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NARRATIVE REVIEW

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Association of *MMP1* gene polymorphisms with breast cancer risk: A narrative review

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Abstract

Background and Aims: Breast cancer is a multifactorial malignancy with different clinicopathological and molecular characteristics. It is the most frequent cancer in women in terms of both incidence and mortality. Matrix metallopeptidase 1 or *MMP1* is a zinc-dependent endopeptidase associated with several physiological processes through the modification of the extracellular matrix and tumor microenvironment. However, previous results did not suggest any concluding remarks on the correlation between *MMP1* gene polymorphisms and the risk of breast cancer.

Methods: A comprehensive literature search was performed in PubMed database to retrieve relevant articles and extract data from suitable ones. The literature written only in English was selected for this review.

Results: A total of 26 articles were included in the present narrative review. From the available studies, it is observed that MMP1 is upregulated in breast cancer tissues and found to be correlated with metastasis and invasion. The expression of *MMP1* gene is mediated by numerous factors, including polymorphisms which act as a potential risk factor for the progression of breast cancer. To establish the correlation between genetic polymorphisms in *MMP1* and the risk of breast cancer, several case-control studies, as well as genetic analyses, have been carried out in different ethnicities. The association of genetic polymorphisms in *MMP1* with the risk and survival of breast cancer in different populations has been reviewed in this study. Moreover, the structural domain of MMP1 and the role of MMP1 in breast cancer metastasis and invasion are also discussed which will help to understand the potential impact of MMP1 as a genetic biomarker.

Conclusions: This review provides an overview of the *MMP1* gene polymorphisms in breast cancer. However, we recommend future studies concentrating on combined analysis of multiple SNPs, gene-gene interactions, and analysis of

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epigenetics, proteomics, and posttranscriptional modifications that will provide the best outcome.

KEYWORDS
association, breast cancer, matrix metalloproteinase 1, *MMP1*, polymorphism, risk

1 | INTRODUCTION

Breast cancer (BC) is the most frequent type of malignancy in females throughout the world and is also the leading reason of mortality among them.[1] Approximately 1.6 million new cases of BC patients are reported every year and the incidence is worryingly increasing during the last few years. Besides, the incidence of mortality due to BC has been the highest among women. According to the report from 2018, almost 626,679 patients (6.6% of all cancer-associated deaths) died globally because of BC.[2,3] In spite of substantial improvements in treatment strategies, BC has been the major cause of mortality in women over the past few decades, making it a global health burden.[4]

BC is considered a multifactorial and heterogenous malignancy with different clinicopathological and molecular characteristics. A combined effect of various potential risk factors including genetic, epigenetic, population structure, environmental, and sedentary lifestyle results in BC.[5,6] Some common factors are physical inactivity, high-fat diet, hormonal imbalance, early or late menstrual cycle, late pregnancy, dense breasts, old age, high-stress level, radiation, or environmental carcinogens.[7] BC is a polygenic malignancy and hereditary BC accounts for around 5%–10% of all diagnosed cases.[8] The microenvironment of breasts consists of an extracellular matrix (ECM) and different stromal cells such as endothelial cells, fibroblasts, immune cells, and adipocytes which play a crucial part in the morphogenesis of mammary duct.[9]

Matrix metalloproteinases (MMPs), also called matrixins, are metal-dependent endopeptidases.[10] MMPs are a family of multigene that commonly associate with diverse physiological and pathological mechanisms in the human body required for development and morphogenesis.[11] Typically, MMPs consist of a secretory amino terminal, a cysteine-switched latency-mediating pro-domain, and a Zn^{2+}-dependent enzymatic domain. Most of the members of the MMPs family also possess a substrate-specific hemopexin domain-containing C-terminal.[12–14] MMPs play a catalytic role during ECM degradation and remodeling.[15] Besides, the activity of some growth factors, proteases, chemokines, cytokines, ligands, proteases, and receptors are also regulated by them. However, loss of MMPs activities leads to angiogenesis, metastasis, cell adhesion, cell migration, differentiation, proliferation, and inflammation, which ultimately develops cancers.[16–21]

Based on the structural domains and specificity to particular substrates, MMPs are broadly classified into five major groups namely, collagenases, stromelysins, matrilysins, gelatinases, and membrane-associated MMPs. MMP1 is from the collagenases group and is one of the most commonly expressed MMPs. It is responsible for the breakdown of collagen type I, II, and III.[22,23] Impaired expression of MMP1 has been reported in multiple cancers including breast,[24] lung,[25] prostate,[26] and colon.[27]

The present review focuses on the association of *MMP1* gene polymorphisms with BC susceptibility, which has not been comprehensively studied or reviewed before. *MMP1* genetic polymorphisms have been implicated in various malignancies according to previous studies, but the findings have been inconclusive. The review aims to shed light on the potential role of *MMP1* gene polymorphisms in BC by discussing their association with BC risk. It also delves into the structure of the MMP1 and explores its potential role in the development and progression of BC.

