The Role of Matrix Metalloproteinase-9 (MMP-9) in Breast Cancer Progression, Histopathological Correlates and Tumor Microenvironment Dynamics: A Narrative Review

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Abstract. Breast cancer progression is shaped by reciprocal interactions among malig-nant cells, stroma, and immune cells. Matrix metalloproteinase-9 (MMP-9), also known as gelatinase B, degrades type IV collagen of the basement membrane and functions as a pleiotropic regulator of invasion, angiogenesis, epithelial–mesenchymal transition, and microenvironmental remodeling. This narrative review synthesizes evidence from ten observational studies (2018–2025) that assessed MMP-9 in breast cancer by immuno-histochemistry, quantitative immunofluorescence, histoscore-based analysis, or serum-based testing, with emphasis on histopathology, tumor micro-environment, and prognosis. Across the reviewed cohorts, higher MMP-9 expression was most consistently associated with aggressive features—higher histological grade, advanced pT stage, lymphovascular invasion, and hormone-receptor negativity. Stromal and macrophage-associated MMP-9 further implicated the tumor microenvironment, particularly in ER-negative and triple-negative disease. Prognostic findings were heterogeneous: some cohorts found no independent survival effect, whereas others reported shorter disease-specific survival or subgroup-specific risk. Overall, MMP-9 bridges aggressive histopathological phenotypes and a pro-metastatic microenvironment, representing a promising prognostic biomarker and candidate therapeutic target whose clinical translation awaits standardized assessment and prospective validation.

Keywords: Breast Cancer, Matrix Metalloproteinase-9, Tumor Microenvironment, Histopathology, Prognosis.

1 Introduction

Breast cancer (BC) is the most frequently diagnosed malignancy among women worldwide, ranking as the most prevalent cancer in 157 of 185 countries and accounting for an estimated 670,000 deaths in 2022 [1]. Although advances in screening have improved early detection, the global burden continues to rise, with breast cancer showing one of the largest recent increases in incidence [2]. Metastatic disease remains the principal cause of breast cancer mortality, responsible for more than 90% of cancer-related deaths [3]. Clinical management is further complicated by marked biological heterogeneity spanning four molecular subtypes—Luminal A, Luminal B, HER2-

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enriched, and triple-negative breast cancer (TNBC)—each with distinct clinical behavior and therapeutic response, with TNBC remaining the most aggressive [1,4]. In routine practice these subtypes are approximated by an immunohistochemical surrogate panel comprising ER, PR, HER2, and Ki-67. Conventional clinicopathological parameters such as tumor size and grade, while essential for treatment planning, are often insufficient to predict individual disease evolution, even in node-negative cases [5,6]. These limitations underscore the need for reliable molecular biomarkers to refine risk stratification and support precision oncology [7,8].

Breast cancer progression is increasingly recognized as a dynamic process driven by reciprocal interactions between malignant cells and the tumor microenvironment (TME) [4,7]. Central to this process is continuous remodeling of the extracellular matrix (ECM), which enables tumor cells to breach natural barriers, invade surrounding tissues, and establish distant colonies [2,9]. Among mediators of ECM degradation, MMP-9 (gelatinase B) has emerged as a critical proteolytic enzyme [9]. By degrading type IV collagen, the principal structural component of the basement membrane, MMP-9 facilitates local infiltration and systemic dissemination [8]. Beyond this structural role, MMP-9 is a pleiotropic regulator of angiogenesis, epithelial–mesenchymal transition (EMT), and pre-metastatic niche formation [3]. Consequently, elevated MMP-9 and associated factors such as PAI-1 and CYR61 have been linked to aggressive histopathology—high grade, lymphovascular invasion, and poor survival [2,10]—positioning MMP-9 as both a prognostic biomarker and a potential therapeutic target [1,6,8,9].

