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Genetic polymorphism of matrix metalloproteinases in breast cancer

Minireview

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The family of human matrix metalloproteinases (MMPs) consists of 24 zinc- and calcium-dependent proteolytic enzymes. MMPs are divided into six subgroups, in terms of differences in the substrate specificity with structural domain architecture. These enzymes are involved in many physiological processes, such as skeletal development, wound healing, scar formation, as well as carcinogenesis. MMPs, fulfilling its function of degradation of extracellular matrix components, are involved in one of the stages of angiogenesis enabling the development, growth and spread of the primary tumor. Therefore, the search for the common polymorphic variants of MMPs, new genetic markers as prognostic factors in breast cancer progress seems to be understandable.

The minireview presents the results of 19 case-control or prospective studies concerning the association of SNPs of genes encoding nine MMPs: MMP-1, -2, -3, -7, -8, -9, -12, -13, -21 with the breast cancer risk, progression and survival.

Key words: matrix metalloproteinases, genetic polymorphism, breast cancer

Breast cancer, one of the leading civilization diseases, has for a number of years already focused attention of clinicians and researchers. It is the most commonly diagnosed cancer in women and is the major cause of death among female cancer patients. GLOBCAN estimates that, among the 12.7 million cancer cases worldwide in 2008, 2.9 million were women with breast cancer, and a million died of this cancer [1]. It is estimated that approximately 10% of the incidence of breast cancer is genetically-related and in most of the cases results from mutations in the genes *BRCA1*, *BRCA2*, *p53*, *ATM*. Attention should also be paid to a number of environmental factors related to diet and occupational exposure, including tobacco smoking, alcohol intake, obesity, shift work at night. Factors considered in the etiology of breast cancer include also endogenous hormonal factors, such as age of occurrence of menarche, menopause, number of births, and exogenous hormonal factors such as use of hormonal contraceptives or hormonal replacement [2, 3]. Currently, a description of cancer cases includes clinical stage and Tumor Nodus Metastases (TNM) clinical classification, hormone receptor status and *BRCA1*, *BRCA2* mutations. All these indicators are still not sufficient to predict the course of the cancer and, therefore, it is important to search for new markers that will enable the patient's prognosis and new predictive markers of cancer risk. As the majority of breast cancer deaths are caused by the invasion of cancer to other, sometimes distant organs, it is believed that it is appropriate to study the role of the enzyme gene polymorphisms that affect the process of angiogenesis largely responsible for the development, growth and metastatic capacity of the primary tumor. Key enzymes involved in these processes include the matrix metalloproteinases (MMPs) participating in an important stage of angiogenesis, namely the degradation of extracellular matrix (ECM) components.

Matrix metalloproteinases. MMPs are proteolytic enzymes whose enzymatic activity depends on zinc and calcium ions. MMPs were discovered in 1962 by Gross and Lapiere, who studied collagenolytic activity in amphibian tissues [4]. MMPs comprise a large family of extracellular proteinases. So far, 24 types of proteolytic enzymes have been found in humans [5].

The basic structural characteristics of these enzymes include a conservative amino acids featuring motif HEXX-HXXGXXH (where H is histidine, E-glutamic acid, G-glycine, X-any amino acid). This catalytic domain binding the zinc ions forms a unique "Met-turn" structure, responsible for the stability and enzymatic activity. Differences in the structural architecture and substrate specificity of MMPs have made it possible to classify MMPs into six subgroups. These subgroups include collagenases, gelatinases, stromelysins, matrilysins, membrane-type MMPs (MT-MMPs) and other MMPs [6]. Substrates for MMPs include both matrix substrates i.e. different types of collagen, gelatin, fibronectin, vitronectin, laminin, and also bioactive substrates, such as interleukin 1β and proMMP-9 [7].

Synthesis of MMPs depends on various factors that may either activate or inhibit the process. MMPs are initially synthesized in cells in the form of preproenzymes and are released as zymogens (proMMPs) into the ECM, except MT-MMPs. Under normal conditions, proMMPs are synthesized by fibroblasts, leukocytes, monocytes, macrophages, neutrophils, endothelial cells and keratinocytes, and in pathological conditions by tumor cells. It has been shown that molecules on the surface of cancer cells stimulate nearby fibroblasts to produce MMP-1, MMP-2, MMP-3, and proMMP-2 activators [8]. Proteolytic activation of proMMPs involves unfolding the active site, as a result of isolating the prodomain from the catalytic domain. Activation and inhibition of MMPs may occur in several stages, ranging from induction of gene transcription, through proenzyme activation to inhibition of active MMPs [9].

