W, Gromadzinska J, Reszka E. Functional polymorphisms in the matrix metalloproteinase genes and their association with bladder cancer risk and recurrence: A mini-review. Int J Urol. 2014;21(8):744-52.
8. Li Y, Sun D-l, Duan Y-n, Zhang X-j, Wang N, Zhou R-m, et al. Association of functional polymorphisms in MMPs genes with gastric cardia adenocarcinoma and esophageal squamous cell carcinoma in high incidence region of North China. Mol biol Rep. 2010;37(1):197-205.
9. Kiani A, Kamankesh M, Vaisi-Raygani A, Moradi M-R, Tanhapour M, Rahimi Z, et al. Activities and polymorphisms of MMP-2 and MMP-9, smoking, diabetes and risk of prostate cancer. Mol Biol Rep. 2020;47(12):9373-83.
10. Yeh Y-C, Sheu B-S. Matrix metalloproteinases and their inhibitors in the gastrointestinal cancers: current knowledge and clinical potential. Metalloproteinases In Medicine. 2014;1:3-13.
11. Atkinson J, Pennington C, Martin S, Anikin V, Mearns A, Loadman P, et al. Membrane type matrix metalloproteinases (MMPs) show differential expression in non-small cell lung cancer (NSCLC) compared to normal lung: correlation of MMP-14 mRNA expression and proteolytic activity. Eur J Cancer. 2007;43(11):1764-71.
12. McColgan P, Sharma P. Polymorphisms of matrix metalloproteinases 1, 2, 3 and 9 and susceptibility to lung, breast and colorectal cancer in over 30,000 subjects. Int J Cancer. 2009;125(6):1473-8.
13. McColgan P, Sharma P. Polymorphisms of matrix metalloproteinases 1, 2, 3 and 9 and susceptibility to lung, breast and colorectal cancer in over 30,000 subjects. Int J Cancer. 2009;125(6):1473-8.
14. Hu C, Weng F, Li L, Dai W, Yan J, Peng L, et al. Association between MMP-9– 1562 C/T polymorphism and susceptibility to digestive cancers: A meta-analysis. Gene. 2018;673:88-94.
15. Laitinen A, Hagström J, Mustonen H, Kokkola A, Tervahartiala T, Sorsa T, et al. Serum MMP-8 and TIMP-1 as prognostic biomarkers in gastric cancer. Tumor Biol. 2018;40(9):1010428318799266.
16. Lièvre A, Milet J, Carayol J, Le Corre D, Milan C, Pariente A, et al. Genetic polymorphisms of MMP1, MMP3 and MMP7 gene promoter and risk of colorectal adenoma. BMC cancer. 2006;6:270.
17. Zhang J, Jin X, Fang S, Wang R, Li Y, Wang N, et al. The functional polymorphism in the matrix metalloproteinase-7 promoter increases susceptibility to esophageal squamous cell carcinoma, gastric cardiac adenocarcinoma and non-small cell lung carcinoma. Carcinogenesis. 2005;26(10):1748-53.
18. Fingleton B. Matrix metalloproteinases: roles in cancer and metastasis. Front Biosci. 2006;11:479-91.
19. Djuric T, Zivkovic M. Overview of MMP biology and gene associations in human diseases. Role Matrix Met Hum Body Pathol. 2017;1:3-33.
20. Banday MZ, Sameer AS, Mir AH, Mokhdomi TA, Chowdri NA, Haq E. Matrix metalloproteinase (MMP)-2,-7 and-9 promoter polymorphisms in colorectal cancer in ethnic Kashmiri population-A case-control study and a mini review. Gene. 2016;589(1):81-9.

21. Löffek S, Schilling O, Franzke C-W. Biological role of matrix metalloproteinases: a critical balance. Eur Respir J. 2011;38(1):191-208.

22. Ii M, Yamamoto H, Adachi Y, Maruyama Y, Shinomura Y. Role of matrix metalloproteinase-7 (matrilysin) in human cancer invasion, apoptosis, growth, and angiogenesis. Exp Biol Med (Maywood). 2006;231(1):20-7.

23. Zare M, Jafari-Nedooshan J, Aghili K, Ahrar H, Jarahzadeh MH, Seifi-Shalamzari N, et al. Association of Mmp-7 -181a>G Polymorphism with Colorectal Cancer and Gastric Cancer Susceptibility: A Systematic Review and Meta-Analysis. Arq Bras Cir Dig. 2019;32(3):e1449.

24. Fanjul-Fernández M, Folgueras AR, Cabrera S, López-Otín C. Matrix metalloproteinases: evolution, gene regulation and functional analysis in mouse models. Biochim Biophys Acta. 2010;1803(1):3-19.

25. Nagase H, Visse R, Murphy G. Structure and function of matrix metalloproteinases and TIMPs. Cardiovasc Res. 2006;69(3):562-73.

26. Yoon SO, Park SJ, Yun CH, Chung AS. Roles of matrix metalloproteinases in tumor metastasis and angiogenesis. J Biochem Mol Biol. 2003;36(1):128-37.

