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Review Article

Matrix Metallopeptidase 3 Polymorphisms: Emerging genetic Markers in Human Breast Cancer Metastasis

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Conflict of Interest
The authors declare that they have no competing interests.

ABSTRACT

Matrix metallopeptidase 3 or *MMP3*, is a zinc-dependent proteolytic enzyme that is involved in various physiological processes via modification of the extracellular matrix. In particular, its over-expression has been associated with cancer metastasis and tumor growth in various cancers including breast cancer. *MMP3* gene expression is regulated by several factors such as DNA polymorphisms which also serve as risk factors for breast cancer. As such, DNA polymorphisms of *MMP3* have the potential to be utilized as genetic biomarkers for prediction and prognosis of metastatic breast cancer. Presently, genome-wide association studies of *MMP3* gene polymorphisms which are associated with breast cancer risk and patient survival in a variety of populations are reviewed. In order to understand the potential role of *MMP3* polymorphisms as genetic markers for breast cancer metastasis, the domain structure of *MMP3*, the regulation of its expression and its role in breast cancer metastasis are also briefly discussed in this review. The emergence of *MMP3* gene polymorphisms as prognostic biomarker candidates for breast cancer metastasis may contribute towards improving targeted therapies and categorization of breast cancer cases in order to provide a better and more accurate prognosis.

Keywords: Breast; Carcinoma; Neoplasm metastasis; Matrix metalloproteinase 3

INTRODUCTION

Matrix metallopeptidase 3, also commonly known as *MMP3* and stromelysin-1, belongs to a group of zinc-dependent proteolytic enzymes [1-5]. It is a 54 kDa protein produced by various cells including the macrophages, stromal fibroblasts, endothelial cells, immune cells and synovial cells during post-natal development of mammary gland, ductal branching and alveolar morphogenesis [6-8]. *MMP3* proteolyzes an extensive range of extracellular matrix (ECM) molecules including types 2, 4, 5, 9, 10, and 11 collagens, elastin, fibronectin, gelatins, laminins and proteoglycans [9]. In addition, it can also cleave various adhesion molecules, growth factors and other MMPs [10]. Due to its role in modification of the ECM, *MMP3* is involved in various physiological processes such as angiogenesis, cell growth and cell invasion [11]. This is supported by studies, which have reported over-expression of *MMP3* in blood, cancer tissues and urine samples of breast cancer patients [11]. *MMP3* gene

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has been regarded as one of the genetic factors that contribute to breast cancer risk [12-15]. This review discusses the potential of *MMP3* polymorphisms as genetic biomarkers in the prediction and prognosis of breast cancer metastasis. Screening of genetic biomarkers will allow the conceptualization of personalized medicine, which may be beneficial for cancer risk management as well as for preventing cancer progression.

DOMAIN STRUCTURE

The domain structure of *MMP3* is composed of several function-specific domains, which include the translocation signal peptide, propeptide, catalytic domain and hemopexin domain (**Figure 1**) [2]. The translocation signal peptide is responsible for translocating *MMP3* through the rough endoplasmic reticulum during synthesis, and is usually cleaved during the secretion of *MMP3* [2,16]. The latent form of the enzyme is preserved by the 80-amino acids propeptide containing a zinc-interacting thiol group, which keeps the catalytic domain intact [17,18]. As the name suggests, the catalytic domain which contains a highly conserved 170-amino acids Zn^{2+} binding sequence, is responsible for the enzymatic activity of *MMP3*. Besides the catalytic zinc, approximately 2 or 3 calcium ions are also present to ensure the stability of the active enzyme. In addition, the substrate specificity of *MMP3* is controlled by a 200-amino acid ellipsoidal disk-shaped hemopexin domain which allows docking of substrates via a hydrophobic pocket. The different substrate specificity between the members of matrix metallopeptidases is due to the variation of the depth of the hydrophobic pocket [17]. As for *MMP3*, its substrates include ECM proteoglycans, elastin, entactin, fibrillins, fibrin, fibronectin, fibulin, laminins, link protein, osteonectin, tenascin, type 3, 4, 5, 9, 10, and 11 collagens, vitronectin, collagenases, E-cadherin, heparin-binding EGF-like growth factor, L-selectin, MMP9 and tumor necrosis factor (TNF)-α [10].