Role of matrix metalloproteinases. MMPs are essential in physiological processes, such as normal development of the skeleton, supporting tissues, repair, wound healing, scar formation, and also participate in the pathogenesis of osteoporosis and the process of carcinogenesis. Their role in disease progression consists primarily in the degradation of the ECM. MMPs contribute to tumor angiogenesis that form new blood vessels, cell adhesion and epithelial to mesenchymal transition. MMPs catalyze the hydrolysis a variety of ECM macromolecules, and structural component of blood vessel basement membranes, destroy the structural barrier preventing the migration of cancer cells and cells involved in the process of morphogenesis. Proteolysis of structures located in the ECM and the breakdown of blood vessel basement membranes allows primary tumor growth and formation of metastatic sites. In addition to degradation of structural components of the microenvironment, MMPs can release from the ECM the signaling molecules, such as cytokines, growth factors and their receptors so important in tumor growth and angiogenesis. These compounds may also be proteolytically converted by MMPs [10, 11, 12]. It has been also found that MMPs inhibit immune responses against tumor cells by damaging interleukin 2 receptors on T cells [13].

Single nucleotide polymorphisms. Changes in DNA sequence occurring between individuals of the species and found in more than 1% of people in the population, are called single nucleotide polymorphisms (SNPs). So far, ten million SNPs that occur on average once every few hundred base pairs have been identified in the human genome [14, 15]. Location of SNPs may affect the efficiency of the process of gene transcription, mRNA stability and may lead to amino acid substitution in the encoded protein, which in turn can alter the function of encoded proteins or their expression at the level of gene and protein.

Identification of proper common genetic variants is a complex and difficult task, which involves the fields of epidemiology and molecular biology. The study of SNPs, among other problems, seeks to identify genetic markers reflecting the risk of the disease. It is believed that the vast majority of SNPs are functionally neutral, and only their small proportion is functionally essential and may contribute to such interindividual variability in the susceptibility to developing various diseases, including cancer. Determination of polymorphisms that predispose to the development of cancer involves examination of the frequency of genotypes in a large and homogeneous population [16]. It is also believed that common genetic variants should also be considered when assessing the prognosis and the treatment of cancer. Such analysis can help to improve the efficiency of detection of cancer, or identify high-risk groups by the use of polygenic tests during implementation of a screening program. The analyses performed currently in the patients to determine the histological type of tumor, hormone receptor status and mutations, are not able to provide reliable prognosis for the effects of applied therapy or disease-free survival [17]. Recent studies on the functional importance of SNPs in the promoter sequence of genes encoding various MMPs have shown their significance for the risk of developing and persistence of many lifestyle-related common diseases, such as coronary heart disease, aneurysms, arthritis, periodontal disease or cancer [18, 19].

Characteristics of selected MMPs in breast cancer. The role of MMPs in breast cancer has not been clearly explained, although it has been analyzed by many authors [20, 21]. Researchers who examine the significance of MMPs polymorphisms have attempted planned selection of individual SNPs. While performing that MMPs targeted genotyping, the authors took into account primarily proven mechanisms describing the impact of functional polymorphisms on the *MMPs* gene transcriptional activity (Table 1). The selected SNPs were also previously analyzed in other cancers, such as lung, stomach, ovarian and bladder cancer. The results of these studies point to a positive correlation between MMPs polymorphism and the susceptibility to develop cancer, tumor invasiveness and further progression of the disease [22, 23].

Studies on the association between genetic polymorphism of MMPs and the risk of breast cancer, progression and disease-free survival that have been performed so far are concerned with the following MMPs: MMP-1, MMP-8 and MMP-13 belonging to the group of collagenases, MMP-2 and MMP-9 gelatinases, MMP-3 stromelysins, MMP-7 matrilysins, MMP-

Table 1. Functional significance of SNPs in MMPs

Gene	dbSNP	Polymorphism	Gene region	Functional significance
MMP-1	rs1799750	-1607 1G/2G	Promoter	*G* insertion generates higher levels of gene transcription
MMP-2	rs243865	-1306 C/T	Promoter	*C* allele possesses higher transcriptional activity
MMP-3	rs3025058	-1171 5A/6A	Promoter	*A* deletion generates higher levels of gene transcription
MMP-7	rs11568818	–181 A/G	Promoter	*G* allele possesses higher transcriptional activity
MMP-9	rs3918242	-1562 C/T	Promoter	*T* allele possesses higher transcriptional activity
MMP-12	rs2276109	-82 A/G	Promoter	*A* allele possesses higher transcriptional activity
	rs652438	1082 A/G	Exon	Substitution *A/G* results in change Asn357Ser. The functional significance has not been determined
MMP-13	rs2252070	-77 A/G	Promoter	Substitution *A/G* generates higher levels of gene transcription
MMP-21	rs10901425	572 C/T	Exon	Substitution *C/T* results in change Ala191Val in N-terminal part of the catalytic domain

12 and MMP-21 to the group of other MMPs. Table 2 shows results of case-control or prospective studies on genetic polymorphism of MMPs in relation to the risk of breast cancer, progression and survival.