Despite this evidence, clinical application of MMP-9 remains limited by substantial heterogeneity across studies [7]. Variation in immunohistochemical scoring, detection methods, patient populations, and subtype distribution has produced inconsistent prognostic findings [4,6,9]. Most available studies are retrospective or cross-sectional, limiting causal inference, and the lack of standardized cutoff values together with differences between tissue-based and circulating measurements further complicates translation [2,3,6,10]. Current evidence therefore remains fragmented across histopathology, microenvironment dynamics, and clinical outcomes [5,8]. Accordingly, this narrative review critically synthesizes the role of MMP-9 in breast cancer progression by integrating histopathological findings, ECM remodeling, tumor microenvironment dynamics, and prognostic implications, and discusses current challenges and future perspectives for MMP-9 as a biomarker and therapeutic target in precision oncology.

Specifically, this review addresses three guiding questions: (i) how MMP-9 mediates extracellular matrix remodeling, invasion, and metastasis in breast cancer; (ii) how MMP-9 expression correlates with histopathological and molecular characteristics; and (iii) what its prognostic and therapeutic implications are within the tumor microenvironment. The objective is to provide an integrated synthesis that clarifies the biological and clinical significance of MMP-9 and informs future precision oncology strategies.

A structured literature search was performed in PubMed and Google Scholar for articles published between 2018 and 2025 (last searched July 2026), using combinations of the terms “MMP-9”, “matrix metalloproteinase-9”, “gelatinase B”,

"breast cancer", "histopathology", "tumor microenvironment", and "prognosis". Original observational studies assessing MMP-9 in human breast cancer by immunohistochemistry, quantitative immunofluorescence, histoscore-based analysis, or serum-based testing were considered eligible, whereas non-English articles, conference abstracts, and studies without histopathological or clinical correlation were excluded. Ten full-text studies met these criteria and form the evidence base synthesized in this narrative review (Fig. 1).

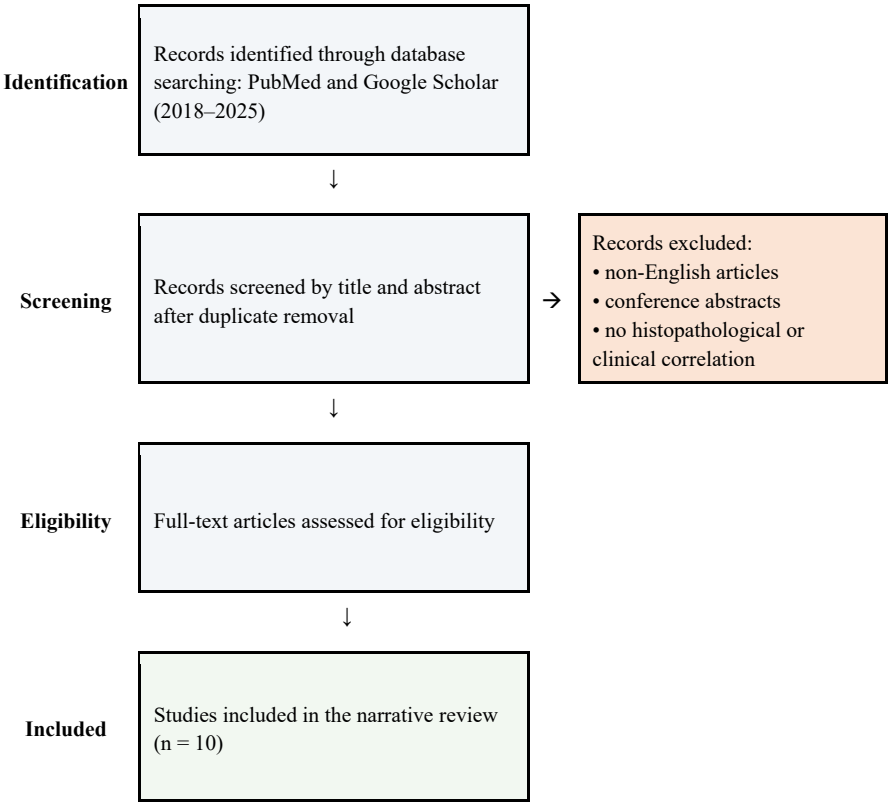


Fig. 1. Flow diagram of study identification and selection. Ten full-text observational studies met the eligibility criteria and were included in the narrative synthesis.