ROLE IN HUMAN CANCER METASTASIS

MMP3, one of the key players in altering the ECM architecture, has been known to promote cancer invasion and metastasis [1,4,8,10]. One of the earlier studies that has discovered the role of *MMP3* in cancer metastasis was conducted by Lochter et al. [8]. In this study, normal mouse mammary epithelial SCp2 cell line that was transiently transfected with auto-activating *MMP3* underwent loss of epithelial morphology and adopted a mesenchymal-like phenotype. This process, which is now commonly known as epithelial-mesenchymal transition (EMT), was also observed in parallel with the cleavage of E-cadherin and disruption of its association with β-catenin. Interestingly, the cells still retained their mesenchymal-like features even after *MMP3* activity was inhibited. A study by Sternlicht et al. [10] discovered that *MMP3* promoted *in vivo* tumorigenicity, development of pre-malignant

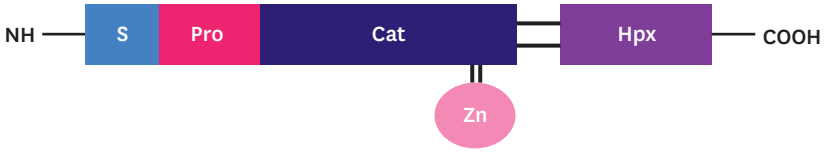

Figure 1. The domain structure of *MMP3* (adapted from Visse and Nagase, 2003). The domain organization of *MMP3* includes S, Pro, Cat, Hpx.
MMP3 = matrix metallopeptidase 3; S = translocation signal peptide; Pro = propeptide; Cat = catalytic domain; Hpx = hemopexin domain.

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and malignant lesions, spontaneous neoplastic progression and genomic instability of the mammary in transgenic mice.

However, there have also been studies reporting that *MMP3* exhibits tumor-inhibiting activities. These results are not conflicting but instead suggest that *MMP3* can exhibit both tumor-promoting and tumor-inhibiting effects based on the substrates that it acts upon. For example, the interaction between *MMP3* and connective tissue growth factor results in the release of angiogenesis-promoting factors [4,16]. *MMP3*-mediated cleavage of other growth factors such as heparin-bound epidermal growth factor and transforming growth factor β promotes cancer cell proliferation and EMT, respectively. In these cases, *MMP3* exhibits its tumor-promoting effects.

However, cleavage of insulin-like growth factor binding protein 3 and 5 (IGF-BP3 and IGF-BP5) by *MMP3* releases active IGFs which inhibit tumor growth [16]. *MMP3* can also cleave plasminogen and type VIII collagen, and therefore produces angiostatin and endostatin, respectively [4,19]. These are angiogenesis-inhibiting factors, and in this case, *MMP3* exhibits its tumor-inhibiting effects. Recent evidence showing that *MMP3* exists not only extracellularly but also intracellularly sheds light into its non-proteolytic functions [20]. An example of this is the induction of apoptosis by intracellular *MMP3* in the murine dopaminergic cells, hepatocytes and myofibroblasts. Its role in activating apoptosis also suggests the tumor-inhibiting effects of *MMP3*.

However, *MMP3* has been shown to be more frequently involved in promoting instead of inhibiting tumor growth. Over-expression of *MMP3* and its role as a prognostic factor have been reported in breast, cervical, colorectal, gastric, lung, melanoma, pancreatic and renal carcinomas [21,22]. Interestingly, the study by Banik et al. [23] has revealed the *in vitro* and *in vivo* roles of *MMP3* in the progression to metastasis in both CMS4 sarcoma and 4T1 mammary carcinoma cell lines as well as in BALB/c mice. In this study, silencing of *MMP3* expression in an aggressive variant of CMS4 cells and 4T1 cells resulted in significant reduction in experimental lung metastases and spontaneous metastasis in the tumor-bearing mice. *MMP3* has also been linked to metastasis by promoting EMT and proteolysis of osteopontin into a soluble active form [8,16]. Osteopontin is widely known to contribute to the migration of breast cancer cells to the bone. In addition, a study by Sipos et al. [12] also reported a linear correlation between stromal *MMP3* expression levels and adenoma-dysplasia-carcinoma sequence, suggesting that its high potential as a biomarker to distinguish early malignancy and dysplasia. In investigating the potential of circulating *MMP3* as a prognostic marker for breast carcinoma, Hassan et al. [13] reported increased levels of serum *MMP3* in patients with invasive ductal and lobular breast carcinoma. In addition, the authors suggested that *MMP3* could also be a good candidate for recurrence detection as increased *MMP3* levels were observed 3 months after the primary surgery, ($p = 0.001$). *MMP3* was also significantly correlated with high tumour grade and advanced stage of breast cancer ($p = 0.001$ and $p = 0.000$, respectively).