27. Decock J, Paridaens R, Ye S. Genetic polymorphisms of matrix metalloproteinases in lung, breast and colorectal cancer. Clin Genet. 2008;73(3):197-211.

28. Beeghly-Fadiel A, Xiang Y-B, Deming SL, Long J-R, Xu W-H, Cai Q, et al. No association between matrix metalloproteinase (MMP)-1, MMP-3, and MMP-7 SNPs and endometrial cancer risk. Cancer Epidemiol Prevention Biomarkers Prev. 2009;18(6):1925-8.

29. Qiu W, Zhou G, Zhai Y, Zhang X, Xie W, Zhang H, et al. No association of MMP-7, MMP-8, and MMP-21 polymorphisms with the risk of hepatocellular carcinoma in a Chinese population. Cancer Epidemiol Biomarkers Prev. 2008;17(9):2514-8.

30. Zhu Y, Spitz MR, Lei L, Mills GB, Wu X. A single nucleotide polymorphism in the matrix metalloproteinase-1 promoter enhances lung cancer susceptibility. Cancer Res. 2001;61(21):7825-9.

31. Hidalgo M, Eckhardt SG. Development of matrix metalloproteinase inhibitors in cancer therapy. J Natl Cancer Inst. 2001;93(3):178-93.

32. Lederle W, Hartenstein B, Meides A, Kunzelmann H, Werb Z, Angel P, et al. MMP13 as a stromal mediator in controlling persistent angiogenesis in skin carcinoma. Carcinogenesis. 2010;31(7):1175-84.

33. Kerbel RS. Tumor angiogenesis. N Engl J Med. 2008;358(19):2039-49.

34. Nishida N, Yano H, Nishida T, Kamura T, Kojiro M. Angiogenesis in cancer. Vasc Health Risk Manag. 2006;2(3):213-9.

35. Gao H, Lan X, Li S, Xue Y. Relationships of MMP-9, E-cadherin, and VEGF expression with clinicopathological features and response to chemosensitivity in gastric cancer. Tumour Biol. 2017;39(5):1010428317698368.

36. Khalid A, Javaid M. Matrix metalloproteinases: new targets in cancer therapy. J Cancer Sci Ther. 2016;8(6):143-53.

37. Zhang J, Jin X, Fang S, Li Y, Wang R, Guo W, et al. The functional SNP in the matrix metalloproteinase-3 promoter modifies susceptibility and lymphatic metastasis in esophageal squamous cell carcinoma but not in gastric cardiac adenocarcinoma. Carcinogenesis. 2004;25(12):2519-24.

38. Rundhaug JE. Matrix metalloproteinases and angiogenesis. J Cell Mol Med. 2005;9(2):267-85.

39. Valastyan S, Weinberg RA. Tumor metastasis: molecular insights and evolving paradigms. Cell. 2011;147(2):275-92.

40. Mareel M, Leroy A. Clinical, cellular, and molecular aspects of cancer invasion. Physiol Rev. 2003;83(2):337-76.

41. Illemann M, Bird N, Majeed A, Sehested M, Laerum OD, Lund LR, et al. MMP-9 is differentially expressed in primary human colorectal adenocarcinomas and their metastases. Mol Cancer Res. 2006;4(5):293-302.

42. Chen N-H, Liu J-W, Zhong J-J. Ganoderic acid T inhibits tumor invasion in vitro and in vivo through inhibition of MMP expression. Pharmacol Rep. 2010;62(1):150-63.

43. Quaranta M, Daniele A, Coviello M, Venneri MT, Abbate I, Caringella ME, et al. MMP-2, MMP-9, VEGF and CA 15.3 in breast cancer. Anticancer Res. 2007;27(5B):3593-600.

44. Valastyan S, Benaich N, Chang A, Reinhardt F, Weinberg RA. Concomitant suppression of three target genes can explain the impact of a microRNA on metastasis. Genes Dev. 2009;23(22):2592-7.

45. Heerboth S, Housman G, Leary M, Longacre M, Byler S, Lapinska K, et al. EMT and tumor metastasis. Clin Transl Med. 2015;4(1):6.

46. Zetter BR. Angiogenesis and tumor metastasis. Annu Rev Med. 1998;49(1):407-24.

47. Steeg PS. Targeting metastasis. Nat Rev Cancer. 2016;16(4):201-18.

48. Chaffer CL, Weinberg RA. A perspective on cancer cell metastasis. Science. 2011;331(6024):1559-64.

49. Gutiérrez-Fernández A, Fueyo A, Folgueras AR, Garabaya C, Pennington CJ, Pilgrim S, et al. Matrix metalloproteinase-8 functions as a metastasis suppressor through modulation of tumor cell adhesion and invasion. Cancer Res. 2008;68(8):2755-63.