2 Breast Cancer Biology and the MMP Family

2.1 Breast Cancer Biology and Histopathological Progression

Breast cancer arises through the accumulation of genetic and epigenetic alterations that transform normal mammary epithelial cells into malignant cells capable of uncontrolled proliferation, invasion, and metastasis [2,7]. These changes may extend beyond the primary tumor, consistent with field cancerization, whereby histologically normal adjacent tissue can already harbor oncogenic alterations [2,6,9]. Clinically, the disease is commonly classified into four molecular subtypes based on immunohistochemical expression of estrogen receptor (ER), progesterone receptor (PR), HER2, and Ki-67 [3]. Luminal A tumors generally carry the most favorable prognosis, whereas Luminal B and HER2-positive tumors display greater proliferative activity; TNBC is the most aggressive subtype owing to high histological grade, early recurrence, and limited therapeutic options [1,5,8].

Histopathological progression typically evolves from ductal carcinoma in situ (DCIS) to invasive carcinoma through progressive loss of cell adhesion and acquisition of invasive properties [1,5,8]. Once tumor cells penetrate the basement membrane, they access surrounding stroma and may disseminate to distant organs through the metastatic cascade [4,10]. This transition requires extensive ECM remodeling, a process largely mediated by matrix metalloproteinases.

2.2 Matrix Metalloproteinases and MMP-9

Matrix metalloproteinases (MMPs) are a family of zinc-dependent endopeptidases responsible for ECM remodeling under both physiological and pathological conditions [2,7]. They regulate tissue repair, morphogenesis, and cell–matrix communication through controlled degradation of structural ECM proteins. MMP activity is tightly regulated by transcriptional control, proteolytic activation of latent proenzymes, and endogenous tissue inhibitors of metalloproteinases (TIMPs), maintaining ECM homeostasis under normal conditions [2,3,7].

Among the family, MMP-9 (gelatinase B) has attracted particular attention for its ability to degrade type IV collagen, the principal component of the basement membrane [6,10]. MMP-9 is synthesized as an inactive zymogen requiring extracellular proteolytic activation [1,3]. Its expression is induced by inflammatory cytokines and growth factors through NF-κB, AP-1, MAPK/ERK, and PI3K/Akt signaling, while its activity is primarily restrained by TIMP-1 [1,4]. Under physiological conditions, MMP-9 participates in tissue remodeling, wound healing, and angiogenesis [9]. In breast cancer, dysregulated MMP-9 promotes basement membrane degradation, ECM remodeling, and tumor-cell invasion, and additionally modulates angiogenesis, immune-cell recruitment, and stromal remodeling—placing it at the center of tumor–microenvironment interactions [5,6,7,10]. These properties provide the mechanistic basis for the sections that follow.

3 Molecular Role of MMP-9 in Breast Cancer Progression

3.1 ECM Remodeling and Tumor Invasion

The ECM and basement membrane maintain tissue architecture and regulate cellular adhesion, migration, and homeostasis [8]. During progression, this organized structure undergoes extensive remodeling that enables tumor cells to invade adjacent tissue [5,8]. As a gelatinase capable of degrading type IV collagen and other ECM components, MMP-9 is one of the principal enzymes responsible [3,5,8]. Basement membrane degradation marks the critical transition from non-invasive to invasive disease [5,8]: increased MMP-9 disrupts basement membrane integrity, facilitates infiltration into surrounding stroma, and enhances migratory capacity and local invasion [3,5,8]. Remodeling is further amplified by cancer-associated fibroblasts (CAFs), which actively produce MMP-9 [4,7]. Histopathological studies consistently show stronger MMP-9 expression at the invasive tumor front and in aggressive subtypes, underscoring its central role in local invasion [4,5,8].