REGULATION OF EXPRESSION

The gene expression of matrix metallopeptidases is largely regulated at the transcriptional level [24]. The expression of *MMP3* is positively regulated by basic fibroblast growth factor, heat shock, interferons, interleukin-1 and TNF; negatively regulated by glucocorticosteroids;

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and also modulated by signaling proteins such as cyclic AMP, E26 transformation-specific proto-oncogene 1 and 2 (ETS1 and ETS2), and protein kinase C [25]. In addition, *MMP3* transcription can also be repressed by nuclear factor κB (NF-κB) [26]. However, the role of post-transcriptional mechanisms in regulating gene expression is also crucial. These mechanisms, including DNA polymorphisms at the 5′-untranslated region (UTR), 3′-UTR and the coding region, may alter messenger RNA (mRNA) structure and regulate mRNA stability [24]. DNA polymorphisms at the promoter region of a gene may also regulate gene expression by tampering interaction between cis elements of the promoter and transcription factors.

GENETIC POLYMORPHISMS

Polymorphisms in the *MMP3* gene, positioned on the long arm of chromosome 11q22.3, have been found to be implicated in many solid cancers. The most commonly studied is the 5A/6A single nucleotide polymorphism (SNP; rs3025058) at nucleotide 1171 of the promoter region [27]. In particular, an allele has 6 adenosines whereas another allele has 5 adenosines; these are due to varied length of polymonomeric track of adenosines at the transcription initiation site [28]. According to the *in vitro* functional analysis of the promoter, the 5A allele exhibits a 2-fold increase of the promoter activity in comparison to the 6A allele in transiently transfected fibroblasts [28,29]. Furthermore, DNA-protein interaction assays have revealed that, unlike the 6A allele which binds strongly to NF-κB, which is a transcriptional repressor, the 5A allele prevents binding of NF-κB to the *MMP3* promoter [26,29]. It has also been reported that the 6A allele also binds strongly to the ZBP-89 transcription factor which represses the promoter activity [24].

Based on numerous genome-wide association analysis, the 5A/6A polymorphism has been linked to breast cancer risk, estrogen receptor status, patient survival and tumor size (**Table 1**) [1]. A pilot study on an Italian Caucasian population has found a strong correlation between the 5A allele and breast cancer susceptibility [30]. Specifically, Ghilardi et al. [30] reported a significant correlation between the 5A allele and subgroups of patients with metastases ($p = 0.01$; odds ratio [OR], 1.96; 95% confidence interval [CI], 1.16–3.30), indicating that the 5A/5A homozygotes have about 2.4 fold higher risk of progressing to metastasis ($p = 0.027$). Furthermore, in a study conducted by Holliday et al. [31], the 5A allele homozygosity contributed to increased *MMP3* secretion and invasion-promoting capacity of tumor-derived fibroblasts isolated from breast cancer patients.

Table 1. *MMP3* polymorphisms and their association with breast cancer in different populations

Subject	Controls	Cases	Polymorphism	Region	The effect of polymorphism on clinical status	*p*-value	Reference
London	19	13	rs3025058 (5A/6A)	Promoter	The 5A/5A genotype and metastasis (based on *in vitro* invasion-promoting capacity)	0.04	[31]
Italian	110	86	rs3025058 (5A/6A)	Promoter	The 5A allele and presence of metastasis	0.01	[30]
Iranian	60	120	rs3025058 (5A/6A)	Promoter	The 5A allele and presence of metastasis	0.074	[32]
Arabic	77	59	rs3025058 (5A/6A)	Promoter	The 6A/6A and 5A/6A genotypes and advanced stage of cancer	< 0.05	[21]
Russian	329	395	rs3025058 (5A/6A)	Promoter	The 5A/6A genotype and degree of malignancy	Not provided	[34]
South Indian	300	300	rs35068180 (5A/6A)	Promoter	The 5A/6A genotype and lymph node status	0.01	[33]
South Indian	300	300	rs35068180 (5A/6A)	Promoter	The 6A-containing genotype and risk of breast cancer	0.01	[33]
Malaysian	-	60	rs679620 (A/G)	Exon	The heterozygotes were protected from lymph node or distant metastasis	0.049	[43]
Malaysian	-	60	rs602128 (T/C)	Exon	The heterozygotes were protected from lymph node or distant metastasis	0.049	[43]
Malaysian	-	60	rs3020919 (A/G)	Intron	The heterozygotes were protected from lymph node or distant metastasis	0.049	[43]

Values are presented as number.