50. Su L, Zhou W, Asomaning K, Lin X, Wain JC, Lynch TJ, et al. Genotypes and haplotypes of matrix metalloproteinase 1, 3 and 12 genes and the risk of lung cancer. Carcinogenesis. 2006;27(5):1024-9.

51. Kouhkan F, Motovali-Bashi M, Hojati Z. The influence of interstitial collagenas-1 genotype polymorphism on colorectal cancer risk in Iranian population. Cancer Invest. 2008;26(8):836-42.

52. Hinoda Y, Okayama N, Takano N, Fujimura K, Suehiro Y, Hamanaka Y, et al. Association of functional polymorphisms of matrix metalloproteinase (MMP)-1 and MMP-3 genes with colorectal cancer. Int J Cancer. 2002;102(5):526-9.

53. Sunami E, Tsuno N, Osada T, Saito S, Kitayama J, Tomozawa S, et al. MMP-1 is a prognostic marker for hematogenous metastasis of colorectal cancer. Oncologist. 2000;5(2):108-14.

54. Liu L, Wu J, Wu C, Wang Y, Zhong R, Zhang X, et al. A functional polymorphism (-1607 1G→ 2G) in the matrix metalloproteinase-1 promoter is associated with development and progression of lung cancer. Cancer. 2011;117(22):5172-81.

55. Ma Y, Yang X, Xie YP, Yi C, Zhao F, Huang Y. Association of Matrix Metalloproteinase1-1607 1G>2G Polymorphism and Lung Cancer Risk: An Update by Meta-Analysis. Asian Pac J Cancer Prev. 2019;20(6):1841-7.

56. Scherf DB, Dally H, Muller P, Werle-Schneider G, Jager B, Edler L, et al. Single nucleotide polymorphisms in matrix metalloproteinase genes and lung cancer chemotherapy response and prognosis. Eur Respir J. 2010;35(2):381-90.

57. Przybylowska K, Kluczna A, Zadrozny M, Krawczyk T, Kulig A, Rykala J, et al. Polymorphisms of the promoter regions of matrix metalloproteinases genes MMP-1 and MMP-9 in breast cancer. Breast Cancer Res Treat. 2006;95(1):65-72.

58. Padala C, Tupurani MA, Puranam K, Gantala S, Shyamala N, Kondapalli MS, et al. Synergistic effect of collagenase-1 (MMP1), stromelysin-1 (MMP3) and gelatinase-B (MMP9) gene polymorphisms in breast cancer. PloS one. 2017;12(9):e0184448.

59. Hughes S, Agbaje O, Bowen RL, Holliday DL, Shaw JA, Duffy S, et al. Matrix metalloproteinase single-nucleotide polymorphisms and haplotypes predict breast cancer progression. Clin Cancer Res. 2007;13(22 Pt 1):6673-80.

60. Motevali BM, Hojati Z, Kouhkan F. Genetic Variation in MMP-1 Promoter Region and Breast Cancer Susceptibility. 2008;19(1):9-14.

61. Balkhi S, Mashayekhi F, Salehzadeh A, Saedi HS. Matrix metalloproteinase (MMP)-1 and MMP-3 gene variations affect MMP-1 and-3 serum concentration and associates with breast cancer. Mol Biol Rep. 2020;47(12):9637-44.

62. Zhou P, Du L-F, Lv G-Q, Yu X-M, Gu Y-L, Li J-P, et al. Current evidence on the relationship between four polymorphisms in the matrix metalloproteinases (MMP) gene and breast cancer risk: a meta-analysis. Breast Cancer Research and Treatment. 2010;127(3):813-8.

63. Hsiao CL, Liu LC, Shih TC, Lai YL, Hsu SW, Wang HC, et al. The Association of

Matrix Metalloproteinase-1 Promoter Polymorphisms with Breast Cancer. In Vivo. 2018;32(3):487-91.

64. Ye S, Dhillon S, Turner SJ, Bateman AC, Theaker JM, Pickering RM, et al. Invasiveness of cutaneous malignant melanoma is influenced by matrix metalloproteinase 1 gene polymorphism. Cancer research. 2001;61(4):1296-8.

65. Kawal P, Chandra A, Rajkumar, Dhole TN, Ojha B. Correlations of polymorphisms in matrix metalloproteinase-1, -2, and -7 promoters to susceptibility to malignant gliomas. Asian J Neurosurg. 2016;11(2):160-6.

66. Li Y, Jin X, Kang S, Wang Y, Du H, Zhang J, et al. Polymorphisms in the promoter regions of the matrix metalloproteinases-1, -3, -7, and -9 and the risk of epithelial ovarian cancer in China. Gynecol Oncol. 2006;101(1):92-6.

67. Kanamori Y, Matsushima M, Minaguchi T, Kobayashi K, Sagae S, Kudo R, et al. Correlation between expression of the matrix metalloproteinase-1 gene in ovarian cancers and an insertion/deletion polymorphism in its promoter region. Cancer Res. 1999;59(17):4225-7.