Metalloproteinase-1. MMP-1, commonly known as collagenase-1, hydrolyzes collagen types: I, II, III, VII, X, gelatin, aggrecan, perlecan, link protein, entactin, tenascin, and other substrates [7]. Studies on cell lines have revealed that MMP-1 is responsible for the invasion and progression of breast cancer and formation of the metastases [24-26]. Polymorphism of *MMP-1* at *-1607* (*rs1799750*) in the promoter region involves the insertion or deletion of guanine (*G*) [27]. The insertion of *G* allele affects the binding site for the E Twenty-Six specific domain transcription factor. Insertion of *G* allele causes that the gene is transcriptionally more active than the gene with one *G* allele [28]. Some research results indicates no relationship between this polymorphism and the risk of breast cancer, disease-free survival and clinical status of patients [29-32]. However, the results of research done by other researchers suggest an increased risk of lymph node metastases in patients with at least one *2G* allele (OR = 1.68, 95% CI: 1.19-2.39), particularly in *2G/2G* homozygotes (OR = 2.14, 95% CI: 1.24-

Table 2. Genetic polymorphism MMPs in relation to breast cancer risk and survival

Gene	Polymorphism, dbSNP	Cases/ Controls	Population	Association (study variables)	Risk estimates * OR or HR (95% CI)	Study
MMP-1	-1607 1G/2G, rs1799750	43/164	Italian	No (BCR)	NSD	Biondi, 2000 [29]
		86/110	Italian	No (BCR, metastases, TNM)	NSD	Ghilardi, 2002 [32]
		145/150	Polish	No (BCR, BR grading)	NSD	Przybylowska, 2004 [33]
				Yes (LNM)	*2G* $p < 0.001$	
		270/300	Polish	No (BCR)	NSD	Przybylowska, 2006 [34]
				Yes (LNM)	*2G/2G* OR = 2.14 (1.24-3.69) *2G* OR = 1.68 (1.19-2.39)	
				Yes (BR grading)	*2G* OR = 2.58 (1.35-4.91)	
		959/952	Swedish	No (BCR, OS)	NSD	Lei, 2007 [30]
		221/-	mixed ethnicities	**Yes (OS)**	*2G/2G* HR = 3.1 (1.1-8.7)	Hughes, 2007 [35]
				Yes (LNM)	*2G/2G* OR = 3.9 (1.7-9.4)	
				No (DFS)	NSD	
		143/-	Caucasian	**Yes (LNM)**	*2G/2G* OR = 2.6 (1.0-6.9)	
		1495/1437	Chinese	No (BCR)	NSD	Beeghly Fadiel, 2009 [31]
	14 x SNPs	1062/1069				
	8 x SNPs	1498/1496				

Table 2. Continued

Gene	Polymorphism, dbSNP	Cases/ Controls	Population	Association (study variables)	Risk estimates * OR or HR (95% CI)	Study
MMP-2	-1306C/T, rs243865	251/-	Austrian	**Yes (tumor size)**	*T/T* $p < 0.006$	Grieu, 2004 [37]
				Yes (negative ER status)	*T/T* $p < 0.002$	
				Yes (OS)	*T/T* (59/70, 84%; $p < 0.001$) among women negative ER status *T/T* (130/157, 84%; $p < 0.001$) among women positive ER status	
		462/509	Chinese	**Yes (BCR)**	*C/T+T/T* OR = 0.46 (0.34-0.63)	Zhou, 2004 [38]
				No (clinical and histochemical features)	NSD	
		959/952	Swedish	No (BCR, OS)	NSD	Lei, 2007 [30]
		89/100	South Brazilian	No (BCR, clinical and histochemical features)	NSD	Roehe, 2007 [41]
		90/96	Mexican	**Yes (BCR)**	*C/C* OR = 2.15 (1.1-4.1) *C/C* OR = 2.66 (1.04-6.96) among women <50 y	Delgado, 2008 [40]
		2557/2506	Chinese	No (BCR)	NSD	Beeghly Fadiel, 2009 [39]
	G/A, rs11644561	2069/2080				
	T/G, rs11643630	2069/2080				
	T/A, rs1005912	2069/2080		**Yes (BCR)**	*T/A* OR = 1.2 (1.0-1.3) *A/A* OR = 1.1 (0.9-1.3)	
	13 x SNPs	2069/2080		No (BCR)	NSD	
	12 x SNPs	2557/2506				
	6 x SNPs	4626/7092				
MMP-3	-1171 5A/6A, rs3025058	43/164	Italian	**Yes (BCR)**	*5A* $p < 0.005$	Biondi, 2000 [29]
		86/110	Italian	**Yes (metastases)**	*5A* OR = 1.96 (1.16-3.30)	Ghilardi, 2002 [32]
				Yes (BCR)	*5A* OR = 1.53 (1.02-2.29)	
				No (TNM)	NSD	
		246/182	Swedish, Czech	No (BCR)	NSD	Lei, 2002 [43]
		500/500	Austrian	No (BCR, clinical and histochemical features, LNM)	NSD	Krippl, 2004 [42]
		221/-	mixed ethnicities	No (LNM, OS, DFS)	NSD	Hughes, 2007 [35]
		143/-	Caucasian	No (LNM)	NSD	
		959/952	Swedish	No (BCR, OS)	NSD	Lei, 2007 [30]
		1495/1437	Chinese	No (BCR)	NSD	Beeghly Fadiel, 2009 [31]
	6 x SNPs	1062/1069				
	9 x SNPs	1498/1496				