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Although there was no statistically significant difference in the *MMP3* SNP status between tumor and non-tumor donors ($p = 0.14$; OR, 3.21; 95% CI, 0.68–15.16), tumor donors with the 5A/5A genotype had higher invasion-promoting capacity in comparison with other genotypes ($p = 0.05$ and $p = 0.07$ for 6A/5A and 6A/6A, respectively) as well as with the same genotype of the non-tumor donors ($p = 0.04$). The same pattern applied also to *MMP3* secretion; tumor fibroblasts with 5A/5A genotype had increased secretion of *MMP3* compared to other genotypes ($p = 0.07$ and $p = 0.009$ for 6A/5A and 6A/6A, respectively) or normal fibroblasts with the same genotype ($p = 0.028$).

Likewise, even though it was not statistically significant, a study on an Iranian population has suggested an association between the 5A allele and breast cancer metastasis ($p = 0.074$; OR, 2.9; 95% CI, 1.04–1.64) [32]. In contrast, the 6A allele was significantly higher in breast cancer patients in South India ($p = 0.023$; OR, 1.3; 95% CI, 0.94–8.9) [33]. Moreover, the 6A/6A homozygotes and 5A/6A heterozygotes had significantly increased risk of breast cancer of 1.89 and 1.65-fold, respectively ($p = 0.01$; OR, 1.89; 95% CI, 1.12–3.20 and $p = 0.01$; OR, 1.65; 95% CI, 1.12–2.43, respectively). In addition, even though the 5A/6A genotype was also significantly associated with lymph node positive patients ($p = 0.01$; OR, 2.58; 95% CI, 1.39–4.8), there was no significant association with patients with distant metastasis. As such, the 5A/6A heterozygotes may have a higher risk of developing aggressive breast cancer but not for reduced survival of breast cancer patients ($p = 0.09$). This is also in agreement with a study by Shevchenko et al. [34] which reported association of the 5A/6A heterozygotes with breast cancer malignancy in a Russian population; and AbdRaboh and Bayoumi [21] found that the frequency of 6A containing genotype was significantly higher in advanced stages of breast cancer patients in a Dubai population ($p < 0.05$; OR, 2.9; 95% CI, 1.04–8.45) but not in patients with distant metastasis.

However, as it is commonly known, the role of genetic polymorphism as a risk factor for cancer is largely influenced by the ethnicity of the population. Furthermore, the outcome of genome-wide association analysis is also predominantly influenced by sample size, hence, conflicting results of *MMP3* polymorphisms have been reported. In most studies, the established association between *MMP3* polymorphism and breast cancer needs to be validated using a larger sample size, proper case-control matching and unbiased studies. A larger sample size may substantially reduce false-positive data compared to a smaller sample size [35]. Regardless of sample size, there are also case-control studies that have reported lack of association between the 5A/6A polymorphism and breast cancer in Austrian, European, Iranian, British, and multi-ethnic American populations [36-41].

As *MMP3* is located adjacent to *MMP1* on chromosome 11q22, several studies have also evaluated the haplotypes of *MMP1* and *MMP3* as genetic markers for breast cancer [9]. Haplotypes refer to the combinations of alleles located at multiple loci on the same chromosome that are transmitted together in a population. It is thought that combination of SNPs between distant genes and/or haplotypes have a stronger effect on the expression of a phenotype. In fact, a haplotype-based analysis is reportedly around 15-50% more powerful than a SNP-based analysis [35]. As expected, the frequency of the haplotype of *MMP1-1607* and *MMP3-1171* (1G-5A) was reported to be higher in the control group, suggesting that this haplotype may contribute to protection against breast cancer ($p < 0.0001$; OR, 0.45; 95% CI, 0.29–0.69) [33]. In addition, a cohort study performed by Hughes et al. [41]in London did not find any correlation between *MMP3-1171* polymorphism and breast cancer. However, they discovered significant associations between 2 haplotypes of *MMP1-1607*, *MMP3-1171*,

MMP7-181, *MMP12-82*, and *MMP13-77* which are clustered together on chromosome 11q22.3, in patients with lymph node metastasis. In particular, the haplotypes 2G-5A-A-A-A ($p = 0.02$; crude hazard ratio [cHR], 2.5; 95% CI, 1.2–5.2) (alleles in order of *MMP1*, *MMP3*, *MMP7*, *MMP12*, and *MMP13*) and 2G-5A-G-A-A ($p = 0.00001$; cHR, 4.5; 95% CI, 2.3–8.8) were also significantly associated with overall survival of the breast cancer patients.