68. Ju W, Kim JW, Park NH, Song YS, Kim SC, Kang SB, et al. Matrix metalloproteinase-1 promoter polymorphism and epithelial ovarian cancer: Does ethnicity matter? J Obstet Gynaecol Res. 2007;33(2):155-60.

69. Devulapalli K, Bhayal AC, Porike SK, Macherla R, Akka J, Nallari P, et al. Role of interstitial collagenase gene promoter polymorphism in the etiology of gastric cancer. Saudi J Gastroenterol. 2014;20(5):309-14.

70. Yan Y, Liang H, Li T, Li M, Li R, Qin X, et al. The MMP-1, MMP-2, and MMP-9 gene polymorphisms and susceptibility to bladder cancer: a meta-analysis. Tumor Biol. 2014;35(4):3047-52.

71. Li Y, Wang Y, Sun H, Zhang Y, Li H, Cong X, et al. Association Between Matrix Metalloproteinase-1, 2, 3 Polymorphisms and Oral Cancer Risk: A Meta-Analysis. Genet Test Mol Biomarkers. 2018;22(8):456-64.

72. Shimizu Y, Kondo S, Shirai A, Furukawa M, Yoshizaki T. A single nucleotide polymorphism in the matrix metalloproteinase-1 and interleukin-8 gene promoter predicts poor prognosis in tongue cancer. Auris Nasus Larynx. 2008;35(3):381-9.

73. Liao CH, Wu HC, Hu PS, Hsu SW, Shen TC, Hsia TC, et al. The Association of Matrix Metalloproteinase-1 Promoter Polymorphisms with Prostate Cancer in Taiwanese Patients. Anticancer Res. 2018;38(7):3907-11.

74. Weng H, Zeng X-T, Wang X-H, Liu T-Z, He D-L. Genetic association between matrix metalloproteinases gene polymorphisms and risk of prostate cancer: A Meta-Analysis. Front Physiol. 2017;8:975.

75. Nikfarjam D, Tafvizi F, Poure MS. Low level of matrix metalloproteinase-1 in patients with bladder cancer and the effect of mmp-1 polymorphism (-1607) on serum mmp-1 levels and the risk of bladder cancer. World Cancer Research Journal. 2018;5(3):e1132.

76. Tao L, Li Z, Lin L, Lei Y, Hongyuan Y, Hongwei J, et al. MMP1, 2, 3, 7, and 9 gene polymorphisms and urinary cancer risk: a meta-analysis. Genet Test Mol Biomarkers. 2015;19(10):548-55.

77. Białkowska K, Marciniak W, Muszyńska M, Baszuk P, Gupta S, Jaworska-Bieniek K, et al. Polymorphisms in MMP-1, MMP-2, MMP-7, MMP-13 and MT2A do not contribute to breast, lung and colon cancer risk in polish population. Hered Cancer Clin Pract. 2020;18:16.

78. Nishioka Y, Kobayashi K, Sagae S, Ishioka S, Nishikawa A, Matsushima M, et al. A single nucleotide polymorphism in the matrix metalloproteinase-1 promoter in endometrial carcinomas. Jpn J Cancer Res. 2000;91(6):612-5.

79. Nasr HB, Mestiri S, Chahed K, Bouaouina N, Gabbouj S, Jalbout M, et al. Matrix metalloproteinase-1 (-1607) 1G/2G and-9 (-1562) C/T promoter polymorphisms: Susceptibility and prognostic implications in nasopharyngeal carcinomas. Clin Chim Acta. 2007;384(1-2):57-63.

80. Kondo S, Wakisaka N, Schell MJ, Horikawa T, Sheen TS, Sato H, et al. Epstein-Barr virus latent membrane protein 1 induces the matrix metalloproteinase-1 promoter via an Ets binding site formed by a single nucleotide polymorphism: enhanced susceptibility to nasopharyngeal carcinoma. Int J Cancer. 2005;115(3):368-76.

81. Bradbury PA, Zhai R, Hopkins J, Kulke MH, Heist RS, Singh S, et al. Matrix metalloproteinase 1, 3 and 12 polymorphisms and esophageal adenocarcinoma risk and prognosis. Carcinogenesis. 2009;30(5):793-8.

82. Hirata H, Naito K, Yoshihiro S, Matsuyama H, Suehiro Y, Hinoda Y. A single nucleotide polymorphism in the matrix metalloproteinase-1 promoter is associated with conventional renal cell carcinoma. Int J Cancer. 2003;106(3):372-4.

83. Fang WL, Liang WB, He H, Zhu Y, Li SL, Gao LB, et al. Association of matrix metalloproteinases 1, 7, and 9 gene polymorphisms with genetic susceptibility to colorectal carcinoma in a Han Chinese population. DNA Cell Biol. 2010;29(11):657-61.

84. Srivastava P, Lone TA, Kapoor R, Mittal RD. Association of promoter polymorphisms in MMP2 and TIMP2 with prostate cancer susceptibility in North India. Arch Med Res. 2012;43(2):117-24.