2 | STRUCTURAL DOMAINS OF MMP1

Generally, MMPs comprise a propeptide domain of around 80 amino acids, an essential metalloproteinase domain (catalytic domain) of around 170 amino acids, a linker (hinge region) peptide of variable lengths (typically 15–65 amino acids), and a hemopexin (Hpx) domain of about 200 amino acids.[28–30] For the activity of a typical MMP, requires a zinc ion (Zn^{2+}) in the catalytic domain beside the proteolytic activation.[31] The human MMP1 structural domains (Figure 1) are mainly an N-terminal catalytic domain, a linker peptide region, and a C-terminal Hpx domain in which the catalytic domain of one monomer connects the Hpx domain of another monomer.[32,33]

The catalytic domain or metalloproteinase domain of a typical MMP1 contains a conserved sequence of three histidine residues necessary for Zn^{2+} chelation. The structure of MMP1 catalytic region is almost analogous to other members of MMPs. In length, it is almost 170 amino acid residues long with a catalytic Zn^{2+} residing in the C-terminal site. The catalytic domain is connected to the hemopexin domain through a short hinge region. Moreover, the MMP1 metalloproteinase domain carries three calcium-binding sites in its structure.[31]

The catalytic domain of MMP1 is followed by the linker or the hinge region consists of a stretch of about 15–65 amino acid residues. Proline residues commonly construct hinge regions, and the presence of the appropriate hinge structure is vital for the process of collagenolysis. These amino acid residues possess an extensive connection with both the catalytic domain and the Hpx domain of MMP1. This close connection is necessary for the stabilization and the concerted action between the domains in MMP1. Mutations in the hinge region drastically reduce the

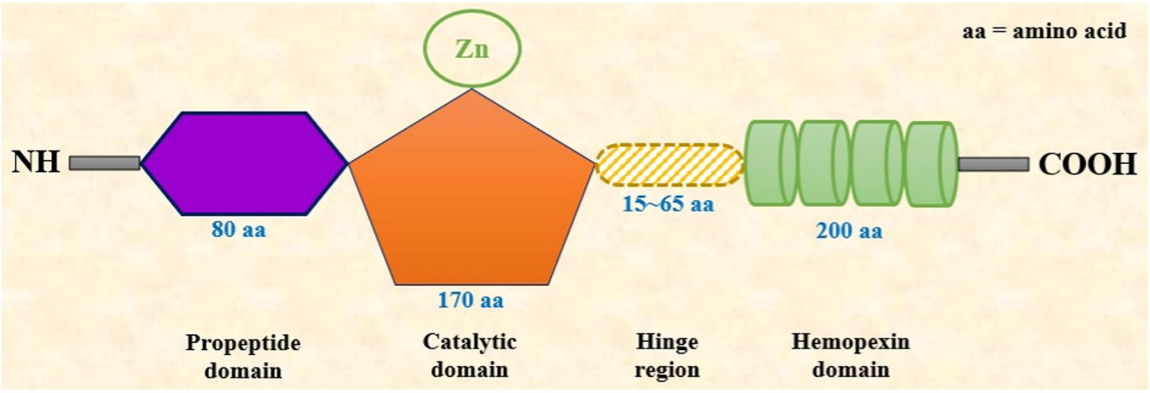

FIGURE 1 Structural domains of MMP1. MMP, matrix metalloproteinase.

collagenolytic activity of MMP1 as a result of the movement restrictions between the catalytic and the Hpx domain.

The hemopexin (Hpx) domain of MMP1 begins with Cys259 residue and makes a complete circular structure by connecting to Cys447. The Hpx domain shows the dramatic effect through a significant displacement to the metalloproteinase domain, which widens the cleft located between these domains arranged on the active site face in this enzyme. This attenuated configuration produces residues of the active site as well as the RWTNNFREY (residues 183 to residues 191) segment crucial for collagenolytic activity. The Hpx domain consists of a β-propeller (4-bladed) structure and a linking disulfide bond (S-S) between the first and the fourth blades. Typically, the center of this propeller structure contains a chloride ion and a calcium ion.[21,33] This domain is necessary for the interactions between other MMPs.[31]

3 | SOURCES AND DISTRIBUTION OF MMP1

MMP1 is produced and secreted by several cells in the human body (Table 1). Connective tissues, proinflammatory cells, and different uteroplacental cells such as endothelial cells, platelets, fibroblasts, osteoblasts, chondrocytes, lymphocytes, smooth muscle cells (SMCs), neutrophils, macrophages, cytotrophoblasts, etc. produce and distribute MMP1. MMP1 has a key function in tissue remodeling via increasing the turnover of multiple ECM proteins such as collagens, gelatin, elastin, proteoglycans, and glycoproteins. Collagen and elastin are two prominent proteins necessary for maintaining the vascular wall's structural integrity. MMP1 breaks down collagen substrates I, II, III, IV, VII, VIII, X, and gelatin with variable efficacies. It also breaks down noncollagen ECM substrates including aggrecan, perlecan, versican, proteoglycan link protein, serpins, nidogen, fibronectin, and tenascin. It also degrades casein, antichymotrypsin, IL1β, pro-tumor necrosis factor-α, SDF1, antitrypsin, proteinase inhibitor, IGF-BP3 and 5.[29,34–36]