Other than the *MMP3-1171* polymorphism, there is rarely any study on other polymorphisms of *MMP3*. In a Shanghai population, Beeghly-Fadiel et al. [42] studied a number of *MMP3* polymorphisms which consisted of 8 promoter polymorphisms (rs615098, rs613804, rs17361668, rs610950, rs645419, rs35068180, rs632478, and rs522616), 1 exonic polymorphism (rs679620), 3 intronic polymorphisms (rs650108, rs655403, and rs639752) as well as 4 polymorphisms at the 3′ downstream flanking region of *MMP3* (rs2155013, rs473238, rs502588, and rs7926920). However, the authors concluded that these polymorphisms were not significantly associated with breast cancer risk. In 2013, 15 SNPs of *MMP3* in Malaysian breast cancer patients that consisted of 8 exonic SNPs and 7 intronic SNPs were reported by Chan [43] (**Figure 2**). Based on an overdominant inheritance model, heterozygous patients of *MMP3* c.133A > G, c.288T > C, and c.626-14A > G might be protected from lymph node or distant metastasis (**Table 1**). This is in contrast to Beeghly-Fadiel et al. [42] who reported no significant association between *MMP3* c.133 A > G (rs679620) and breast cancer susceptibility. In addition, *in silico* functional analysis has revealed that several SNPs may have major and minor effects on the secondary structures of mRNA, resulting in increased mRNA instability, reduced half-life and *MMP3* gene expression [43]. The *MMP3* SNPs that have been predicted to exert minor changes to the secondary structure were c.1164C > T (ss244234690) and c.1200A > G (ss244234692) whereas the SNPs that confer major alterations to the secondary

