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ORIGINAL STUDY

MMP-7 Expression and rs11225307 Polymorphism in Breast Cancer and Fibroadenoma: A Molecular Study in Basrah, Iraq

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ABSTRACT

Breast cancer (BC) progression relies heavily on extracellular matrix degradation, mediated in part by matrix metalloproteinase-7 (MMP-7). While overexpression of MMP-7 has been implicated in multiple cancers, data from Middle Eastern populations remain limited.

This study examined MMP-7 gene expression and polymorphism patterns, with emphasis on rs11225307, in breast cancer versus benign fibroadenoma (FA) tissues among women in Basrah, Iraq. Thirty-seven BC and twenty-three FA patients were enrolled. MMP-7 mRNA expression was quantified using qRT-PCR and normalized to β-actin, while polymorphisms were analyzed through Sanger sequencing of eight SNPs and allele-specific PCR for rs11225307. Statistical significance was set at $p < 0.05$.

MMP-7 expression was significantly upregulated in BC tissues, showing a 4.4-fold increase compared to FA ($\Delta\Delta$Ct, $p < 0.05$). Sequencing revealed monomorphic wild-type genotypes across eight SNP sites. However, rs11225307 exhibited polymorphism, with allele frequencies of A (86%) and C (14%) and genotype distributions of AA (74%), AC (24%), and CC (2%). No significant association was observed between MMP-7 expression and tumor grade.

Conclusion: Elevated MMP-7 expression is a distinguishing molecular feature of breast cancer compared to fibroadenoma in this Iraqi cohort, supporting its role as a marker of tumor aggressiveness. While most tested SNPs were conserved, rs11225307 showed polymorphic variation, warranting further investigation into its prognostic significance. These findings reinforce MMP-7 as a promising biomarker and potential therapeutic target in breast cancer.

Keywords: Breast cancer, Fibroadenoma, MMP-7, Gene expression, Polymorphism, rs11225307, Basrah, Fold-change, Genotype frequencies

1. Introduction

Breast cancer remains the most prevalent malignancy among women worldwide and a leading cause of cancer mortality, Metastasis accounts for the great majority of breast cancer fatalities [1].

Breast cancer is the most common cancer among Iraqi females. There were 8,708 cases among females. Represented 34.8% of all cancer cases diagnosed among females. The five governorates with the highest ASR were Erbil 92.3/100,000, followed by Baghdad with 83.8/100,000, then Karbala with 80/100,000, Al-Najaf with 71.4/100,000 and Al-Basrah with 69/100,000 [2, 3].

One worrying trend in recent years has been the rise in cancer rates in Iraq. Approximately two-thirds of

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all cancer fatalities occur in low- and middle-income countries (LMICs), where the burden of cancer is rising. This may be explained by rising life expectancy along with shifting trends in behavioral risk factors—such as alcohol and tobacco use, obesity, physical inactivity, and poor diet—that are linked to an increased risk of non-communicable diseases. [4].

The incidence rate of breast cancer is estimated to reach 3.2 million by 2050. Lifetime risk of developing breast cancer in every woman in the United States is 12.4% or one in eight women [5].

The etiology of breast cancer may entail a combination of environmental and genetic risk factors. Numerous population studies show that genetic variables, such as gene polymorphisms and the existence of mutations may be significant risk factors that impact each person's unique susceptibility to breast cancer. [6, 7]. Central to the aggressive behavior of malignant tumors is their ability to invade surrounding tissues and metastasize to distant sites. This process is heavily reliant on the degradation of the extracellular matrix (ECM), a function primarily attributed to a family of zinc-dependent endopeptidases known as matrix metalloproteinases (MMPs) [8, 9]. Among the diverse MMP family, Matrix Metalloproteinase-7 (MMP-7), also known as matrilysin-1, stands out due to its unique structural features and broad substrate specificity. Unlike many other MMPs, MMP-7 lacks a C-terminal hemopexin domain, making it the smallest secreted MMP. Its substrates include proteoglycans, fibronectin, elastin, and various collagens, contributing to ECM remodeling. MMP-7 is a downstream target gene of the canonical Wnt/β-catenin pathway, which is crucial for cell growth, differentiation, and metastasis. Activation of this pathway leads to β-catenin translocation to the nucleus, where it induces transcription of target genes including cyclin D1, c-Myc, and MMP-7 itself. Dysregulation of Wnt/β-catenin enhances MMP-7 expression, promoting tumor invasion and metastasis [10].

Normally, E-cadherin binds β-catenin at the cell membrane, sequestering it and limiting its availability for Wnt signaling. Cleavage or downregulation of E-cadherin releases β-catenin, increasing its cytoplasmic and nuclear levels, thereby activating Wnt target gene expression, including MMP-7, creating a positive feedback loop that supports cancer cell proliferation and metastasis [11].

Beyond ECM degradation, MMP-7 is implicated in a range of cellular processes, including cell adhesion, apoptosis, and angiogenesis, all of which are critical in tumor development and progression. Its widespread expression in epithelial cells of various organs, including the breast, liver, intestine, and reproductive organs, further highlights its potential involvement in both normal tissue homeostasis and disease states [8, 9].