85. Habel AF, Ghali RM, Bouaziz H, Daldoul A, Hadj-Ahmed M, Mokrani A, et al. Common matrix metalloproteinase-2 gene variants and altered susceptibility to breast cancer and associated features in Tunisian women. Tumor Biol. 2019;41(4):1010428319845749.

86. Slattery ML, John E, Torres-Mejia G, Stern M, Lundgreen A, Hines L, et al. Matrix metalloproteinase genes are associated with breast cancer risk and survival: the Breast Cancer Health Disparities Study. PloS one. 2013;8(5):e63165.

87. Grieu F, Li WQ, Iacopetta B. Genetic polymorphisms in the MMP-2 and MMP-9 genes and breast cancer phenotype. Breast Cancer Res Treat. 2004;88(3):197-204.

88. Zhu XM, Sun WF. Association between matrix metalloproteinases polymorphisms and ovarian cancer risk: A meta-analysis and systematic review. PloS one. 2017;12(9):e0185456.

89. Miao X, Yu C, Tan W, Xiong P, Liang G, Lu W, et al. A functional polymorphism in the matrix metalloproteinase-2 gene promoter (-1306C/T) is associated with risk of development but not metastasis of gastric cardia adenocarcinoma. Cancer Res. 2003;63(14):3987-90.

90. Wu LM, Zhang F, Xie HY, Xu X, Chen QX, Yin SY, et al. MMP2 promoter polymorphism (C-1306T) and risk of recurrence in patients with hepatocellular carcinoma after transplantation. Clin Genet. 2008;73(3):273-8.

91. Xu E, Lai M, Lv B, Xing X, Huang Q, Xia X. A single nucleotide polymorphism in the matrix metalloproteinase-2 promoter is associated with colorectal cancer. Biochemical Biophs Res Commun. 2004;324(3):999-1003.

92. Saeed HM, Alanazi MS, Parine NR, Shaik J, Semlali A, Alharbi O, et al. Matrix metalloproteinase-2 (-1306 c>t) promoter polymorphism and risk of colorectal cancer in the Saudi population. Asian Pac J Cancer Prev. 2013;14(10):6025-30.

93. Kang MJ, Jung SA, Jung JM, Kim SE, Jung HK, Kim TH, et al. Associations between single nucleotide polymorphisms of MMP2, VEGF, and HIF1A genes and the risk of developing colorectal cancer. Anticancer Res. 2011;31(2):575-84.

94. Yu C, Pan K, Xing D, Liang G, Tan W, Zhang L, et al. Correlation between a single nucleotide polymorphism in the matrix metalloproteinase-2 promoter and risk of lung cancer. Cancer Res. 2002;62(22):6430-3.

95. Radunovic M, Nikolic N, Milenkovic S, Tomanovic N, Boricic I, Dimitrijevic M, et al. The MMP-2 and MMP-9 promoter polymorphisms and susceptibility to salivary gland cancer. J BUON. 2016;21(3):597-602.

96. Lin C-M, Zeng Y-L, Xiao M, Mei X-Q, Shen L-Y, Guo M-X, et al. The relationship between MMP-2-1306C> T and MMP-9-1562C> T polymorphisms and the risk and prognosis of T-cell acute lymphoblastic leukemia in a Chinese population: a case-control study. Cell Physiol Biochem. 2017;42(4):1458-68.

97. Yu C, Zhou Y, Miao X, Xiong P, Tan W, Lin D. Functional haplotypes in the promoter of matrix metalloproteinase-2 predict risk of the occurrence and metastasis of esophageal cancer. Cancer Res. 2004;64(20):7622-8.

98. Srivastava P, Kapoor R, Mittal RD. Association of single nucleotide polymorphisms in promoter of matrix metalloproteinase-2, 8 genes with bladder cancer risk in Northern India. Urol Oncol. 2013;31(2)247-54.

99. Kubben FJ, Sier CF, Meijer MJ, van den Berg M, van der Reijden JJ, Griffioen G, et

al. Clinical impact of MMP and TIMP gene polymorphisms in gastric cancer. Br J Cancer. 2006;95(6):744-51.

100. Adabi Z, Mohsen Ziaei SA, Imani M, Samzadeh M, Narouie B, Jamaldini SH, et al. Genetic Polymorphism of MMP2 Gene and Susceptibility to Prostate Cancer. Arch Med Res. 2015;46(7):546-50.

101. Liutkevicius V, Lesauskaite V, Liutkeviciene R, Vaiciulis P, Uloza V. Matrix Metalloproteinases (MMP-2,-3,-9) Gene Polymorphisms in Cases of Benign Vocal Fold Lesions and Laryngeal Carcinoma. In Vivo. 2020;34(1):267-74.

102. Zhou Y, Yu C, Miao X, Tan W, Liang G, Xiong P, et al. Substantial reduction in risk of breast cancer associated with genetic polymorphisms in the promoters of the matrix metalloproteinase-2 and tissue inhibitor of metalloproteinase-2 genes. Carcinogenesis. 2004;25(3):399-404.