Table 2. Continued

Gene	Polymorphism, dbSNP	Cases/ Controls	Population	Association (study variables)	Risk estimates * OR or HR (95% CI)	Study
MMP-7	-181A/G, rs11568818	221/-	mixed ethnicities	No (LNM, OS, DFS)	NSD	Hughes, 2007 [35]
		143/-	Caucasian	No (LNM)	NSD	
		1079/1082	Chinese	No (BCR)	NSD	Beeghly Fadiel, 2008 [46]
		~1050/-	Chinese	**Yes (OS)**	*G*/G HR = 6.7 (2.4-18.6)	Beeghly Fadiel, 2009 [44]
				Yes (DFS)	*G*/G HR = 5.2 (1.9-14.4)	
	C/T, rs12184413	1079/1082	Chinese	**Yes (BCR)**	*T*/*T* OR = 0.7 (0.6-0.9) *T*/*T* OR = 0.6 (0.4-0.8) among post-menopausal women	Beeghly Fadiel, 2008 [46]
		~1050/-	Chinese	**Yes (DFS)**	*T*/*T* HR = 0.5 (0.3-0.9)	Beeghly Fadiel, 2009 [44]
				Yes (OS)	*T*/*T* HR = 0.4 (0.2-0.9)	
	A/G, rs10895304	1079/1082	Chinese	**Yes (BCR)**	*G* OR = 1.9 (1.2-3.0) among pre-menopausal women	Beeghly Fadiel, 2008 [46]
		~1050/-	Chinese	No (OS, DFS)	NSD	Beeghly Fadiel, 2009 [44]
	T/C, rs7935378	1079/1082	Chinese	**Yes (BCR)**	*C* OR = 1.9 (1.2-3.0) among pre-menopausal women	Beeghly Fadiel, 2008 [46]
		~1050/-	Chinese	No (OS, DFS)	NSD	Beeghly Fadiel, 2009 [44]
	A/T, rs880197	1079/1082	Chinese	No (BCR)	NSD	Beeghly Fadiel, 2008 [46]
		~1050/-	Chinese	No (OS, DFS)	NSD	Beeghly Fadiel, 2009 [44]
	G/A, rs17098318	1079/1082	Chinese	No (BCR)	NSD	Beeghly Fadiel, 2008 [46]
		~1050/-	Chinese	**Yes (DFS)**	*A*/*A* HR = 4.2 (1.3-13.4)	Beeghly Fadiel, 2009 [44]
				Yes (OS)	*A*/*A* HR = 7.0 (2.2-22.8)	
	A/G, rs11225307	1079/1082	Chinese	No (BCR)	NSD	Beeghly Fadiel, 2008 [46]
		~1050/-	Chinese	**Yes (DFS)**	*G*/*G* HR = 0.5 (0.3-0.9)	Beeghly Fadiel, 2009 [44]
				No (OS)	NSD	
	A/T, rs11225297	1079/1082	Chinese	No (BCR)	NSD	Beeghly Fadiel, 2008 [46]
		~1050/-	Chinese	**Yes (OS)**	*A*/*T* HR = 0.7 (0.5-0.9) *T*/*T* HR = 0.3 (0.1-0.8)	Beeghly Fadiel, 2009 [44]
				Yes (DFS)	*T*/*T* HR = 0.4 (0.2-0.8)	
	A/C, rs17352054	1079/1082	Chinese	No (BCR)	NSD	Beeghly Fadiel, 2008 [46]
		~1050/-	Chinese	No (OS, DFS)	NSD	Beeghly Fadiel, 2009 [44]
	C/T, rs495041	1079/1082	Chinese	**Yes (BCR)**	*C*/*T* HR = 1.6 (1.1-2.3) among post-menopausal women	Beeghly Fadiel, 2008 [46]
		~1050/-	Chinese	No (OS, DFS)	NSD	Beeghly Fadiel, 2009 [44]