MMP-7 exhibits broad substrate specificity against a variety of non-ECM molecules, such as insulin-like growth factor binding proteins (IGFBPs), heparin-binding epidermal growth factor (HB-EGF), and Fas ligand, as well as ECM components like elastin, proteoglycans, fibronectin, type IV collagen, and E-cadherin [12].

Best known as a contributor to tumor invasion and metastasis, a growing body of evidence also implicates MMP-7 in earlier stages of tumorigenesis, including cellular transformation, cell survival, tumor growth, angiogenesis, and evasion of immune surveillance [13].

Both the ductal and glandular epithelium of the breast usually express MMP-7, and breast carcinomas have been shown to express it at noticeably higher levels than nearby non-tumor tissues. Numerous additional malignancies, such as those of the esophagus, stomach, pancreatic, lung, and colon/rectum, have also been linked to MMP-7 overexpression [14].

Overexpression of MMP-7 has been associated with increased tumor aggressiveness, poor prognosis, lymph node metastasis, and resistance to therapy in various cancers, including breast cancer, the transcriptional level is the primary regulator of MMP-7 expression. Despite extensive studies on matrix metalloproteinase-7 (MMP-7), molecular data from Middle Eastern populations, particularly Iraq, remain sparse [15–17].

Previous research has consistently demonstrated elevated MMP-7 protein levels in numerous human cancer tissues, including gastric, pancreatic, colorectal, esophageal, and ovarian cancers. This upregulation often correlates with tumor invasion and metastasis, cementing MMP-7's reputation as a key player in oncogenesis. However, its specific role and expression patterns in breast cancer, particularly in comparison to benign breast conditions like fibroadenoma, warrant deeper investigation. While some studies suggest MMP-7's involvement in breast cancer progression, contradictory data exist, indicating the need for a more comprehensive analysis.

Genetic variations such as single nucleotide polymorphisms (SNPs) in the MMP-7 gene may influence its expression and activity, potentially affecting breast cancer susceptibility and progression. Elevated MMP-7 expression associates strongly with tumor progression and metastasis in diverse ethnic cohorts; however, the precise polymorphic variations influencing MMP-7 activity and their clinical relevance in Iraqi breast cancer patients have not been thoroughly elucidated [18–20].

Benign breast tumors like fibroadenomas (FA) differ pathologically and molecularly from malignant breast cancers, often exhibiting lower proliferative and invasive capacities. Understanding molecular distinctions, including MMP-7 expression and polymorphisms, may provide insights into tumor biology and improve diagnostic accuracy [20].

This study aims to investigate the expression level of the MMP-7 gene in breast cancer versus fibroadenoma tissues, assess the frequency of significant polymorphisms in the MMP-7 gene, and explore their possible impact on breast tumor characteristics in a population from Basrah, Iraq because some SNPs in MMP-7 have been linked to increased enzyme activity or altered expression, which may influence cancer aggressiveness. Our study uniquely addresses this critical gap by investigating both the expression levels and polymorphic variations of MMP-7, with particular emphasis on the rs11225307 SNP, in breast cancer compared to benign fibroadenoma tissues within a Basrah, Iraq cohort. This dual molecular and genetic characterization provides novel insights into the tumor biology exclusive to this population and lays foundational groundwork for potential diagnostic and therapeutic innovations tailored to regional genetic contexts.

2. Materials and methods

2.1. Patient cohort and sample collection

Tissue and blood samples were collected from a carefully selected cohort of patients diagnosed with either breast carcinoma or fibroadenoma. All participants provided informed consent, and the study adhered to ethical guidelines for human research.

2.2. Study population

A cross-sectional study was conducted involving 37 female patients with newly diagnosed primary breast cancer (BC) (before any treatment), 23 patients diagnosed with benign fibroadenoma (FA) their age ranged from (16–78) years old. Tissue samples (fresh tissue and FFPE) and peripheral blood samples were collected from BC and FA patients at Basrah Teaching Hospital and private laboratories between April 2024 and February 2025. All the involved patients from Basrah city, non of them were smoker.

Histopathological examination of all patients with BC revealed invasive ductal carcinoma (IDC) 20 with in grade 2 and 17 within grade 3.

2.3. Inclusion criteria

- patients with newly diagnosed primary breast cancer (Not receiving any treatment yet)
- patient with fibroadenoma

2.4. Exclusion criteria (for both BC and FA patients)

- Recurrent or metastasis breast tumor,
- other malignancy
- Autoimmune disease
- Patient on chemotherapy or biological therapy or steroid
- pregnant female

2.5. Sample collection and processing

Tissue Samples: Fresh tumor and benign tissues were collected, preserved in RNA later solution to stabilize RNA, and stored at 4°C before RNA extraction. For FFBE, tissue blocks sectioned using a microtome fitted with a sterilized blade to prevent cross-contamination. Sections of 5 micrometers in thickness were obtained and placed into 1.5 mL Eppendorf tubes, with each tube containing a total of 200–400 micrometers of tissue. These samples were subsequently stored at –4 °C to maintain sample integrity prior to gene expression analysis [21].

Blood Samples: Venous blood samples were collected in EDTA tubes were used for genomic DNA extraction as in [22].