103. Hajihoseini S, KHALIL BM, Khosravi A, Ghezelsofla E, Ghaderi A. Prognostic significance of MMP2 and MMP9 functional promoter single nucleotide polymorphisms in head and neck squamous cell carcinoma. 2011;14(2):137-44.

104. Zhang H, Li G, Zhang Z, Wang S, Zhang S. MMP-2 and MMP-9 gene polymorphisms associated with cervical cancer risk. Int J Clin Exp Pathol. 2017;10(12):11760-5.

105. Zhou Y, Yu C, Miao X, Wang Y, Tan W, Sun T, et al. Functional haplotypes in the promoter of matrix metalloproteinase-2 and lung cancer susceptibility. Carcinogenesis. 2005;26(6):1117-21.

106. Dofara SG, Chang S-L, Diorio C. Gene Polymorphisms and Circulating Levels of MMP-2 and MMP-9: A Review of Their Role in Breast Cancer Risk. Anticancer Res. 2020;40(7):3619-31.

107. Habel AF, Ghali RM, Bouaziz H, Daldoul A, Hadj-Ahmed M, Mokrani A, et al. Common matrix metalloproteinase-2 gene variants and altered susceptibility to breast cancer and associated features in Tunisian women. Tumour Biol. 2019;41(4):1010428319845749.

108. Fakhoury HM, Noureddine S, Tamim H, Chmaisse H, Makki R. Association of MMP3-1171(5A>6A) polymorphism with lung cancer in Lebanon. Genet Test Mol Biomarkers. 2012;16(8):988-90.

109. Sun T, Gao Y, Tan W, Ma S, Zhang X, Wang Y, et al. Haplotypes in matrix metalloproteinase gene cluster on chromosome 11q22 contribute to the risk of lung cancer development and progression. Clin Cancer Res. 2006;12(23):7009-17.

110. Ghilardi G, Biondi ML, Caputo M, Leviti S, DeMonti M, Guagnellini E, et al. A single nucleotide polymorphism in the matrix metalloproteinase-3 promoter enhances breast cancer susceptibility. Clin Cancer Res. 2002;8(12):3820-3.

111. Ibrahim FAER, Elfeky SE, Haroun M, Ahmed MAE, Elnaggar M, Ismail NAE, et al. Association of matrix metalloproteinases 3 and 9 single nucleotide polymorphisms with breast cancer risk: A case-control study. Mol Clin Oncol. 2020;13(1):54-62.

112. Motovali-Bashi M, Hojati Z, Hajihoseiny S, Hemmati S. The stromelysin-1 5A/5A genotype enhances colorectal cancer cell invasion in Iranian population. J Res Med Sci. 2012;17(10):962-6.

113. Srivastava P, Mandhani A, Kapoor R, Mittal RD. Role of MMP-3 and MMP-9 and their haplotypes in risk of bladder cancer in North Indian cohort. Ann Surg Oncol. 2010;17(11):3068-75.

114. Beeghly-Fadiel A, Long JR, Gao YT, Li C, Qu S, Cai Q, et al. Common MMP-7 polymorphisms and breast cancer susceptibility: a multistage study of association and functionality. Cancer Res. 2008;68(15):6453-9.

115. Białkowska K, Marciniak W, Muszyńska M, Baszuk P, Gupta S, Jaworska-Bieniek K, et al. Association of zinc level and polymorphism in MMP-7 gene with prostate cancer in Polish population. PloS one. 2018;13(7):e0201065.

116. Alakus H, Afriani N, Warnecke-Eberz U, Bollschweiler E, Fetzner U, Drebber U, et al. Clinical impact of MMP and TIMP gene polymorphisms in gastric cancer. World J Surg. 2010;34(12):2853-9.

117. Wieczorek E, Reszka E, Wasowicz W, Grzegorczyk A, Konecki T, Sosnowski M, et al. MMP7 and MMP8 genetic polymorphisms in bladder cancer patients. Cent European J Urol. 2014;66(4):405-10.

118. Yueh TC, Wu CN, Hung YW, Chang WS, Fu CK, Pei JS, et al. The Contribution of MMP-7 Genotypes to Colorectal Cancer Susceptibility in Taiwan. Cancer Genomics Proteomics. 2018;15(3):207-12.

119. Motovali-Bashi M, Sadeghi Z, Hemati S. Relationship between-181 (A/G) region single nucleotide polymorphisms of matrilysin gene promoter and the onset and prevalence of colorectal cancer using tetra-primer ARMS PCR and RFLP-PCR techniques. Basic & Clinical Cancer Research. 2015;7(2&3):20-31.

120. Beeghly-Fadiel A, Zheng W, Lu W, Long J, Zheng Y, Cai H, et al. Replication study for reported SNP associations with breast cancer survival. J Cancer Res Clin Oncol. 2012;138(6):1019-26.