Table 2. Continued

Gene	Polymorphism, dbSNP	Cases/ Controls	Population	Association (study variables)	Risk estimates * OR or HR (95% CI)	Study
MMP-8	A/G, rs10895353 C/T, rs7943404 C/T, rs2508383 A/G, rs1320632 A/T, rs17099436 A/G, rs1940475 A/T, rs1892986	140/-	Belgium	No (clinical and histochemical features, LNM)	NSD	Decock, 2007 [50]
	A/G, rs1276284	140/-	Belgium	No (clinical and histochemical features)	NSD	
				Yes (LNM)	*G* OR = 0.6 (0.3-0.9)	
	C/T, rs11225395	140/-	Belgium	No (clinical and histochemical features)	NSD	
				Yes (LNM)	*T* OR = 0.6 (0.4-0.9)	
		~1100/-	Chinese	No (clinical and histochemical features, OS)	NSD	
				Yes (DFS)	*T* HR = 0.7 (0.5-0.9) among patients with earlier stage cancer	
MMP-9	-1562C/T, rs3918242	251/-	Austrian	**Yes (non ductal tumor type)**	*T* $p < 0.02$	Grieu, 2004 [37]
				Yes (positive ER status)	*T* $p < 0.033$	
				Yes (absence of present *p53* mutation)	*T* $p < 0.025$	
				Yes (OS)	*C/T* $p < 0.06$	
		270/300	Polish	**Yes (BR grading)**	*T* OR = 2.61 (1.33-4.87)	Przybylowska, 2006 [34]
				No (BCR)	NSD	
		221/-	mixed ethnicities	**Yes (LNM)**	*C/T* OR = 3.6 (1.2-11.1)	Hughes, 2007 [35]
				No (OS, DFS)	NSD	
		143/-	Caucasian	**Yes (LNM)**	*C/T* OR = 9.1 (1.7-48.4)	
		959/952	Swedish	**Yes (BCR)**	*T/T* OR = 1.88 (0.97-3.63)	Lei, 2007 [30]
				No (OS)	NSD	
		96/100	South Brazilian	No (BCR, clinical and histochemical features)	NSD	Roehe, 2007 [41]
	T/A, rs3918241	5408/2899	Chinese	No (BCR)	NSD	Beeghly Fadiel, 2011 [52]
	G/A, rs2274756 C/T, rs4810482 G/A, rs17576 C/G, rs2250889	~1058/~1063				
	T/C, rs3918249 A/G, rs6065912	~2000/~2000				
MMP-12	-82A/G, rs2276109	1129/1129	Chinese	No (BCR, clinical and histochemical features, OS, DFS)	NSD	Shin, 2005 [54]
		221/-	mixed ethnicities	No (LNM, OS, DFS)	NSD	Hughes, 2007 [35]
		143/-	Caucasian	No (LNM)	NSD	
	1082A/G, rs652438	1129/1129	Chinese	No (BCR, clinical and histochemical features, OS, DFS)	NSD	Shin, 2005 [54]
MMP-13	-77A/G, rs2252070	959/952	Swedish	No (BCR, OS)	NSD	Lei, 2007 [30]
		221/-	mixed ethnicities	No (LNM, OS, DFS)	NSD	Hughes, 2007 [35]
		143/-	Caucasian	No (LNM)	NSD	
MMP-21	572 C/T, rs10901425	76/320	Russian	No (BCR, clinical and histochemical features)	NSD	Shagisultanova, 2004 [56]

Studies that have associated with BCR, LNM, TNM, ER status, BR grading, OS or DFS have been noted in bold

*The reference is the common homozygote genotype or common allele

Abbreviations: BCR, breast cancer risk; LNM, lymph node metastasis; TNM, tumor, nodus, metastasis; ER, estrogen receptor status; BR, Bloom-Richardson grading; OS, overall survival; DFS, disease-free survival; HR, hazard ratio; OR, odds ratio; NSD, no significant difference

3.69) [33, 34]. Research conducted in 2007 by Hughes et al. confirmed the increased risk of lymph node metastases in *2G/2G* homozygotes (OR = 3.9, 95% CI: 1.7-9.4) [35].

Metalloproteinase-2. MMP-2, also known as gelatinase A or collagenase IV, uses collagen types: I, IV, V, VII, X, XI, elastin, gelatin fibronectin, laminin-5, brevican, neurocan, decorin, BM-40, vitronectin, aggrecan, and other substrates [7]. In an in vitro experiment, it was noted that the polymorphism at *-1306C/T* (*rs243865*) affects gene expression of *MMP-2*. Transcriptional activity of *MMP-2* with the thymine (*T*) allele is lower than the cytosine (*C*) allele [36]. It was suggested, that *C/T* substitution abolish Sp1 transcription factor binding site in the *MMP-2* gene [36, 37]. The results of the survey conducted among the Chinese population by Zhou and colleagues suggest a reduced risk of breast cancer for *C/T* and *T/T* genotype (OR = 0.46, 95% CI: 0.34-0.63) [38]. On the other hand, Beeghly-Fadiel et al. reported a tendency to increased risk of breast cancer in *T/T* homozygotes (OR = 1.4, 95% CI: 0.9-2.4) [39]. Delgado et al. have demonstrated high risk of developing breast cancer for the *C/C* genotype (OR = 2.15, 95% CI: 1.1-4.1) [40]. Test results from other centers do not show a relationship between this polymorphism and the risk of breast cancer [30, 41]. For that MMP, other SNPs showing a relationship of polymorphism with the risk of breast cancer for *rs1005912* (OR = 1.2, 95% CI: 1.0-1.3), *rs11644561* (OR = 0.6, 95% CI: 0.3-1.0), *rs11643630* (OR = 0.8, 95% CI: 0.7-1.0) have been also tested. Analysis of 32 other SNPs showed no relationship with the risk of breast cancer [39].