2.6. RNA extraction and qRT-PCR for MMP-7 gene expression

Total RNA was extracted using the Vivantis Technologies Sdn Bhd kit (Malysia) kit following manufacturer protocols. RNA quality and concentration were measured by NanoDrop spectrophotometer. The RNA sample is first subjected to reverse transcription to synthesize complementary DNA (cDNA) by using 5x RT Master Mix supplied by Tinzyme Co., Limited (China). The process includes an initial incubation step at 42 °C for 15 minutes to allow the reverse transcriptase enzyme to synthesize cDNA from the RNA template. This is followed by a heat inactivation step at 85 °C for 5 seconds to terminate the enzyme activity and stabilize the synthesized cDNA. The resulting cDNA samples were kept for further examination at –20 °C.

Quantitative real-time PCR (qRT-PCR) was performed by Macrogen Real-Time PCR Master Mix Kit with SYBR Green dye using specific forward and reverse primers for MMP-7 as in Kumar et al. [23].

β-actin, a housekeeping gene, served as an internal gene for normalization. The qRT-PCR amplification procedure involved the following steps: Initial Denaturation: The reaction mixture was first heated to 95 °C for 15 second, Denaturation: Each cycle started with denaturation at 95 °C for 15 seconds, denaturation at 95 °C for 15 seconds , annealing: the temperature was then lowered to 60 °C for 60 seconds , extension: Finally, at 72 °C for 60 seconds, the DNA polymerase extended the primers to synthesize the new DNA strands. This cyclic process was repeated 40 times. The Ct evaluations for the target gene as well as for the housekeeping gene (ß- actin), were performed automatically by the instrumental default framework. The expression levels of MMP7 gene was relatively quantified using (ß- actin) as a housekeeping gene (HK) to normalize the data. The ΔΔCT method by (Livak & Schmittgen [24].

2.7. DNA extraction and genotyping for polymorphism analysis

Genomic DNA was extracted from whole blood using Geneaid (Genomic DNA extraction Kit (Taiwan). Eight SNPs (rs2496458918, rs1858692543, rs12289049, rs1858692655, rs2496458877, rs781157070, rs370692111, rs900569423) were screened by PCR amplification with a pair of primers designed by this study as in "Table 1", PCR product size was (564 bp fragment) which detected by 1.5% agarose gel electrophoresis followed by Sanger sequencing. Another SNP (rs11225307) was genotyped as in Fig. 6 using allele-specific PCR as in [25] with primers designed by this study for selective amplification of the A and C alleles as in "Table 1". PCR amplification protocol as following: Initial Denaturation (95 °C for 5 minutes, 1 time), Denaturation (95 °C for 30 seconds, repeated 35 cycles), Annealing (55–58 ° C for 40 seconds, repeated 35 cycles), Extension (72 °C for 45 seconds, repeated 35 cycles), Final Extension (72 °C for 10 minutes, 1 time):

2.8. Statistical analysis

SPSS version 26 was used for statistical analysis. The Shapiro-Wilk test used to assess whether a data sample comes from a normally distributed population p-value is less than 0.05 which indicated the data are not normally distributed. Gene expression differences between BC and FA groups were analyzed using the Mann–Whitney U test. Genotype and allele frequencies were calculated, and Hardy-Weinberg equilibrium (HWE) was assessed by comparing the observed and expected genotype frequencies ($\chi 2$ test) for the cases of BC. Statistical significance was accepted at $p < 0.05$.

3. Results and discussion

The mean age of BC patients was 45 years (range 27–76), while the FA group had a mean age of 35.3 years (range 16–51) as in Fig. 1. BC tumor grade was nearly evenly distributed: Grade II (54.1%), Grade III (45.9%) as in Fig. 2. Quantitative RT-PCR analysis showed that MMP-7 mRNA expression was significantly elevated in breast cancer tissues compared to fibroadenoma as in Fig. 3. The median fold change in MMP-7 expression reached 4.4-fold in the breast cancer group versus the fibroadenoma group, with

Table 1. Primers for *MMP-7* gene polymorphism (designed by this study).

Gene	Technique	Product size (bp)	Annealing Temperature	Primer name	Oligonucleotide sequence (5'-3')
MMP7	Sequencing For 8 SNPs: rs2496458918 rs1858692543 rs12289049 rs1858692655 rs2496458877 rs781157070 rs370692111 rs900569423	564 bp	58 C	MmpF MmpR	TTTCTTACCTCCTCGCGCAAA GAATTCACAGGAACCAAAGGCAA
	Allele Specific for: (rs11225307) SNP	423 bp 284 bp 195 bp	55 C	MmpF-out MmpR-out Allele A AlleleC common reverse primer	TAGCAACAGGTCATATACCACTTCTCAG TCATAGAATACACTTACACAAACCCAGG GCAAGTATTTGTGTGTCTAAACGCAT GCTCAATACATTACCTTTTCAATGTTTGAC CTTCCCAAACTCC