121. Decock J, Long J-R, Laxton RC, Shu X-O, Hodgkinson C, Hendrickx W, et al. Association of matrix metalloproteinase-8 gene variation with breast cancer prognosis. Cancer Res. 2007;67(21):10214-21.

122. González-Arriaga P, López-Cima MF, Fernández-Somoano A, Pascual T, Marrón MG, Puente XS, et al. Polymorphism+ 17 C/G in matrix metalloprotease MMP8 decreases lung cancer risk. BMC cancer. 2008;8:378.

123. Feng J, Chen Y, Hua W, Sun X, Chen Y, Liu Y, et al. The MMP-8 rs11225395 Promoter Polymorphism Increases Cancer Risk of Non-Asian Populations: Evidence from a Meta-Analysis. Biomolecules. 2019;9(10):570.

124. Decock J, Long JR, Laxton RC, Shu XO, Hodgkinson C, Hendrickx W, et al. Association of matrix metalloproteinase-8 gene variation with breast cancer prognosis. Cancer Res. 2007;67(21):10214-21.

125. Sadeghi M, Motovali-Bashi M, Hojati Z. MMP-9 promoter polymorphism associated with tumor progression of breast cancer in Iranian population. International Journal of Integrative Biology. 2009;6(1):33-7.

126. Hemati S, Sadeghi M, Motovali-Bashi M, Sahebi A, Malekshahi ZV. Higher plasma MMP-9 level in breast cancer patients with MMP-9 promoter T allele. Journal of Biological Research. 2010;13:113-8.

127. Motovali-Bashi M, Sadeghi M, Hemmati S. Serum MMP-9 level associated with initiation and progression steps of breast cancer in the Iranian population. Reproductive sciences. 2010;17(6):585-9.

128. Wu MH, Tzeng HE, Wu CN, Yueh TC, Peng YC, Tsai CH, et al. Association of Matrix Metalloproteinase-9 rs3918242 Promoter Genotypes With Colorectal Cancer Risk. Anticancer Res. 2019;39(12):6523-9.

129. Xing L-L, Wang Z-N, Jiang L, Zhang Y, Xu Y-Y, Li J, et al. Matrix metalloproteinase-9-1562C> T polymorphism may increase the risk of lymphatic metastasis of colorectal cancer. World J Gastroenterol. 2007;13(34):4626-9.

130. Park KS, Kim SJ, Kim KH, Kim JC. Clinical characteristics of TIMP2, MMP2, and MMP9 gene polymorphisms in colorectal cancer. J Gastroenterol Hepatol. 2011;26(2):391-7.

131. Matsumura S, Oue N, Hamai Y, Kitadai Y, Fujii K, Chayama K, et al. A single nucleotide polymorphism in the MMP-9 promoter is correlated with tumor progression and malignant phenotype of gastric cancer. American Association for Cancer Research. 2004.

132. Matsumura S, Oue N, Nakayama H, Kitadai Y, Yoshida K, Yamaguchi Y, et al. A single nucleotide polymorphism in the MMP-9 promoter affects tumor progression and invasive phenotype of gastric cancer. J Cancer Res Clin Oncol. 2005;131(1):19-25.

133. Peng Z, Jia J, Gong W, Gao X, Ma P, Jin Z, et al. The association of matrix metalloproteinase-9 promoter polymorphisms with gastric cancer risk: a meta-analysis. Oncotarget. 2017;8(58):99024-32.

134. Sfar S, Saad H, Mosbah F, Gabbouj S, Chouchane L. TSP1 and MMP9 genetic variants in sporadic prostate cancer. Cancer Genet Cytogenet. 2007;172(1):38-44.

135. Grieu F, Li WQ, Iacopetta B. Genetic polymorphisms in the MMP-2 and MMP-9 genes and breast cancer phenotype. Breast Cancer Res Treat. 2004;88(3):197-204.

136. Ranuncolo SM, Armanasco E, Cresta C, Bal de Kier Joffe E, Puricelli L. Plasma MMP-9 (92 kDa-MMP) activity is useful in the follow-up and in the assessment of prognosis in breast cancer patients. Int J Cancer. 2003;106(5):745-51.

137. Wang Y, Fang S, Wei L, Wang R, Jin X, Wen D, et al. No association between the C-1562T polymorphism in the promoter of matrix metalloproteinase-9 gene and non-small cell lung carcinoma. Lung Cancer. 2005;49(2):155-61.

138. Rollin J, Régina S, Vourc'h P, Iochmann S, Bléchet C, Reverdiau P, et al. Influence of MMP-2 and MMP-9 promoter polymorphisms on gene expression and clinical outcome of non-small cell lung cancer. Lung Cancer. 2007;56(2):273-80.

139. Lei H, Hemminki K, Altieri A, Johansson R, Enquist K, Hallmans G, et al. Promoter polymorphisms in matrix metalloproteinases and their inhibitors: few associations with breast cancer susceptibility and progression. Breast cancer research and treatment. 2007;103(1):61-9.