4 | FUNCTION OF MMP1 IN BC PROGRESSION

Metastasis and invasion of cancer cells happen as a result of several key steps like malignant cell detachment at the main origin, angiogenesis, cellular proliferation, invasion in local regions, intravasation of tumors into the vasculature system, and extravasation of tumors at the distant region. Metastasis and invasion also need different physical barriers, for example, the basement membrane and the surrounding connective tissues.[37] MMP1 is a calcium-dependent zinc-containing collagenase that is upregulated in a variety of cancers and involves tumor metastasis and invasion as well as cell proliferation, differentiation, migration, angiogenesis, apoptosis, and immune defense. Moreover, studies showed an inverse correlation between MMP1 overexpression and survival in cancer patients.[38–40]

The activity of MMP1 is tightly controlled in normal tissues by proteolytic cleavage, including the negative regulation of TIMPs (tissue inhibitors of metalloproteinases), which is less expressed in malignant tissues. Again, the lower transcription level of MMP1 in normal epithelia is increased in response to various stimuli, for instance, cytokines, chemokines, growth factors, and several hormones.[41] In breast carcinoma, particularly basal-type cancers, MMP1 is upregulated and shows extensive metastatic properties. It is also associated with progression and relapse-free survival leading to poor prognosis of BC. There is also a statistically significant difference between stromal cells MMP1 positivity and luminal A, B, and TNBC (triple-negative BC). Most importantly, MMP1 expression at the BC level carries an independent prognostic value.[42]

A recent study by Wang et al.[43] reported that the MMP1 protein expression level is significantly higher ($p < 0.05$) in TNBC tissues than in estrogen receptor-positive (ER^{+}) and epidermal growth factor 2 receptor-positive ($EGF2R^{3+}$) BC tissues. Moreover, the MMP1 level was significantly elevated in the stromal cells of metastatic lymph node tissues than that of the nonmetastatic tissues in BC. They showed that MMP1 small hairpin RNA in MDA-MB-231 and MCF-7 cells drastically reduced migration, proliferation, and invasion knocking down MMP1 expression, and suggested that MMP1 is differentially regulated in BC.

TABLE 1 Location, tissue distribution and substrates of *MMP1* gene.

Name	Chromosomal location	MW pro/active	Distribution	Collagen substrates	Noncollagen substrates	Other targets and substrates
MMP1	11q22.3	55/45 KDa	Endothelium, intima, fibroblasts, SMCs, vascular adventitia, platelets, varicose veins	I, II, III, IV, VII, VIII, X, and gelatin	Aggrecan, perlecan, versican, proteoglycan link protein, serpins, nidogen, tenascin	Casein, antichymotrypsin, IL1β, pro-TNFα, SDF1, antitrypsin, proteinase inhibitor, IGF-BP3 and 5

Abbreviations: IL, interleukin; MMP, matrix metalloproteinase; SMC, smooth muscle cell; TNF, tumor necrosis factor.

Another study by Shen et al.[38] demonstrated that upregulated MMP1 leads to the activation of paracrine protease-activated receptor 1 (PAR1) and promotes growth and distant metastasis of BC tissues. Moreover, the high expression level of MMP1 is correlated with worse survival in all BC patients including ER^+ patients. Furthermore, MMP1 increased invasiveness in BC tissues through vascular endothelial growth factor as well as bone morphogenetic protein 2/4. Some recent studies also explicated that MMP1 enhanced tumor cell migration via degrading specific cell adhesion and cell-matrix adhesion regulatory substrates. This interaction ultimately leads to tumor metastasis and invasion.[44] A previous study by Eiró et al.[45] described that MMP1 expression in host defense cells is linked with the sequential metastasis in the lymphatic system (sentinel lymph nodes, SLN) of BC tissues. An updated analysis by Eiró et al.[46] reported a significant correlation of enhanced MMP1 expression with tumor size and histological grade in BC.

MMP1 upregulation has been identified and confirmed as an important factor for BC metastasis. It has been described that expression of MMP1 is greater in invasive ductal carcinoma (both nonspecific and lymph node metastatic nonspecific) than the normal tissues and lymph node tissues in BC.[47] Cierna et al.[48] also reported that elevated MMP1 expression is correlated with evolution, dissemination, worse prognosis, and shortened survival rate in breast tumor. Moreover, MMP1 induces epithelial to mesenchymal transition promoting the invasiveness of BC cells. The expression of MMP1 in BC samples based on the sample types, individual cancer stages, patient's race, patient's gender, patient's age, BC subclass, menopause status, and nodal metastasis status is depicted in Figure 2A–H. The expression data were retrieved from the publicly available ULCAN database (https://ualcan.path.uab.edu/index.html).

5 | ASSOCIATION OF GENETIC POLYMORPHISMS IN *MMP1* WITH BC

Almost 90%–95% of BC cases are thought to be sporadic types and result from the combination of both genetic and environmental factors. According to the polygenic models, a combination of numerous low-risk genes with polymorphisms in the genome sequence can enhance several diseases' vulnerability.[49] The *MMP1* expression level might be greatly influenced by polymorphisms, especially single nucleotide polymorphisms (SNPs) that are positioned within or near the promoter site of the *MMP1* gene. The association of different genetic polymorphisms of *MMP1* has been studied for cancers, especially in BC (Table 2).