3.2 Epithelial–Mesenchymal Transition and Angiogenesis

Beyond ECM degradation, MMP-9 promotes progression by facilitating EMT and angiogenesis, two processes that enhance invasion and metastatic potential [3,8]. During EMT, disruption of epithelial integrity reduces adhesion and increases motility, enabling invasion of adjacent tissue [3,8]. Elevated MMP-9 correlates with circulating tumor cells (CTCs), particularly those with mesenchymal characteristics, indicating a greater likelihood of systemic dissemination, most evident in aggressive subtypes including TNBC and HER2-positive disease [1,2,3]. MMP-9 also contributes to angiogenesis by remodeling the ECM and increasing the availability of matrix-bound pro-angiogenic factors; basement membrane degradation facilitates endothelial migration and neovessel formation required for sustained growth [6,7]. Continuous crosstalk among tumor cells, fibroblasts, and macrophages reinforces this pro-angiogenic milieu [4,7]. Together, EMT and angiogenesis are complementary mechanisms through which MMP-9 supports invasion and metastatic competence.

3.3 Metastatic Dissemination

Metastasis is the leading cause of breast cancer mortality, and accumulating evidence indicates that MMP-9 contributes to multiple stages of the metastatic cascade [8,10]. Following ECM and basement membrane degradation, elevated MMP-9 activity enhances local invasion and intravasation into blood and lymphatic vessels [3,5]. Clinical studies consistently associate high MMP-9 with advanced pathological stage, lymph node metastasis, and distant disease [5,9,10], and patients with metastatic disease generally exhibit higher tissue or circulating MMP-9 than those with localized tumors [2,10]. Elevated MMP-9 also correlates with shorter disease-free and breast cancer-specific survival, particularly in aggressive subtypes and tumors with extensive

stromal remodeling [7,8]. Although the mechanisms of metastatic colonization remain incompletely understood, current evidence identifies MMP-9 as an active mediator of progression rather than merely a marker of advanced disease [3,7,8].

4 Histopathological Evidence of MMP-9 Expression

4.1 Expression Patterns and Clinicopathological Correlations

MMP-9 is consistently overexpressed in invasive breast cancer relative to normal mammary tissue and benign lesions [5,8]. Immunohistochemistry shows weak or absent expression in normal epithelium and DCIS, whereas invasive carcinoma exhibits strong cytoplasmic staining in tumor cells together with prominent stromal expression [4,8]. MMP-9 is frequently localized within CAFs and tumor-associated macrophages (TAMs), reflecting active involvement in ECM remodeling and tumor–stroma interactions [7,8].

Across observational studies, elevated MMP-9 is associated with unfavorable features—higher histological grade, advanced stage, larger tumor size, lymphovascular invasion, and lymph node metastasis—with expression greatest at the invasive front [4,5,8,9]. Several studies, however, report no significant association with selected variables, likely reflecting differences in populations, scoring systems, and methodology [5,6]. Expression also varies by subtype: it is generally highest in TNBC and HER2-positive tumors, whereas findings in luminal cancers are inconsistent [1,2,3,4,7,8]. These observations indicate that the biological significance of MMP-9 is subtype-dependent and should be interpreted within the broader clinicopathological context. The major associations across the reviewed studies are summarized in Table 1.

Table 1. Histopathological associations between MMP-9 expression and breast cancer characteristics across the reviewed studies.

Histopathological Feature	Overall Evidence	Clinical Interpretation	Supporting Studies
Histological grade	Higher MMP-9 consistently associated with higher grade and poor differentiation.	More aggressive phenotype; greater invasive potential.	[5,8,9]
Pathological tumor stage (pT)	Increased MMP-9 frequently observed in advanced stage.	Progressive local growth and tissue invasion.	[3,8,10]
Lymphovascular invasion	Higher MMP-9 reported in tumors with LVI.	Enhanced metastatic capability via vascular spread.	[3,9]
Lymph node involvement	Associations reported, though not entirely consistent.	Possible regional spread; requires validation.	[6,10]
ER status	MMP-9 tends to be higher in ER-negative tumors.	Biologically aggressive disease; poorer prognosis.	[7,8]

Histopathological Feature	Overall Evidence	Clinical Interpretation	Supporting Studies
HER2 status	Elevated MMP-9 reported in HER2-positive tumors; heterogeneous.	Subtype-specific interactions needing further study.	[2,4]
Triple-negative (TNBC)	TNBC consistently shows high MMP-9 and stromal activity.	Marker of highly aggressive subtypes.	[1,7,8]
Proliferation (Ki-67)	MMP-9 positively associated with Ki-67 index.	Enhanced proliferative activity and aggressiveness.	[9]
Overall prognosis	High MMP-9 generally associated with poorer survival; varies.	Promising prognostic biomarker pending validation.	[3,7,8]

Collectively, these findings indicate that elevated MMP-9 expression marks a more aggressive breast cancer phenotype. Their prognostic significance is considered in the following subsection.