140. Elander N, Söderkvist P, Fransén K. Matrix metalloproteinase (MMP)-1,-2,-3 and-9 promoter polymorphisms in colorectal cancer. Anticancer Res. 2006;26(1B):791-5.

141. Li W, Jia MX, Wang JH, Lu JL, Deng J, Tang JX, et al. Association of MMP9-1562C/T and MMP13-77A/G Polymorphisms with Non-Small Cell Lung Cancer in Southern Chinese Population. Biomolecules. 2019;9(3):107.

142. Roncevic J, Djoric I, Selemetjev S, Jankovic J, Dencic TI, Bozic V, et al. MMP-9-1562 C/T single nucleotide polymorphism associates with increased MMP-9 level and activity during papillary thyroid carcinoma progression. Pathology. 2019;51(1):55-61.

143. Roehe AV, Frazzon AP, Agnes G, Damin AP, Hartman AA, Graudenz MS. Detection of polymorphisms in the promoters of matrix metalloproteinases 2 and 9 genes in breast cancer in South Brazil: preliminary results. Breast Cancer Res Treat. 2007;102(1):123-4.

144. Beeghly-Fadiel A, Lu W, Shu XO, Long J, Cai Q, Xiang Y, et al. MMP9 polymorphisms and breast cancer risk: a report from the Shanghai Breast Cancer Genetics Study. Breast Cancer Res Treat. 2011;126(2):507-13.

145. Xu T, Zhang S, Qiu D, Li X, Fan Y. Association between Matrix Metalloproteinase 9 Polymorphisms and Breast Cancer Risk: An Updated Meta-Analysis and Trial Sequential Analysis. Gene. 2020;759:144972.

146. Hu Z, Huo X, Lu D, Qian J, Zhou J, Chen Y, et al. Functional polymorphisms of matrix metalloproteinase-9 are associated with risk of occurrence and metastasis of lung cancer. Clin Cancer Res. 2005;11(15):5433-9.

147. Cotignola J, Reva B, Mitra N, Ishill N, Chuai S, Patel A, et al. Matrix Metalloproteinase-9 (MMP-9) polymorphisms in patients with cutaneous malignant melanoma. BMC Med Genet. 2007;8:10.

148. Yang ZH, Li SN, Liu JX, Guo QX, Sun XW. MMP-9 polymorphisms are related to serum lipids levels but not associated with colorectal cancer susceptibility in Chinese population. Mol Biol Rep. 2012;39(10):9399-404.

149. Kader AK, Liu J, Shao L, Dinney CP, Lin J, Wang Y, et al. Matrix metalloproteinase polymorphisms are associated with bladder cancer invasiveness. Clin Cancer Res. 2007;13(9):2614-20.

150. Liu L, Sun J, Li G, Gu B, Wang X, Chi H, et al. Association between MMP-12-82A/G polymorphism and cancer risk: a meta-analysis. Int J Clin Exp Med. 2015;8(8):1189-904.

151. S VANN, Skarstedt M, Lofgren S, Zar N, Andersson RE, Lindh M, et al. Gene polymorphism of matrix metalloproteinase-12 and -13 and association with colorectal cancer in Swedish patients. Anticancer Res. 2013;33(8):3247-50.

152. Chen T-Y, Li Y-C, Liu Y-F, Tsai C-M, Hsieh Y-H, Lin C-W, et al. Role of MMP14 gene polymorphisms in susceptibility and pathological development to hepatocellular carcinoma. Ann Surg Oncol. 2011;18(8):2348-56.

153. Ng SC, Wang PH, Lee YC, Lee CY, Yang SF, Shen HP, et al. Impact of matrix metalloproteinase-11 gene polymorphisms on development and clinicopathologcial variables of uterine cervical cancer in Taiwanese women. Int J Med Sci. 2019;16(6):774-82.

154. Rosell A, Cuadrado E, Ortega-Aznar A, Hernández-Guillamon M, Lo EH, Montaner J. MMP-9-positive neutrophil infiltration is associated to blood-brain barrier breakdown and basal lamina type iv collagen degradation during hemorrhagic transformation after human ischemic stroke. Stroke. 2008;39(4):1121-6.

155. Bendrik C, Karlsson L, Dabrosin C. Increased endostatin generation and decreased angiogenesis via MMP-9 by tamoxifen in hormone dependent ovarian cancer. Cancer Lett. 2010;292(1):32-40.

156. Deryugina EI, Quigley JP. Tumor angiogenesis: MMP-mediated induction of intravasation-and metastasis-sustaining neovasculature. Matrix Biol. 2015;44-46:94-112.

157. Wittekind C, Neid M. Cancer invasion and metastasis. Oncology. 2005;69(Suppl 1):14-6.

158. Bourboulia D, Stetler-Stevenson WG. Matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs): Positive and negative regulators in tumor cell adhesion. Semin Cancer Biol. 2010;20(3):161-8.

159. Brand K. Cancer gene therapy with tissue inhibitors of metalloproteinases (TIMPs). Curr Gene Ther. 2002;2(2):255-71.