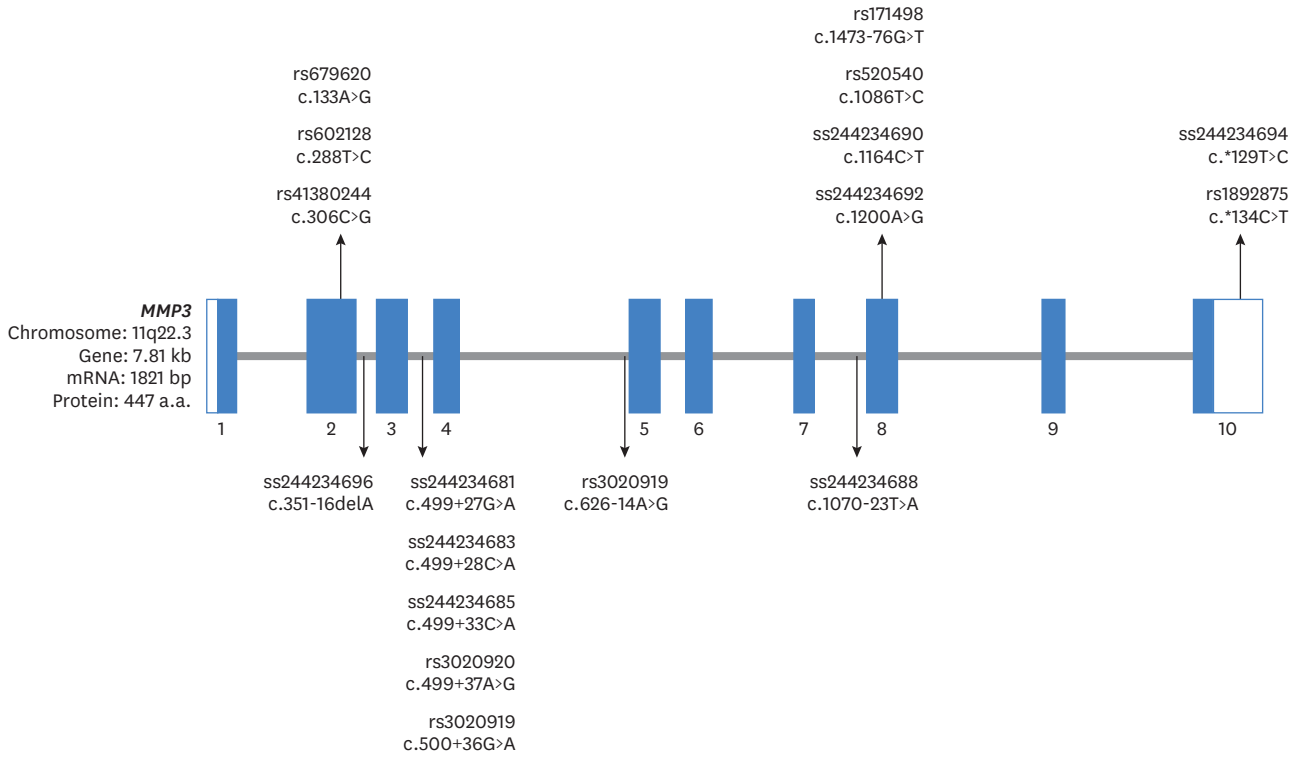

Figure 2. Schematic representatives of *MMP3* gene with localisation of single nucleotide polymorphisms [43].
MMP3 = matrix metallopeptidase 3; mRNA = messenger RNA.

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structure were c.133A > G (rs679620), c.288T > C (rs602128), c.306C > G (rs41380244) and c.*129T > C (ss244234694). All mentioned SNPs, except for c.133 A > G, were synonymous.

Recently, the advances in high-throughput technology have allowed for rapid, accurate and efficient SNP profiling. This makes SNPs one of the best choices as biomarkers for breast cancer screening. However, it is important to understand that an individual SNP marker alone may not effectively provide an accurate breast cancer risk assessment, but it may do so together with either a series of SNP markers (SNP haplotypes) or coupled with other genetic biomarkers such as epigenetic factors, post-transcriptional modifications, and proteomics factors.

CONCLUSION

Biomarkers capable of predicting tumor recurrence, formation of secondary tumor or therapeutic outcomes are highly desirable as they will help clinicians in the treatment management of breast cancer patients. The possibility of engaging *MMP3* as a cancer biomarker in the clinical setting remains exciting but caution needs to be exercised because *MMP3* polymorphisms have been reported to be strongly influenced by ethnicity. Hence, studies focusing on the discovery of SNPs and the validation of their association with breast cancer metastasis will greatly improve their utility in risk prediction. Recognizing the limitation of individual SNP biomarkers in predicting the prognosis of breast cancer, it is suggested to use haplotypes as biomarkers because they are more informative than individual SNPs. In addition, the existence of powerful statistical software allows *in silico* analysis of the functional significance of these genetic variants. Moreover, the reliability of such *in silico* analysis can be further improved through *in vitro* functional analysis. In conclusion, *MMP3* polymorphisms have high potential as prognostic biomarkers that would provide a more accurate prognosis and better decision making for treatment of breast cancer patients.

REFERENCES

1. 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:e63165.
PUBMED | CROSSREF
2. Chaudhary AK, Nadkarni AH, Pandya S, Ghosh K. Matrix metalloproteinase and its inhibitors in cancer progression. In: Dhalla NS, Chakraborti S. Role of Proteases in Cellular Dysfunction. New York (NY): Springer; 2014. p.147-58.
3. Ting WC, Chen LM, Pao JB, Yang YP, You BJ, Chang TY, et al. Genetic polymorphisms of matrix metalloproteinases and clinical outcomes in colorectal cancer patients. Int J Med Sci 2013;10:1022-7.
PUBMED | CROSSREF
4. Duffy MJ, Maguire TM, Hill A, McDermott E, O'Higgins N. Metalloproteinases: role in breast carcinogenesis, invasion and metastasis. Breast Cancer Res 2000;2:252-7.
PUBMED | CROSSREF
5. Nabeshima K, Inoue T, Shimao Y, Sameshima T. Matrix metalloproteinases in tumor invasion: role for cell migration. Pathol Int 2002;52:255-64.
PUBMED | CROSSREF
6. Yang X, Hu JW, Qiu MT, Li M, Yin R, Wang J, et al. Association of matrix metalloproteinase-3 -1171(5A>6A) polymorphism with cancer risk: a meta-analysis of 41 studies. PLoS One 2014;9:e87562.
PUBMED | CROSSREF
7. Decock J, Thirkettle S, Wagstaff L, Edwards DR. Matrix metalloproteinases: protective roles in cancer. J Cell Mol Med 2011;15:1254-65.
PUBMED | CROSSREF