Recent research showed that due to the differences in ethnicity, the susceptibility, incidence, and survival rate of BC varies among different populations. Besides, genetic differences also contribute to racial or ethnic variations in BC patients. To evaluate the effect of genes and their variants, a collaborative case-control investigation in Hispanic and non-Hispanic white females was carried out by Slattery et al.[22] They carried out a large study on 3592 BC cases and 4183 healthy controls from the United States and Mexico to examine the association of nine genetic variants including rs5854 (C/T), rs17293823 (G/A), rs996999 (C/T), rs17293761 (C/T), rs7945189 (C/T), rs7125062 (T/C), rs470358 (C/T), rs475007 (A/T), rs1144393 (T/C) in *MMP1* gene with BC risk. Among them, 4 SNPs, namely, rs5854 (C/T), rs996999 (C/T), rs7125062 (T/C), and rs1144393 (T/C) were found to be significantly ($p < 0.05$) correlated with overall BC risk. SNP rs996999 (C/T) in the *MMP1* gene showed the strongest association in females with the most Native American ancestry (odds ratio [OR] = 1.61; 95% confidence interval [CI] = 1.09–2.40; $p = 0.039$).

Accumulating evidence revealed that insertion of a single guanine base (1G/2G polymorphism) in the *MMP1* gene promoter area generates a new binding region for the AP1 transcription factor, which attenuates the transcription level of *MMP1*.[61] The influence of rs1799750 1G/2G polymorphism on the *MMP1* expression level, incidence, and progression of BC was investigated in a case-control study. In that study, the genotypes and alleles distribution of the 1G/2G variant in *MMP1* on 270 BC patients and 300 healthy women in the Polish population were examined. The study showed that the 2G/2G genotype and the 2G allele carriers (OR = 2.14; 95% CI = 1.24–3.69 and OR = 1.68; 95% CI = 1.19–2.39, respectively) are significantly associated ($p < 0.001$) with a higher possibility of axillary lymph node metastasis among BC patients. They also suggested the contribution of *MMP1* to the local invasion and therefore, established *MMP1* as a BC progression marker.[50] To evaluate the association of rs1799750 1G/2G variant in the progression of BC, Przybylowska et al.[62] also conducted a case-control study on 135 subjects. They reported that 2G allele percentage was significantly greater in lymph node-metastasis cases than in the nonmetastasis subjects ($p < 0.001$).

Again, a case-control study by Padala et al.[54] showed that the promoter site genetic polymorphism of the *MMP1* gene (rs1799750

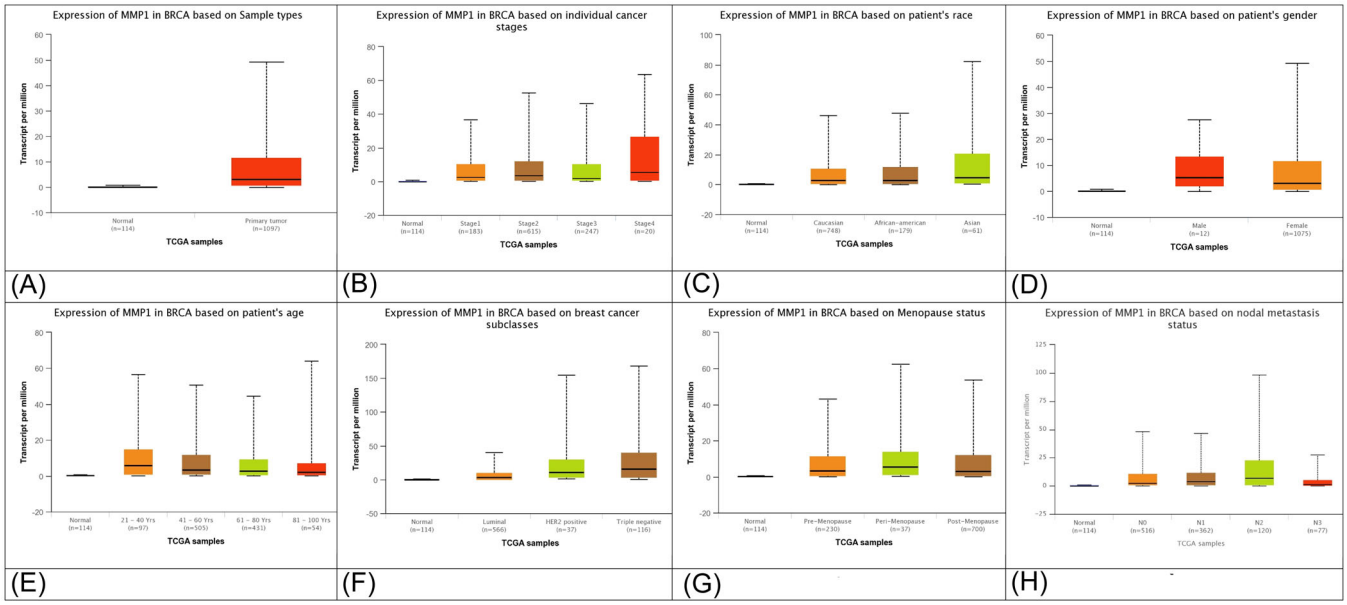

FIGURE 2 MMP1 expression based on the sample types (A), individual cancer stages (B), patient's race (C), patient's gender (D), patient's age (E), breast cancer subclass (F), menopause status (G), and nodal metastasis status (H). Expression data was retrieved from the publicly available ULCAN database (https://ualcan.path.uab.edu/index.html). MMP, matrix metalloproteinase.