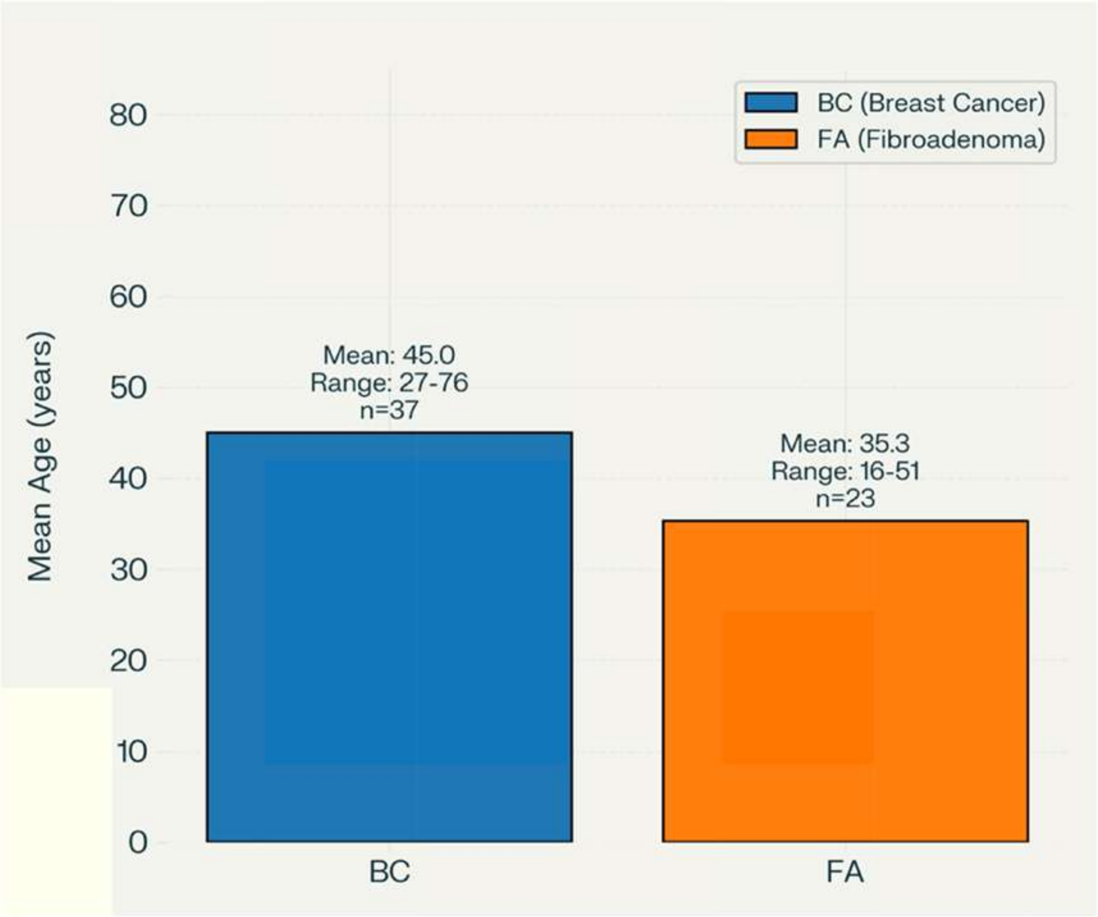

Fig. 1. Age mean of the study groups. Bar graph showing the mean age of patients diagnosed with breast cancer (BC; mean = 45 years, range = 27–76) and benign fibroadenoma (FA; mean = 35.3 years, range = 16–51). Error bars represent standard deviation. BC: breast cancer; FA: fibroadenoma. The age difference highlights the demographic characteristics of both cohorts.

a p-value less than 0.05 indicating statistical significance as in Fig. 4. This upregulation is consistent with previous reports, which found fold changes ranging from 2.5 to 5.0 with $p < 0.01$ in breast and colorectal cancers (Sizemore et al., 2014; Beeghly-Fadiel et al., 2009).

Genotyping for the MMP-7 rs11225307 SNP in breast cancer patients displayed genotype frequencies of 74% for AA, 24% for AC, and 2% for CC genotypes, while allele frequencies were 86% (A) and 14% (C) as in Tables 4 and 5. The genotype distribution was consistent with Hardy-Weinberg equilibrium ($p = 0.94$), supporting the validity of the observed distribution as in Table 3. Comparable frequencies for major and minor alleles have been reported in breast cancer genomic studies.

Matrix metalloproteinase-7 (MMP-7) plays a critical role in the progression of breast cancer primarily through its capacity to degrade extracellular matrix components, thereby facilitating tumor invasion and metastasis. This study's finding of a significant 4.4-fold upregulation of MMP-7 gene expression in breast cancer tissues compared to fibroadenoma aligns well with current literature that underscores MMP-7 as a key contributor to malignant transformation and cancer aggressiveness. Recent studies have expanded our understanding of MMP-7's multifaceted role not only in extracellular matrix remodeling but also in modulating cellular adhesion, apoptosis, and angiogenesis, processes essential to tumorigenesis and metastatic cascade [28–31].

The overexpression of MMP-7 observed here corroborates findings from regional and global cohorts [32, 33], emphasizing its potential utility as a molecular marker to distinguish malignant breast tumors from benign lesions such as fibroadenoma [34].