Metalloproteinase-3. MMP-3, known also as stromelysin-1, catalyzes the hydrolysis of collagen types: II, III, IV, V, IX, X, XI, gelatin, fibronectin, vitronectin, laminin, entactin, tenascin, elastin, aggrecan, link protein, perlecan, decorin, fibrin/fibrinogen, and other substrates [7]. Polymorphism of *MMP-3* gene involving insertion or deletion of adenine (*A*) at *-1171 5A/6A* (*rs3025058*), affects the strength of transcription factor binding and promoter activity [42]. Ye and colleagues in their in vitro study found that *5A* allele is characterized by about 2-fold higher promoter activity than *6A* allele [19]. The first study of this SNP reported elevated risk of breast cancer in women with *5A* allele ($p < 0.005$) [29], but this has not been confirmed by other studies [30, 31, 42, 43]. The next study report a relationship between *MMP-3 5A/5A* genotype and the frequency of metastases (OR = 1.96, 95% CI: 1.16-3.30) [32]. No relationship of this polymorphism with the length of survival in breast cancer has been proven to occur [30, 35].

Metalloproteinase-7. MMP-7, known also as matrilysin-1 or PUMP-1, is an enzyme hydrolyzing the ECM components, such as aggrecan, entactin, laminin, vitronectin, fibrin/fibrinogen, tenascin, gelatin, fibronectin, collagen types: IV, V, IX, X, XI, and other substrates [7]. *A/G* substitution at *-181* (*rs11568818*) affects the transcriptional activity of *MMP-7* gene and leads to changes in the expression of this gene. So the *G* allele may cause an increase in gene transcription, and thus increase enzyme activity [45]. The first study of a diverse group of breast cancer patients, predominantly Caucasians, showed no relationship between the substitution *A/G*, and lymph node metastasis and survival [35]. Beeghly-Fadiel et al. studying a Chinese population confirmed no association with the risk of breast cancer for this polymorphism and six other ones in the gene encoding this enzyme. At the same time a significant relationship between cancer risk and the *rs12184413 T/T* genotype (OR = 0.7, 95% CI: 0.6-0.9) and *rs10895304 G* allele (OR = 1.9, 95% CI: 1.2-3.0), *rs7935378 C* allele (OR = 1.9, 95% CI: 1.2-3.0) has been shown to occur, but only for pre-menopausal women [46]. In further studies, Beeghly-Fadiel et al. showed a significant correlation between the survival time of women with breast cancer and the *rs11568818 G* allele (HR = 6.7, 95% CI: 2.4-18.6), *rs11225297 A/T* genotype (HR = 0.7, 95% CI: 0.5-0.9) and *T/T* (HR = 0.3, 95% CI: 0.1-0.8), *rs11225307 G/G* (HR = 0.5, 95% CI: 0.3-0.9), *rs12184413 T/T* (HR = 0.5, 95% CI: 0.3-0.9), *rs17098318 A/A* (HR = 4.2, 95% CI: 1.3-13.4). For the other SNPs of this gene, *rs17352054*, *rs495041*, *rs10895304*, *rs7935378*, *rs880197* but showed no dependence with the course of the disease [44].

Metalloproteinase-8. MMP-8, or collagenase-2, hydrolyzes collagen types: I, II, III, VII, X, gelatin, entactin, tenascin, aggrecan, and other substrates [7]. Studies on the susceptibility to skin cancer conducted in mice showed that MMP-8, paradoxically, has a protective role, since the absence of the *MMP-8* gene resulted in an increased incidence of skin tumors in male mice [47]. This result was confirmed in the study on human breast cancer cells, where increased expression of that MMP resulted in lower tumor invasiveness [48]. These reports and the finding that the SNP of *MMP-8* gene affects the expression of MMP-8 [49], aroused the interest of Decock et al. who in 2007 presented the results for nine different SNPs, selected from the HapMap database. The studies showed no association between the SNPs and the tumor size, the histologic grade or subtype of breast cancer. However, a correlation has been shown to occur between lymph node metastasis and four SNPs *rs1940475 G* allele ($p = 0.03$), *rs1892986 A* allele ($p = 0.03$), *rs1276284 A* allele ($p = 0.03$), *rs11225395 T* allele ($p = 0.02$). Decock et al. also using blood samples from breast cancer patients from an extensive database (Shanghai Breast Cancer Study) have confirmed that the *MMP-8* (*rs11225395*) with *T* allele is associated with lower frequency of metastasis to lymph nodes compared with *C* allele and with longer survival of patients with early stage cancer [50].