8. Lochter A, Galosy S, Muschler J, Freedman N, Werb Z, Bissell MJ. Matrix metalloproteinase stromelysin-1 triggers a cascade of molecular alterations that leads to stable epithelial-to-mesenchymal conversion and a premalignant phenotype in mammary epithelial cells. J Cell Biol 1997;139:1861-72.
PUBMED | CROSSREF
9. Munhoz FB, Godoy-Santos AL, Santos MC. MMP-3 polymorphism: genetic marker in pathological processes (review). Mol Med Rep 2010;3:735-40.
PUBMED
10. Sternlicht MD, Lochter A, Sympson CJ, Huey B, Rougier JP, Gray JW, et al. The stromal proteinase *MMP3*/stromelysin-1 promotes mammary carcinogenesis. Cell 1999;98:137-46.
PUBMED | CROSSREF
11. Hadler-Olsen E, Winberg JO, Uhlin-Hansen L. Matrix metalloproteinases in cancer: their value as diagnostic and prognostic markers and therapeutic targets. Tumour Biol 2013;34:2041-51.
PUBMED | CROSSREF
12. Sipos F, Germann TM, Wichmann B, Galamb O, Spisák S, Krenács T, et al. *MMP3* and CXCL1 are potent stromal protein markers of dysplasia-carcinoma transition in sporadic colorectal cancer. Eur J Cancer Prev 2014;23:336-43.
PUBMED | CROSSREF
13. Hassan SA, Hammam O, Htwe TT, Ghanem HZ. Possible diagnostic/prognostic role of survivin and *MMP3* in breast cancer disease. J Multidiscip Eng Sci Technol 2015;2:3121-7.
14. 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 Res Treat 2007;103:61-9.
PUBMED | CROSSREF
15. Liu D, Guo H, Li Y, Xu X, Yang K, Bai Y. Association between polymorphisms in the promoter regions of matrix metalloproteinases (MMPs) and risk of cancer metastasis: a meta-analysis. PLoS One 2012;7:e31251.
PUBMED | CROSSREF
16. Lynch CC, Matrisian LM. Matrix metalloproteinases in tumor-host cell communication. Differentiation 2002;70:561-73.
PUBMED | CROSSREF
17. Nagase H, Visse R, Murphy G. Structure and function of matrix metalloproteinases and TIMPs. Cardiovasc Res 2006;69:562-73.
PUBMED | CROSSREF
18. Nagase H, Woessner JF Jr. Matrix metalloproteinases. J Biol Chem 1999;274:21491-4.
PUBMED | CROSSREF
19. Koujan SE, Gargarib BP, Khalili M. Matrix metalloproteinases and breast cancer. Thrita 2015;4:e21959.
20. Jobin PG, Butler GS, Overall CM. New intracellular activities of matrix metalloproteinases shine in the moonlight. Biochim Biophys Acta Mol Cell Res 2017;1864:2043-55.
PUBMED | CROSSREF
21. AbdRaboh NR, Bayoumi FA. Gene polymorphism of matrix metalloproteinases 3 and 9 in breast cancer. Gene Rep 2016;5:151-6.
CROSSREF
22. Mehner C, Miller E, Nassar A, Bamlet WR, Radisky ES, Radisky DC. Tumor cell expression of *MMP3* as a prognostic factor for poor survival in pancreatic, pulmonary, and mammary carcinoma. Genes Cancer 2015;6:480-9.
PUBMED
23. Banik D, Netherby CS, Bogner PN, Abrams SI. *MMP3*-mediated tumor progression is controlled transcriptionally by a novel IRF8-*MMP3* interaction. Oncotarget 2015;6:15164-79.
PUBMED | CROSSREF
24. Yan C, Boyd DD. Regulation of matrix metalloproteinase gene expression. J Cell Physiol 2007;211:19-26.
PUBMED | CROSSREF
25. Weber GF. Molecular mechanisms of cancer. Dordrecht: Springer Netherlands; 2007.
26. Krishnaveni D, Bhayal AC, Shravan KP, Jyothy A, Pratibha N, Venkateshwari A. Heterozygosity of stromelysin-1 (rs3025058) promoter polymorphism is associated with gastric cancer. Indian J Cancer 2015;52:251-4.
PUBMED | CROSSREF
27. Xiangpo P, Shuzhen L, Jianfeng G, Haiyu L, Haipeng R, Hunanxin W, et al. Current evidence on the association between four polymorphisms in the matrix metalloproteinases (MMP) gene and breast cancer metastasis. J Environ Anal Chem 2015;2:151.