In Fibroadenoma the Wnt pathway is typically inactive. β-catenin is bound in a destruction complex and targeted for degradation. It does not enter the nucleus.

In Carcinoma: Mutations in key genes (e.g., in APC or β-catenin itself) or upstream Wnt signaling lead to β-catenin stabilization and nuclear translocation [35].

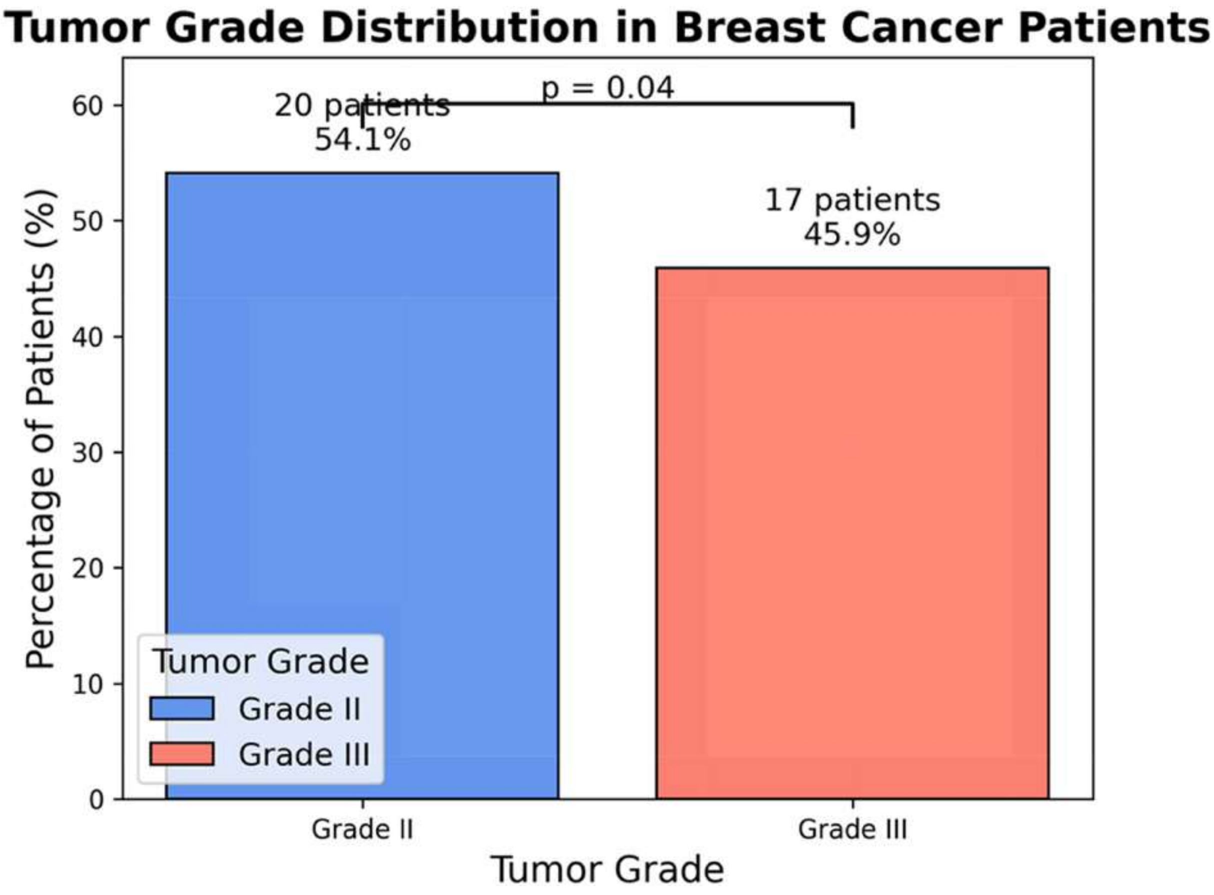

Fig. 2. Distribution of BC patients based on grade of the tumor. Bar chart indicating the histological grades of breast cancer (BC) patients included in the study. Tumor grades were distributed as follows: Grade II (20 cases, 54.1%) and Grade III (17 cases, 45.9%). These grades reflect tumor differentiation and aggressiveness. BC: breast cancer**.**