Because the reviewed studies applied heterogeneous scoring systems and cutoff values, direct numerical comparison of MMP-9 positivity across cohorts was not feasible; the individual studies and their principal findings are summarized in Table 2.

Table 2. Characteristics of the ten observational studies included in this narrative review. Abbreviations: BC, breast cancer; CTC, circulating tumour cell; IF, immunofluorescence; IHC, immunohistochemistry; TME, tumour microenvironment.

Study (year)	Ref.	Method / specimen	Molecular focus	Key finding relevant to this review
Hung et al. (2025)	[1]	Genotyping (MMP-9 polymorphisms)	TNBC	MMP-9 polymorphisms significantly associated with TNBC risk.
Karimova et al. (2025)	[2]	Serum (circulating MMP-9, CYR61)	HER2+/HER2−	Circulating MMP-9 and CYR61 differ by HER2 status.
Kalavska et al. (2021)	[3]	IHC (tumour cells) + CTC analysis	Mixed	Tumour-cell MMP-9 linked to tumour characteristics and CTCs.
Čamdžić et al. (2021)	[4]	IHC (stroma/TME)	All subtypes	TME MMP-9 varies with clinicopathological parameters and subtype.
Mohammadizadeh & Bagherian-Dehkordi (2021)	[5]	IHC	Invasive BC	MMP-9 related to selected clinicopathological prognostic factors.
Priyanka & Nandini (2024)	[6]	IHC (MMP-9, IL-8)	Node-negative BC	MMP-9/IL-8 explored in patients without lymph-node involvement.
Pelekanou et al. (2018)	[7]	Quantitative IF (CD68/CD163/MMP-9)	ER+ vs ER−	Macrophage MMP-9 co-localization predicts survival differently by ER status.

Study (year)	Ref.	Method / specimen	Molecular focus	Key finding relevant to this review
Joseph et al. (2020)	[8]	IHC (large cohort)	All subtypes	Elevated MMP9 is an independent predictor of shorter survival.
Trivedi et al. (2025)	[9]	IHC (MMP-9, Ki-67)	Invasive BC	MMP-9 correlates with Ki-67, tumour grade and stage.
Áleman et al. (2025)	[10]	Serum (fibrinolytic components, MMP-9)	Early vs metastatic	MMP-9 higher in metastatic than early-stage disease.

4.2 Prognostic Implications

Numerous studies support an association between elevated MMP-9 and poor outcomes. High expression within tumor cells and stromal compartments has been linked to shorter breast cancer-specific survival, increased recurrence risk, and reduced disease-free survival, particularly in TNBC and HER2-positive disease [3,8]. Stromal MMP-9—especially within TAMs—has also been associated with adverse prognosis, highlighting the microenvironment's contribution to progression [7,8].

Nevertheless, the independent prognostic value of MMP-9 is inconsistent. In some cohorts, significance diminishes after adjustment for established factors such as stage, grade, and age [7], whereas others identify cytoplasmic MMP-9 as an independent predictor of shorter survival [8]. Variability in scoring methods, differences in tissue sampling, and the inability of conventional assays to distinguish active MMP-9 from inactive pro-MMP-9 contribute substantially to this heterogeneity [3,5,7]. Overall, MMP-9 is a promising histopathological marker of aggressiveness whose role as an independent prognostic marker remains inconclusive, pending standardized assessment, prospective validation, and subtype-specific analysis.