1G/2G) is correlated with the development of breast carcinoma in the South Indian population. The study reported that the 2G allele of *MMP1* rs1799750 had enhanced transcriptional activity. The frequency of 2G allele was also reported to be linked with twofolds enhanced risk in the patients with BC than the controls suggesting that *MMP1*-1607 1G/2G gene polymorphism might have a greater association with BC.

However, a controversial relationship between *MMP1* and BC risks has also been reported in different populations. The association between rs1799750 in *MMP1* (1G/2G) and the risk of BC is recently investigated in a study of 598 subjects (299 BC cases and 299 healthy controls) from Poland. In this study, the results did not show any significant correlation between 1G/2G polymorphism and BC progression.[16] The 2G allele of the rs1799750 SNP in the *MMP1* gene promotes the transcriptional activity of *MMP1* by creating a binding region for Ets transcription factors. A study on 959 BC cases and 952 controls in the Swedish population evaluated the linkage between the *MMP1* gene rs1799750 and BC. However, no statistically significant association of this polymorphism was observed with BC risk.[51] Biondi et al.[52] also observed a lack of association between *MMP1* rs1799750 and BC in an Italian case-control investigation on 43 BC cases and 164 healthy volunteers.

Notably, the *MMP1* level in serum has been found to be reduced in patients with BC than the healthy subjects. Again, the 1G/2G promoter polymorphic site of *MMP1* determines the levels of *MMP1* influencing the susceptibility of an individual to BC. A case-control study by Hsiao et al.[53] investigated the relationship of rs1799750 polymorphism in *MMP1* to BC among the Taiwanese population. In the study, the rs1799705 polymorphic genotypes were evaluated on 1232 patients and 1232 controls but did not find any statistically significant correlation with the development of BC. The study concluded that rs1799750 may not contribute to the susceptibility of BC in the Taiwanese.

Emerging evidence showed that *MMP1* is the most abundant MMP located under the control of the AP1 transcriptional factor which binds to the promoter site of mitogen-activated protein kinase via polyomavirus enhancer activator 3 (Pea3) protein. The *MMP1* expression level was found to be significantly elevated in the atypical ductal hyperplasia compared to that of the benign BC as well as in the invasive BC than that of the in situ BC. *MMP1* gene rs1799750 (1G/2G) polymorphism was investigated in 1232 BC cases and 1232 healthy women from Taiwan. However, the study indicated no significant association between the 1G/2G or 1G/1G genotypes with BC susceptibility.[55]

No statistically significant correlations were observed in a study in 86 BC patients and 110 controls in Italy by Ghilardi et al.[56] with the tumor, node, metastasis (TNM) stage during diagnosis of BC and between the *MMP1* gene rs1799750 (1G/2G) polymorphism. The distribution of the *MMP1* promoter allelic variant also demonstrated no statistically significant variations between metastatic cases and controls or between metastatic and nonmetastatic cases or between nonmetastatic cases and controls. However, they failed to establish any statistically significant link between 1G/2G polymorphism in the *MMP1* gene and BC.

Another study by Balkhi[7] and colleagues examined the association between circulating levels of rs1799750 polymorphism and BC in a sample of 200 subjects. In the study, the frequencies of different genotypes for rs1799750 were observed. Among the BC cases, the frequencies were reported as 74% for the 2G/2G genotype, 2% for the 1G/2G genotype, and 24% for the 1G/1G

TABLE 2 *MMP1* gene polymorphisms and their association with breast cancer.