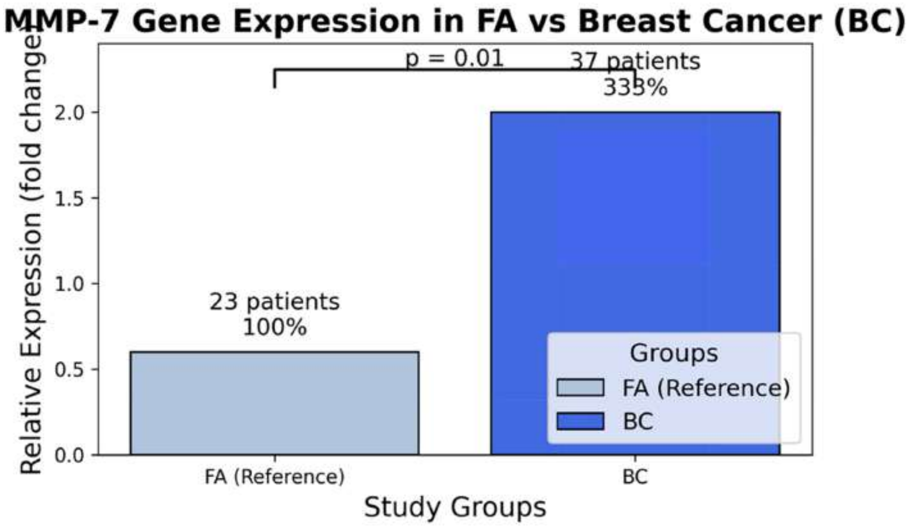

Fig. 3. Relative Expression Levels of MMP-7 mRNA in Breast Cancer and Fibroadenoma Tissues. Bar graph showing quantitative real-time PCR analysis of MMP-7 mRNA in breast cancer (BC) and fibroadenoma (FA) tissue samples. Expression was normalized to the β-actin housekeeping gene. BC samples exhibited a 4.4-fold increase in MMP-7 transcript levels compared to FA (p < 0.05 $p < 0.05$). Error bars indicate interquartile range. BC: breast cancer; FA: fibroadenoma; MMP-7: matrix metalloproteinase-7.

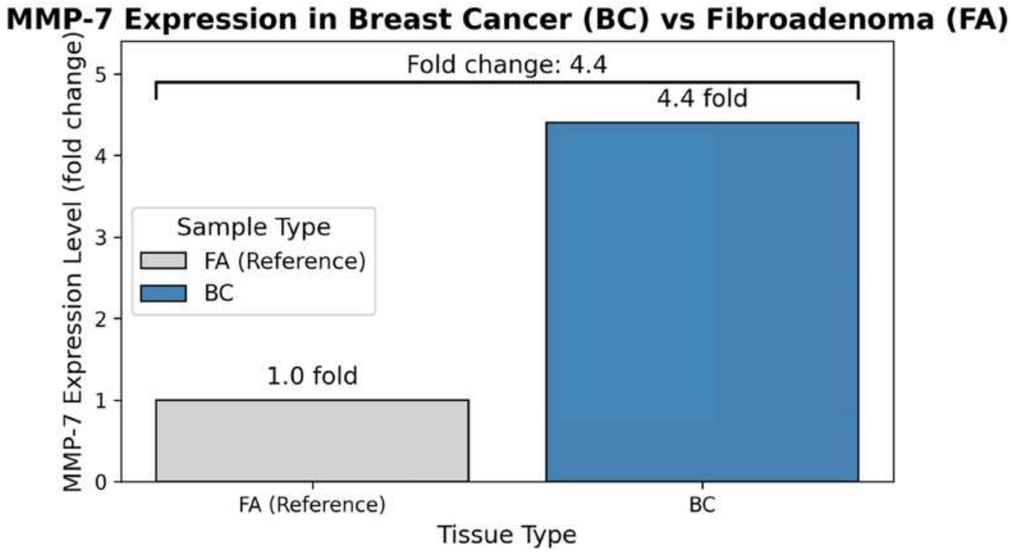

Fig. 4. *MMP-7* fold change analysis in BC and FA samples. The bar graph presents the relative fold change in MMP-7 gene expression between breast cancer (BC) and fibroadenoma (FA) tissues. Expression values were calculated using the $\Delta\Delta$Ct method, with normalization to β-actin. The BC group showed a statistically significant 4.4-fold higher MMP-7 expression (p < 0.05 $p < 0.05$, Mann–Whitney U test), reinforcing the association of MMP-7 with malignancy.