Metalloproteinase-9. MMP-9, commonly referred to as gelatinase B, hydrolyzes gelatin, collagen types: I, IV, V, VII, X, XI, elastin, fibronectin, vitronectin, aggrecan, link protein, laminin, and other substrates [7]. There are indications that the polymorphism of *MMP-9* at *-1562C/T* (*rs3918242*) affects gene expression of MMP-9 and *T* allele is associated with a 1.5-fold higher transcriptional activity compared with the *C* allele [51]. Grieu et al. in 2004 were the first to show a possible ($p < 0.06$) association of *C/T* and *T/T* genotypes with a better prognosis of patients with breast cancer compared with the *C/C* genotype [37]. The results of Hughes et al. indicate a relationship between the risk of metastasis and C/T genotype (OR = 3.6,

95% CI: 1.2-11.1) [35]. However Przybylowska et al. showed that the *T* allele is associated with high risk of increased malignancy of breast cancer (OR = 2.61, 95% CI: 1.33-4.87) [34]. Lei et al. studies show no effect of genotype on the increased risk of breast cancer and subsequent prognosis of survival for the *T/T* genotype [30]. Roehe and colleagues who have examined this polymorphism, in turn, report no dependence between the risk and clinicopathological features of breast cancer [41]. Beeghly-Fadiel and colleagues also studied other SNPs for *MMP-9* gene, but their results do not indicate a relationship with the risk of breast cancer [52].

Metalloproteinase-12. MMP-12 is also called macrophage elastase or metalloelastase. It uses elastin, laminin, fibronectin, fibrin/fibrinogen, proteoglycan, and other substrates [7]. Analysis of the results of in vitro strudies demonstrates that *MMP-12* polymorphism at *-82* which consists in the substitution *A*/*G*, present in the promoter region, is associated with increased transcriptional activity for the *A* allele, because this allele affects the binding of transcription factor AP-1 [53]. The studies of polymorphism in that metalloproteinase did not show, however, an association with the risk of breast cancer with clinical stage [54], metastases to lymph nodes [35] or patient survival [35, 54]. For that MMP, *A/G* polymorphism at *1082* (*rs652438*) has been tested, which is located in the coding region of the hemopexin domain. As a result of substitution of *A*/*G*, asparagine (Asn) is changed to serine (Ser) in an amino acid in codon 357. Functional significance of this polymorphism has not been clearly explained. There was no link between this polymorphism and risk of developing breast cancer. However, an association has been confirmed with the time of survival of women with breast cancer. *MMP-12 A/G* or *G/G* genotype gave poor survival prognosis, compared to *A/A* genotype (HR = 1.36, 95% CI: 0.92-2.00) [54].

Metalloproteinase-13. MMP-13 has a common name collagenase-3 and uses collagen types: I, II, III, VII, X, gelatin, aggrecan, tenascin, entactin, and other substrates [7]. It has been shown that the *A*/*G* substitution at *-77* (*rs2252070*) makes the gene transcriptionally activated, which brings with it increased activity of enzyme. In 2007, Hughes and colleagues studied patients with breast cancer in whom there was no association between the polymorphism and lymph node metastases or survival [35]. Also Lei et al., based on case-control study, showed no significant link between this polymorphism and the risk of developing breast cancer or survival time [30].

Metalloproteinase-21. MMP-21 also called XMMP, is the proteinase hydrolyzing gelatin [7]. Polymorphism at *572* (*rs10901425*) associated with the *C*/*T* substitution in this gene leads to an amino acid change from alanine (Ala) to valine (Val) in codon *191* of the catalytic domain [55]. In a study conducted in 2004 by Shagisultanova et al. among healthy women and breast cancer patients, there was no link between this polymorphism progression and the development of the breast cancer [56].