SNPs	Major/minor allele	MAF	Population	Cases/controls	OR	95% CI	*p* value	References
rs5854	C/T	0.60	United States and Mexico	3592/4183	0.82	0.69–0.97	0.018	Slattery et al.[22]
rs17293823	G/A	0.21	United States and Mexico	3592/4183	N/A	N/A	N/A	Slattery et al.[22]
rs996999	C/T	0.45	United States and Mexico	3592/4183	1.23	1.01–1.50	0.039	Slattery et al.[22]
rs17293761	C/T	0.15	United States and Mexico	3592/4183	N/A	N/A	N/A	Slattery et al.[22]
rs7945189	C/T	0.15	United States and Mexico	3592/4183	N/A	N/A	N/A	Slattery et al.[22]
rs7125062	T/C	0.70	United States and Mexico	3592/4183	1.15	1.01–1.32	0.03	Slattery et al.[22]
rs470358	C/T	0.84	United States and Mexico	3592/4183	N/A	N/A	N/A	Slattery et al.[22]
rs475007	A/T	0.90	United States and Mexico	3592/4183	N/A	N/A	N/A	Slattery et al.[22]
rs1144393	T/C	0.60	United States and Mexico	3592/4183	0.94	0.85–1.04	0.03	Slattery et al.[22]
rs1799750	1G/2G	0.49	Poland	270/300	1.68	1.19–2.39	<0.05	Przybylowska et al.[50]
rs1799750	1G/2G	0.76	Poland	299/299	1.08	0.70–1.67	>0.05	Białkowska et al.[16]
rs1799750	1G/2G	N/A	Sweden	959/952	N/A	N/A	>0.05	Lei et al.[51]
rs1799750	1G/2G	0.19	Italy	43/164	1.51	0.65–3.50	>0.05	Biondi et al.[52]
rs1799750	1G/2G	0.44	Taiwan	1232/1232	1.03	0.91–1.18	>0.05	Hsiao et al.[53]
rs1799750	1G/2G	0.58	South India	300/300	2.01	1.57–2.59	<0.05	Padala et al.[54]
rs1799750	1G/2G	0.44	Taiwan	1232/1232	0.99	0.89–1.11	>0.05	Su et al.[55]
rs1799750	1G/2G	0.53	Italy	86/110	0.97	0.65–1.45	>0.05	Ghilardi et al.[56]
rs1799750	1G/2G	0.25	Iran	100/100	0.21	0.14–0.33	<0.05	Balkhi et al.[7]
rs1799750	2G/1G	0.35	China	3016/3007	1.0	0.8–1.30	0.45	Beeghly-Fadiel et al.[57]
rs484915	A/T	0.34	China	3016/3007	1.1	0.9–1.50	0.76	Beeghly-Fadiel et al.[57]
rs1155764	T/G	0.20	China	3016/3007	0.8	0.5–1.30	0.90	Beeghly-Fadiel et al.[57]
rs509332	A/G	0.13	China	3016/3007	1.4	0.8–2.70	0.54	Beeghly-Fadiel et al.[57]
rs470206	G/A	0.13	China	3016/3007	1.3	0.7–2.50	0.46	Beeghly-Fadiel et al.[57]
rs2075847	T/C	0.24	China	3016/3007	1.1	0.7–1.50	0.71	Beeghly-Fadiel et al.[57]
rs498186	A/C	0.46	China	3016/3007	1.0	0.8–1.20	0.73	Beeghly-Fadiel et al.[57]
rs475007	T/A	0.36	China	3016/3007	0.9	0.7–1.20	0.77	Beeghly-Fadiel et al.[57]
rs996999	T/C	0.49	China	3016/3007	1.0	0.8–1.30	0.79	Beeghly-Fadiel et al.[57]
rs470558	G/A	0.11	China	3016/3007	1.0	0.5–2.00	0.58	Beeghly-Fadiel et al.[57]
rs2071232	C/T	0.50	China	3016/3007	1.0	0.8–1.20	0.69	Beeghly-Fadiel et al.[57]
rs7125062	C/T	0.30	China	3016/3007	1.0	0.7–1.30	0.74	Beeghly-Fadiel et al.[57]
rs1938901	T/C	0.44	China	3016/3007	1.0	0.8–1.20	0.63	Beeghly-Fadiel et al.[57]
rs470747	T/C	0.09	China	3016/3007	0.9	0.3–2.10	0.77	Beeghly-Fadiel et al.[57]
rs2071231	T/G	0.21	China	3016/3007	0.7	0.5–1.10	0.98	Beeghly-Fadiel et al.[57]
rs470215	A/G	0.09	China	3016/3007	0.9	0.4–2.10	0.38	Beeghly-Fadiel et al.[57]
rs5854	C/T	0.08	China	3016/3007	0.7	0.2–2.10	0.67	Beeghly-Fadiel et al.[57]
rs7945189	C/T	0.07	China	3016/3007	0.7	0.3–1.80	0.64	Beeghly-Fadiel et al.[57]
rs470504	C/T	0.13	China	3016/3007	1.0	0.6–2.00	0.52	Beeghly-Fadiel et al.[57]
rs1939008	A/G	0.43	China	3016/3007	1.0	0.8–1.20	0.77	Beeghly-Fadiel et al.[57]

TABLE 2 (Continued)

SNPs	Major/minor allele	MAF	Population	Cases/controls	OR	95% CI	*p* value	References
rs11225422	A/G	0.20	China	3016/3007	1.1	0.8–1.50	0.63	Beeghly-Fadiel et al.[57]
rs470226	G/A	0.12	China	3016/3007	0.7	0.4–1.30	0.52	Beeghly-Fadiel et al.[57]
rs7127735	A/G	0.21	China	3016/3007	1.1	0.8–1.40	0.41	Beeghly-Fadiel et al.[57]
rs1799750	1G/2G	0.42	United Kingdom	126[a]/92[b]	1.84	1.25–2.70	<0.05	Hughes et al.[58]
rs1799750	1G/2G	0.47	Russia	358/746	1.02	0.85–1.22	0.83	Pavlova et al.[59]
rs1799750	2G/1G	0.46	Russia	239/556	1.00	0.80–1.24	0.99	Pavlova et al.[60]
rs1799750	2G/1G	0.46	Russia	119/190	1.05	0.75–1.45	0.78	Pavlova et al.[60]