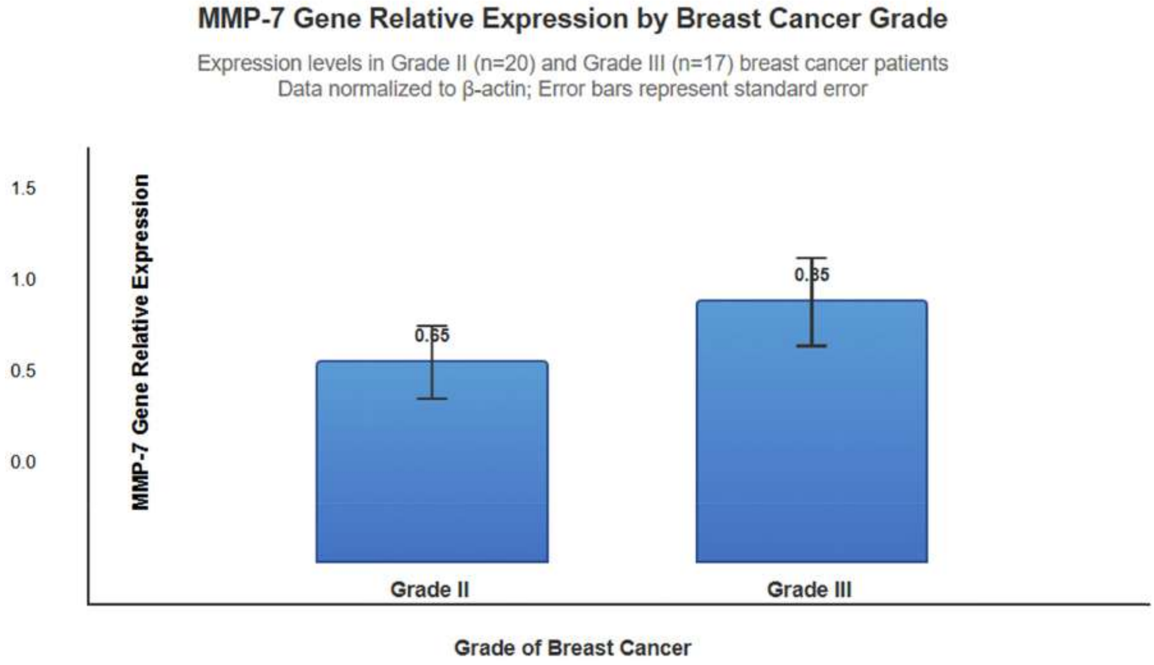

Fig. 5. The relation of Relative Expression of *MMP-7* gene to the tumor grade in BC patients. Boxplot depicts MMP-7 mRNA expression levels, as measured by qRT-PCR, stratified by histological tumor grade: Grade II ($n = 20$) and Grade III ($n = 17$) among breast cancer (BC) patients. No statistically significant difference was found between grades (p > 0.05 $p > 0.05$), suggesting that MMP-7 expression may be independent of histological grade. BC: breast cancer; MMP-7: matrix metalloproteinase-7.

Mechanistically, MMP-7 expression is driven by oncogenic signaling pathways, including the Wnt/β-catenin cascade, which is often aberrantly activated in carcinoma but remains inactive in benign breast tissue. Moreover, inflammatory cytokines prevalent in the tumor microenvironment, such as TNF-α and IL-1β, contribute to sustained MMP-7 induction via NF-κB and AP-1 transcription factors, creating a pro-invasive milieu absent in fibroadenomas [36–38] This chronic inflammatory signaling axis likely accounts for the pronounced MMP-7 expression in malignant tissues [39]

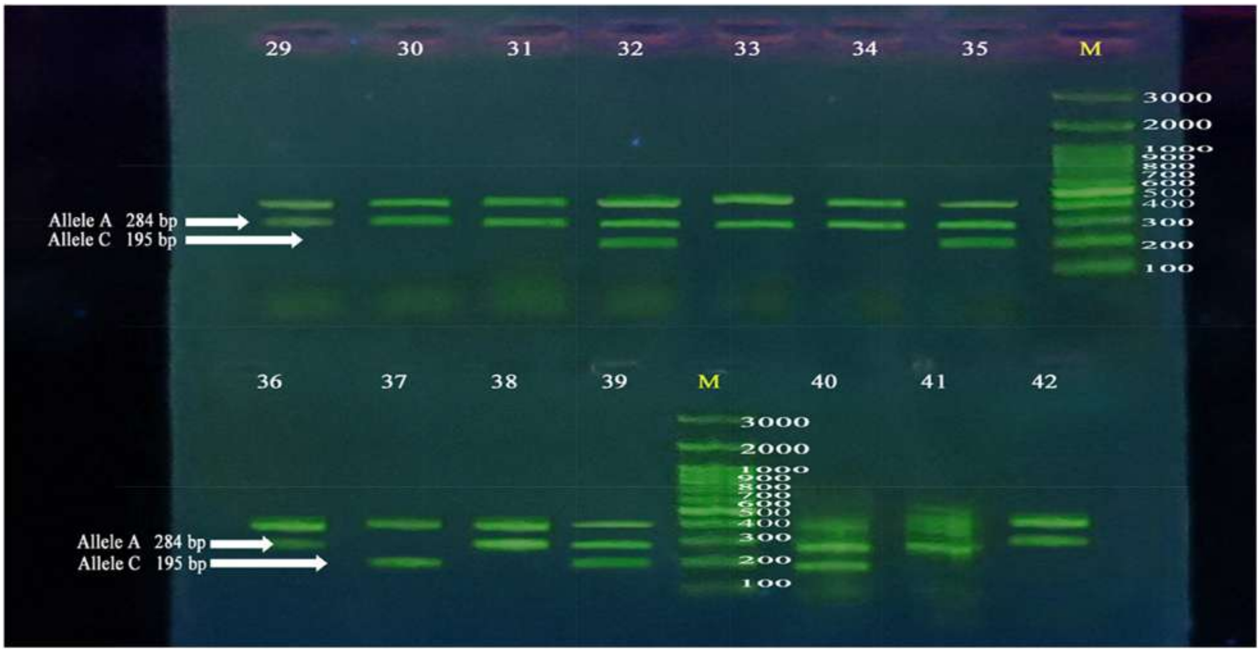

Fig. 6. Agarose Gel Electrophoresis for *MMP7* Gene (423 & 284 & 195 bp) for Allele specific ((rs11225307) SNP) Representative agarose gel image demonstrates allele-specific PCR results for MMP-7 rs11225307 SNP. Lanes show: AA genotype (284 bp band + 423 bp control), AC genotype (284 bp, 195 bp, and 423 bp bands), and CC genotype (195 bp band + 423 bp control). Genotype frequencies were AA (74%), AC (24%), and CC (2%), with allele frequencies of A (86%) and C (14%). SNP: single nucleotide polymorphism; PCR: polymerase chain reaction.