5 MMP-9 in the Tumor Microenvironment

5.1 Stromal and Immune Cell Interactions

MMP-9 is a key regulator of communication between tumor cells and the TME, coordinating interactions that promote progression [7,8]. Beyond ECM degradation, it is produced by multiple stromal populations—CAFs, TAMs, and infiltrating immune cells—sustaining a proteolytic microenvironment that favors invasion [4,7,8]. CAFs contribute to remodeling through MMP-9 production and promote invasion by modifying the surrounding stroma [4,8], while TAMs, particularly the CD68+/CD163+ phenotype, exhibit high MMP-9 and associate with poor outcomes [7]. MMP-9 also shapes the immune landscape: increased expression accompanies macrophage infiltration and an immunosuppressive milieu, suggesting a role in immune evasion [7,8]. Together, these stromal and immune interactions establish a permissive environment supporting growth, invasion, and dissemination [4,7,8].

5.2 Therapeutic Implications Within the Microenvironment

Recognition of the central role of MMP-9 has shifted therapeutic interest from broad-spectrum MMP inhibition toward selective strategies targeting MMP-9 and its stromal interactions [7,8]. Selective inhibition is expected to preserve the physiological functions of other MMPs while reducing toxicity. Because MMP-9 is highly expressed in CAFs and TAMs, stromal-targeted approaches may disrupt reciprocal signaling and limit remodeling [7], and its association with immune-cell infiltration suggests that modulating MMP-9 could complement immunotherapy [7]. Although MMP-9-targeted therapies remain investigational, current evidence supports their potential within precision oncology, particularly for aggressive subtypes with high MMP-9 [1,7,8].

6 Clinical Implications and Future Perspectives

6.1 Clinical Implications

MMP-9 has considerable potential as a biomarker for diagnosis, prognostic assessment, and risk stratification [2,8,10]. Increased tissue and circulating levels are consistently associated with malignant disease and are generally higher in advanced-stage than localized disease [9,10], suggesting MMP-9 may complement conventional evaluation, though diagnostic performance is not yet validated for routine use [7,10]. As a prognostic marker, elevated expression in tumor and stromal compartments is frequently associated with adverse features, shorter disease-free survival, and poorer breast cancer-specific survival, especially in TNBC and HER2-positive disease [3,6,8]. Integrating MMP-9 with established indicators—grade, stage, hormone-receptor status, and Ki-67—may improve identification of high-risk patients [6,8,9]. However, most studies are retrospective and methodologically heterogeneous, so prospective validation is required before routine implementation [3,4,6,7,10].

6.2 Future Perspectives

Future research should address the methodological limitations that hinder translation. A priority is developing standardized methods that distinguish biologically active MMP-9 from its inactive precursor, since conventional immunohistochemistry measures protein expression rather than enzymatic activity [3,8]. Standardized scoring and multicenter prospective studies are needed to establish meaningful cutoff values and improve reproducibility [6,7,10]. MMP-9 should be integrated into multimarker panels rather than evaluated alone [2,6,7], and advances in digital pathology and AI-assisted image analysis may provide objective assessment of its spatial distribution within the TME [7]. Therapeutically, interest has shifted toward selective MMP-9 inhibition, and future studies should examine its combination with existing targeted therapies and immunotherapy to overcome resistance in aggressive subtypes [3,7]. Although investigational, these strategies represent an important step toward translating biological knowledge into clinical practice.

7 Conclusion

This review positions MMP-9 as an important contributor to breast cancer progression through ECM remodeling, tumor invasion, and metastatic dissemination. By degrading basement membrane components, particularly type IV collagen, MMP-9 facilitates tumor-cell migration while reshaping the microenvironment through dynamic interactions with CAFs and TAMs. Elevated expression is consistently associated with aggressive clinicopathological features—higher grade, advanced stage, lymphovascular invasion, and unfavorable subtypes such as TNBC and HER2-positive disease—and MMP-9 additionally promotes EMT, angiogenesis, and immune modulation across multiple stages of progression. These findings support its potential as both a prognostic biomarker and a therapeutic target. Nevertheless, current knowledge remains insufficient for routine implementation: most studies are retrospective and heterogeneous, and conventional methods reflect protein expression rather than enzymatic activity. Future multicenter prospective studies, standardized protocols, and integration into multimarker precision oncology frameworks are essential to translate current evidence into clinically applicable strategies.

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