Abbreviations: CI, confidence interval; MAF, minor allele frequency; MMP, matrix metalloproteinase; N/A, not available; OR, odds ratio.
[a]Node positive.
[b]Node negative.

genotype. In comparison, among the healthy volunteers, the frequencies were 38% for the 2G/2G genotype, 2% for the 1G/2G genotype, and 60% for the 1G/1G genotype. The observed differences in genotype frequencies between the two groups were found to be statistically significant ($p < 0.05$). Furthermore, they found that individuals with the 2G/2G genotype had a significantly increased risk of developing BC compared to those with the 1G/1G genotype (OR = 4.86; $p < 0.001$). They also found a significantly increased serum level of MMP1 in BC patients compared to healthy volunteers.

The study conducted by Beeghly-Fadiel et al.[57] focused on evaluating the association between individual genetic polymorphisms across the *MMP1* gene and BC risk in a two-phase case-control study. The study specifically included women from the Shanghai Breast Cancer Study, with a total sample size of 6023 participants. In their study, the authors investigated 23 SNPs from the *MMP1* gene. However, their analysis did not find any significant correlation between these SNPs and BC risk among the participants.

In a study investigating the association between rs1799750 polymorphism of the *MMP1* gene and the metastatic spread of BC, researchers evaluated 126 lymph node-negative and 92 lymph node-positive patients. The findings demonstrated a significant and independent association between the 2G/2G genotype and lymph node-positive disease. For mixed ethnicities, the odds ratio was 3.9 (95% CI = 1.7–9.4), while for Caucasians, it was 2.6 (95% CI = 1.0–6.9). This suggests that individuals with the 2G/2G genotype are at an increased risk of lymph node metastasis. The study also revealed that the 2G/2G genotype was linked to reduced survival, with a hazard ratio of 3.1 (95% CI = 1.1–8.7). However, the impact on survival was dependent on lymph node status, indicating that the genotype's effect may vary depending on whether the patient has lymph node-positive or lymph node-negative disease. Additionally, two haplotypes of the *MMP1* 2G allele were significantly linked to lymph node-positive disease and survival outcomes.[58]

In a case-control study conducted among Caucasian women in Russia, Pavlova et al.[59] investigated the association between *MMP* gene polymorphisms and BC risk. The study included a total of 358 affected women with BC and 746 controls. The researchers focused on 10 SNPs in five different *MMP* genes, including *MMP1*, *MMP2*, *MMP3*, *MMP8*, and *MMP9* based on their relevance to BC from earlier studies. Although the findings of the study demonstrated a significant association between *MMP* gene polymorphisms and BC susceptibility in the Caucasian women of Russia, no statistically significant link was reported for *MMP1* rs1799750 polymorphism. Another study published by Pavlova and others[60] in the same year (2022) explored the potential modifying effect of obesity on the association between these 10 polymorphisms and BC risk. In this study, the authors categorized the same samples ($n = 1104$) into two groups based on their body mass index (BMI): BMI ≥ 30 (119 BC and 190 control) and BMI < 30 (239 BC and 556 control). The findings of the study revealed an overall significant modifying effect of obesity on the association between *MMP* genes and BC risk in postmenopausal women. However, the authors did not find any significant link between rs1799750 and BC risk.

Some meta-analyses[63–67] were also performed to evaluate the correlation between *MMP1* genetic variation and the risk of BC. However, these studies failed to establish any statistically significant link between *MMP1* polymorphism and BC risk,[63–66] except the study by Sui et al.[67] where they showed a reduced risk of BC in the heterozygous model in the overall population.

6 | LITERATURE SEARCH STRATEGIES

This narrative review was conducted by following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for systematic review.[68] We carried out a comprehensive literature search in PubMed database (https://pubmed.ncbi.nlm.nih.gov/) as summarized in Figure 3. We have used the following search keywords: "*MMP1*," "matrix metalloproteinase 1," "*MMP1* and breast cancer," "*MMP1* and carcinogenesis or malignancy," "polymorphisms in *MMP1*," "*MMP1* metastasis and invasion." We have also reviewed

