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

Shafinah Ahmad Suhaimi, Soon Choy Chan, Rozita Rosli

1UPM-MAKNA Cancer Research Laboratory, Institute of Bioscience, Universiti Putra Malaysia, 43400 Serdang, Malaysia
2Perdana University School of Foundation Studies, MAEPS Building, MARDI Complex, Serdang, Malaysia

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 proteolyses 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
Matrix Metallopeptidase 3 as Genetic Biomarkers for Breast Cancer Metastasis

Author Contributions
Conceptualization: Suhaimi SA, Rosli R; Funding acquisition: Rosli R; Supervision: Chan SC, Rosli R; Writing - original draft: Suhaimi SA; Writing - review & editing: Chan SC, Rosli R.

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 Zn²⁺ 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 metalloproteinases 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.
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 metalloproteinases 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;

https://ejbc.kr

https://doi.org/10.4048/jbc.2020.23.e17

3/9
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.
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,
Matrix Metallopeptidase 3 as Genetic Biomarkers for Breast Cancer Metastasis

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 (<i>p</i> = 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 (<i>p</i> = 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]. Based on an overdominant inheritance model, heterozygous patients of MMP3 c.133 A > G, c.288 T > 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.1164 C > T (ss244234690) and c.1200 A > G (ss244234692) whereas the SNPs that confer major alterations to the secondary

![Figure 2](https://ejbc.kr)  
**Figure 2.** Schematic representatives of MMP3 gene with localisation of single nucleotide polymorphisms [43].  
MMP3 = matrix metallopeptidase 3; mRNA = messenger RNA.  
https://doi.org/10.4048/jbc.2020.23.e17
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: Dhallan NS, Chakraborti S. Role of Proteases in Cellular Dysfunction. New York (NY): Springer; 2014. p.147-58. PUBMED | CROSSREF

3. Tang 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.

9. Munhoz FB, Godoy-Santos AL, Santos MC. MMP-3 polymorphism: genetic marker in pathological processes [review]. Mol Med Rep 2010;3:735-40.

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.

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.

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.

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.

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.

16. Lynch CC, Matrisian LM. Matrix metalloproteinases in tumor-host cell communication. Differentiation 2002;70:561-73.

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

18. Nagase H, Woessner JF Jr. Matrix metalloproteinases. J Biol Chem 1999;274:21491-4.

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.

21. AbdRaboh NR, Bayoumi FA. Gene polymorphism of matrix metalloproteinases 3 and 9 in breast cancer. Gene Rep 2016;5:151-6.

22. Mehner C, Miller E, Nassar A, Bamber WR, Radisky ES, Radisky DC. Tumor cell expression of MMP9 as a prognostic factor for poor survival in pancreatic, pulmonary, and mammary carcinoma. Genes Cancer 2015;6:480-9.

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.

24. Yan C, Boyd DD. Regulation of matrix metalloproteinase gene expression. J Cell Physiol 2007;211:19-26.

25. Weber GF. Molecular mechanisms of cancer. Dordrecht: Springer Netherlands; 2007.

26. Krishnaveni D, Bhayal AC, Shravan KP, Jyothy A, Pratibha N, Venkateshwarl A. Heterozygosity of stromelysin-1 (rs3025058) promoter polymorphism is associated with gastric cancer. Indian J Cancer 2015;52:251-4.

27. Xiangpo F, 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.

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.

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.

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.

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

33. Padala C, Tupurani MA, Puranam K, Ganta 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.

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.

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.

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.

37. Motovali-Bashi M, Hojati Z, Hajiboseini 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. Krippel 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.

39. Knechtel G, Hofmann G, Gerger A, Renner W, Langsenlehner T, Szakandera 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.

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, Aghaje O, Bowen RJL, 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.

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.

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