28. Srivastava P, Kapoor R, Mittal RD. Impact of MMP-3 and TIMP-3 gene polymorphisms on prostate cancer susceptibility in North Indian cohort. Gene 2013;530:273-7.
PUBMED | CROSSREF

29. Ye S, Eriksson P, Hamsten A, Kurkinen M, Humphries SE, Henney AM. Progression of coronary atherosclerosis is associated with a common genetic variant of the human stromelysin-1 promoter which results in reduced gene expression. J Biol Chem 1996;271:13055-60.
PUBMED | CROSSREF

30. 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;8:3820-3.
PUBMED

31. Holliday DL, Hughes S, Shaw JA, Walker RA, Jones JL. Intrinsic genetic characteristics determine tumor-modifying capacity of fibroblasts: matrix metalloproteinase-3 5A/5A genotype enhances breast cancer cell invasion. Breast Cancer Res 2007;9:R67.
PUBMED | CROSSREF

32. Motevalibashi M, Hojati Z, Haji Hosseini S. The function of SNP at -1171 MMP-3 promoters in susceptibility to breast cancer in Isfahan population. Iran J Biol 2008;20:399-405.

33. 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:e0184448.
PUBMED | CROSSREF

34. Shevchenko AV, Konenkov VI, Garbukov EI, Stakheeva MN. Associating of polymorphism in the promoter regions of genes of metalloproteinase (MMP2, MMP3, MMP9) with options of the clinical course of breast cancer in Russian women. Vopr Onkol 2014;60:630-5.
PUBMED

35. Rebbeck TR, Ambrosone CB, Bell DA, Chanock SJ, Hayes RB, Kadlubar FF, et al. SNPs, haplotypes, and cancer: applications in molecular epidemiology. Cancer Epidemiol Biomarkers Prev 2004;13:681-7.
PUBMED

36. Lei H, Zaloudik J, Vorechovsky I. Lack of association of the -1171 (5A) allele of the *MMP3* promoter with breast cancer. Clin Chem 2002;48:798-9.
PUBMED

37. Motovali-Bashi M, Hojati Z, Hajihoseiny S. The role of matrix metalloproteinase-3 functional 5A/6A promoter polymorphism in tumor cell progression and metastasis of breast cancer. Iran J Biotechnol 2008;6:45-9.

38. Krippl P, Langsenlehner U, Renner W, Yazdani-Biuki B, Köppel H, Leithner A, et al. The 5A/6A polymorphism of the matrix metalloproteinase 3 gene promoter and breast cancer. Clin Cancer Res 2004;10:3518-20.
PUBMED | CROSSREF

39. Knechtel G, Hofmann G, Gerger A, Renner W, Langsenlehner T, Szkandera J, et al. Analysis of common germline polymorphisms as prognostic factors in patients with lymph node-positive breast cancer. J Cancer Res Clin Oncol 2010;136:1813-9.
PUBMED | CROSSREF

40. AACR Annual Meeting. Polymorphisms in matrix metalloproteinase genes 1, 3, 9, and 12 and risk of breast cancer: the multiethnic cohort study. San Diego: AACR; 2008.

41. 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;13:6673-80.
PUBMED | CROSSREF

42. Beeghly-Fadiel A, Cai Q, Lu W, Long J, Gao YT, Shu XO, et al. No association between matrix metalloproteinase-1 or matrix metalloproteinase-3 polymorphisms and breast cancer susceptibility: a report from the Shanghai Breast Cancer Study. Cancer Epidemiol Biomarkers Prev 2009;18:1324-7.
PUBMED | CROSSREF

43. Chan SC. Identification and analysis of single nucleotide polymorphisms in matrix metallopeptidase 2 and 3 genes in Malaysian breast cancer patients [doctor's thesis]. [Serdang]: Universiti Putra Malaysia; 2013.