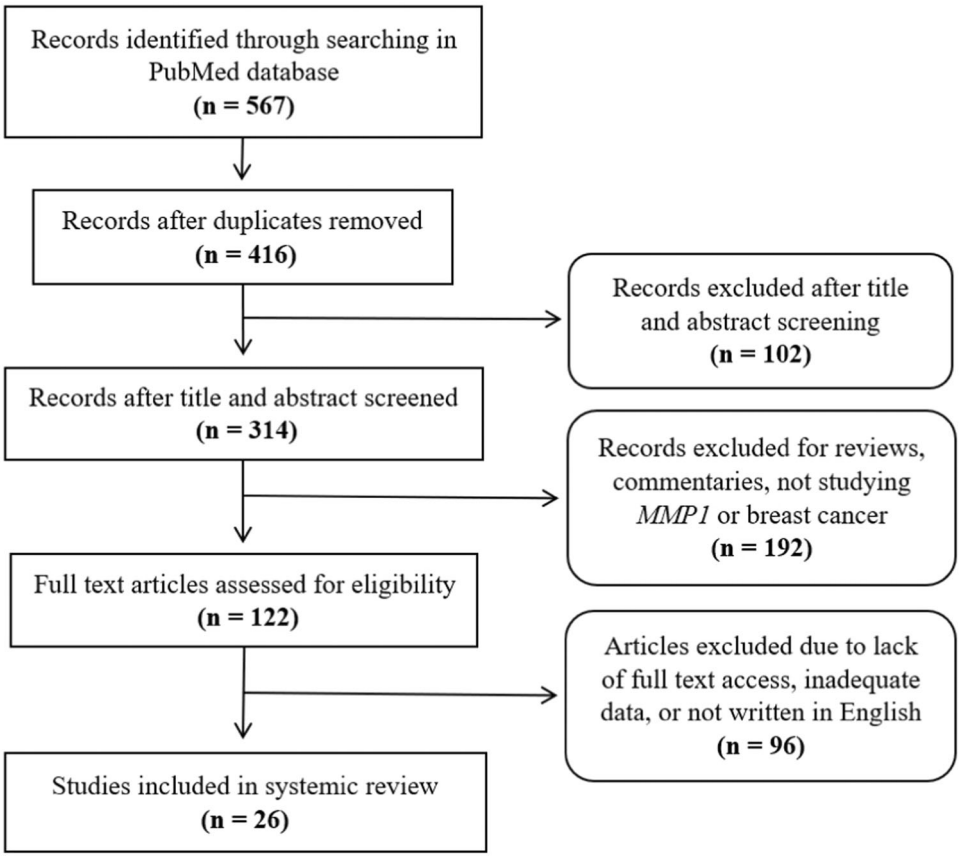

FIGURE 3 Flow diagram of literature search and selection for systemic review.

the bibliographic list of relevant articles to extract data from suitable ones. The literature written only in English was retrieved for our review.

A total of 567 studies were collected from searching the PubMed database. After the removal of 151 duplicates, 416 articles remained for analyzing the title and abstracts. 102 articles were removed after the title and abstract screening. Excluding reviews, commentaries, not relating to *MMP1* and not studying cancers except BC, a total of 122 articles remained. Due to a lack of full-text access and inappropriate data, 95 articles were removed. One article was further excluded due to being written in other than English. Finally, 26 articles were included in the present systematic review.

7 | FUTURE PERSPECTIVES

It is already established that the role of genetic polymorphism as a risk factor for cancer development is largely influenced by the ethnicity, geographical, and biological diversity of the population.[69,70] Moreover, the findings of genome-wide association studies are also markedly affected by the small sample size. As a result, inconsistent results have been observed from the genetic association studies aimed to establish the correlation between *MMP1* gene variants and the risk of progression of BC. In most of the studies, the published results must be validated using a larger sample size, appropriate matching between cases and controls, and unbiased investigations. Besides, a comparatively greater sample size may substantially decrease the amount of false-positive data.[60]

However, the recent advances in high-throughput technology have permitted fast, accurate, and efficient profiling of SNPs making them appropriate choices as biomarkers for screening BC. Furthermore, understanding the effect of SNPs of a particular gene individually or in combination is very important to get the proper outcome from genetic studies.[71] Individual SNP markers alone cannot effectively provide an accurate assessment of BC risk. A combination of multiple SNPs analysis (haplotype analysis), gene-gene interactions, understanding molecular pathways, and study with other factors including epigenetics, proteomics, posttranscriptional modifications, and others may provide the best output in future studies.

8 | CONCLUSION

MMP1 is a zinc-dependent endopeptidase that is upregulated in BC tissues and is associated with BC metastasis and invasion. The expression of MMP1 is mediated by numerous factors, including polymorphisms which act as a prominent risk factor in the progression of breast carcinogenesis. The correlation between

genetic polymorphisms in *MMP1* and BC risk has been analyzed in various case-control studies in different ethnicities which is inconsistent. This is the first review concentrating on the correlation of different genetic polymorphisms in *MMP1* with the risk and survival of BC as well as the structural domain of *MMP1* and the role of *MMP1* in BC metastasis and invasion. Our present review provides an overview of the *MMP1* gene polymorphisms in BC. However, further studies are needed focusing on combined analysis of multiple SNPs, gene-gene interactions, and analysis of epigenetics, proteomics, and posttranscriptional modifications that will provide the best outcome.

AUTHOR CONTRIBUTIONS

Tahmina Akter: data curation; formal analysis; methodology; visualization; writing—original draft. **Abdul Aziz**: data curation; formal analysis; methodology; visualization; writing—original draft. **Mohammad Safiqul Islam**: writing—review & editing. Md. **Shahid Sarwar**: conceptualization; supervision; writing—review & editing.

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CONFLICT OF INTEREST STATEMENT

Mohammad Safiqul Islam is an Editorial Board member of Health Science Reports and a co-author of this article. To minimize bias, he was excluded from all editorial decision-making related to the acceptance of this article for publication.

DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings of this study are available within the article [and/or] its supplementary materials.

TRANSPARENCY STATEMENT

The lead author Shahid Sarwar affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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