Conclusions. The first study on genetic polymorphism of MMPs in women with breast cancer was conducted in 2000. Since then, polymorphisms of MMPs belonging to nine different groups were analyzed among breast cancer patients of different ethnicity, and the results were published in 19 papers. Based on published results of these studies, four meta-analyses have been prepared [57-60]. Those analyses were combined with the results of individual studies in order to increase statistical power and exclude the false positive or negative results. The results of the meta-analysis published by McColgan et al. point to a lack of association between the risk of breast cancer and the *MMP-1 -1607 1G/2G* (*rs1799750*), *MMP-2 -1306C/T* (*rs243865*), *MMP-3 -1171 5A/6A* (*rs3025058*) and *MMP-9 -1562C/T* (*rs3918242*) polymorphisms. Estimated OR for *MMP-1 1G/2G* heterozygotes was 1.61 95% CI: 0.76–1.77; p = 0.49 and (OR = 1.08, 95% CI: 0.66–1.76; p = 0.75) for *2G/2G* variant heterozygotes, compared against 1G/1G common genotype. *MMP-2 C/T* genotype when compared against the *C/C* (OR = 0.66, 95% CI: 0.40–1.07; p = 0.09) or *T/T* genotype when compared against the *C/T* and *T/T* (OR = 0.95, 95% CI: 0.54-1.66; p = 0.86) was not related with breast cancer risk. Similarly, this meta-analysis showed lack of association between breast cancer risk and *MMP-3* common *5A/5A* genotype (OR = 0.94, 95% CI: 0.53–1.65; p = 0.83) or rare *6A/6A* genotype (OR = 0.71, 95% CI: 0.38–1.33; p = 0.29) and *MMP-9* heterozygote (OR = 1.07, 95% CI: 0.88–1.30; p = 0.50) or *T/T* genotype (OR = 1.03, 95% CI: 0.16–6.75; p = 0.98) [59]. These conclusions were confirmed in two other meta-analyses by Peng et al., where it was found that those polymorphisms are not likely to be a major risk factor for breast cancer, but should be taken into account because the risk may be increased as a result of exposure to certain environmental factors [57, 58]. On the other hand, Zhou and colleagues studying the same four polymorphisms, demonstrated for *MMP-2 -1306C/T* (*rs243865*) a significantly high risk of breast cancer associated with *C/C* genotype (OR = 1.27, 95% CI: 1.10-1.47; p = 0.001), and a significantly low risk of breast cancer associated with *C/T* genotype (OR = 0.78, 95% CI: 0.67-0.91; p = 0.001). They demonstrated no significant difference for the remaining of the analyzed polymorphisms (*MMP-1 -1607 1G/2G*, *MMP-3 -1171 5A/6A*, *MMP-9 -1562C/T*). The authors of that study conclude that *MMP-2* (*rs243865*) polymorphism may contribute to better assessment of the risk of breast cancer [60]. However, the results obtained in this meta-analysis have been received by other scientists as unreliable and not convincing. This is evidenced by two letters to the editor by He [61] and Wu et al. [62], in which the authors commented on this meta-analysis. They suggest to perform a new more accurate estimation in meta-analysis of MMPs polymorphism and cancer risk. Moreover, there is also a necessity to perform a pooled-analysis.

Recent genome-wide association studies (GWAS), where hundreds of thousands of SNPs are genotyped simultaneously in very large study populations, have identified several risk alleles to be associated with breast cancer. Most of these studies were conducted in women of European ancestry, but also in Chinese and Ashkenazi Jewish populations. Although GWAS

led to the identification of unique breast cancer susceptibility loci and confirmed previously reported ones, MMPs variants do not seem to be breast cancer genetic markers [63].

MMPs display characteristics responsible for the processes of tumor vascularization (proangiogenic activity), thereby contributing to local tumor growth and formation of metastases and, therefore, seem to be a good target in the search for new factors in the etiology and treatment of cancer in general and breast cancer in particular. However, the complexity of the interoperable system of different types of cells in the intercellular space, numerous metabolic pathways, the presence of inhibitors of MMPs and growth factors, leading to activation or inhibition of MMPs make it very difficult to determine unambiguously their role. Besides, they are combined into a network of interdependencies and, therefore, overexpression of one of MMPs may cause changes in the expression or activity of other MMPs.

Data collected in this work confirm the impact of various genetic polymorphisms of MMPs on breast cancer risk, and also on the prognosis of women with breast cancer. Unfortunately, none of the reported studies has shown that any of the nine described polymorphisms of MMPs may serve as a genetic marker to assess the risk of developing breast cancer or its further progression.

As the impact of the known mechanism of action of functional polymorphisms of MMPs in specific types of breast cancer in women is not clear, it is believed that further study of these enzymes' SNPs are inevitable and necessary. Therefore, valuable research, in addition to determine the risk of breast cancer, should also consider additional factors, such as ethnicity, gene-gene and gene-environment interactions. The influence of some polymorphisms on the risk of cancer is often observable only in combination or as a result of interaction with environmental factors, because cancer is a disease that involves many factors and mechanisms. To create an effective tool for early cancer detection and prognosis, it is necessary to extend our understanding of its etiology and explore new mechanisms, such as those affecting the transcriptional activity of *MMPs* genes, and thus the process of tumor progression. Perhaps studying the relationship between SNPs in one or more MMPs that have a common effect on the risk of developing cancer and its further progression, i.e. evaluation of MMPs haplotypes, will provide additional and more precise information on the role MMPs in the development of breast cancer, as well as information on their role in cancer therapy, by adjusting it to the individual's genotype pattern.

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