Table 2. Polymorphism frequency for *MMP7* Gene (for 8 SNPs) resulting by sequencing.

Group	Polymorphism	No.	Polymorphism frequency	Allele	Allele frequency	Chi Square
rs2496458918	TT	50	1.0	T	1.0	\
	TC	0	0.0	C	0.0	
	CC	0	0.0			
rs1858692543	AA	50	1.0	A	1.0	\
	AT	0	0.0	T	0.0	
	TT	0	0.0			
rs12289049	TT	50	1.0	T	1.0	\
	TC	0	0.0	C	0.0	
	CC	0	0.0			
rs1858692655	CC	50	1.0	C	1.0	\
	CA	0	0.0	A	0.0	
	AA	0	0.0			
rs2496458877	TT	50	1.0		1.0	\
	TC	0	0.0		0.0	
	CC	0	0.0			
rs781157070	GG	50	1.0	G	1.0	\
	GA	0	0.0	A	0.0	
	AA	0	0.0			
rs370692111	TT	50	1.0	T	1.0	\
	TA	0	0.0	A	0.0	
	AA	0	0.0			
rs900569423	CC	50	1.0	C	1.0	
	CG	0	0.0	G	0.0	
	GG	0	0.0			

In contrast to some studies reporting associations between MMP-7 expression and higher tumor grade, this study did not detect significant differences between grades II and III as in Fig. 5 [40, 41]. This discrepancy may reflect sample size limitations or tumor heterogeneity, suggesting that MMP-7's role as a biomarker may be independent of histopathological grade. Interestingly, while the eight screened SNPs in

Table 3. Polymorphism frequency & Allele frequency for *MMP7* Gene (rs11225307 SNP) analyzed by Allele specific for detection of The Hardy-Weinberg equilibrium.

Group	Polymorphism	No.	Polymorphism frequency	Allele	Allele frequency	Chi Square
rs11225307	AA	37	0.74	A	0.86	0.00055
	AC	12	0.24	C	0.14	
Allele specific	CC	1	0.02			

Table 4. Genotypes frequency for MMP7 Gene (rs11225307 SNP) analyzed by Allele specific.

genotypes	Count	Frequency	Percentage (%)
AA	37	0.74	74%
AC	12	0.24	24%
CC	1	0.02	2%
Total	50		100%

Table 5. Alleles frequency for MMP7 Gene (rs11225307 SNP) analyzed by Allele specific.

Allele	Count	Frequency	Percentage (%)
A	86	0.86	86%
C	14	0.14	14%

the MMP-7 gene were monomorphic in this Iraqi cohort, polymorphism at rs11225307 was evident and merits as in Table 2 further functional exploration. Prior reports indicate that rs11225307 and similar polymorphisms can modulate breast cancer prognosis, potentially by influencing MMP-7 transcriptional activity or enzyme function, thereby altering tumor behavior and patient outcomes [27].

The absence of high-risk SNP variants herein suggests that gene expression changes and tumor microenvironment factors predominantly drive MMP-7-mediated tumor progression in this population. This highlights the importance of integrated molecular and genetic analyses to unravel the complexities of breast cancer biology. Furthermore, the protective associations attributed to some polymorphisms including rs11225307 may offer promising avenues for personalized prognostication and targeted therapies.

Future research should encompass larger cohorts with multi-omics strategies to validate these findings and elucidate the precise molecular mechanisms underlying MMP-7's oncogenic impact. Functional assays investigating rs11225307 are particularly warranted to understand its regulatory influence and potential as a therapeutic target. Collectively, these updated insights strengthen the case for MMP-7 as a valuable biomarker and possible intervention point in breast cancer management.

Based on recent studies (2023–2025), the role of MMP-7 in breast cancer continues to be strengthened as a significant biomarker and therapeutic target. Recent research indicates that MMP-7 levels in plasma are markedly elevated in early-stage endometrial and breast cancers, underscoring its importance in tumor progression [42] Its involvement encompasses not only ECM degradation but also intracellular signaling pathways that promote proliferation, invasion, and metastasis [8, 42].

Further, studies utilizing complex network analysis of tumor microenvironments [43] highlight MMP-7's extensive interactions within the tumor microenvironment, implicating it in facilitating intricate pathways of tumor growth and immune evasion. These findings support the therapeutic potential of MMP-7 inhibition, which has been shown to reduce tumor invasiveness and improve prognosis in experimental models [44].

Additionally, recent biomarkers studies suggest that plasma MMP-7, alone or in combination with markers like CA125, shows higher diagnostic specificity in early-stage cancers compared to traditional markers such as CA125 alone models [42]. Such advancements advocate for further validation of MMP-7 as a minimally invasive diagnostic and prognostic tool, aiding early detection and treatment monitoring.

Collectively, these findings align with broader evidence positioning MMP-7 as a promising diagnostic and prognostic biomarker. Moreover, they highlight the need for functional studies elucidating rs11225307's mechanistic influence on MMP-7 activity and its potential as a therapeutic target. Future research expanding cohort sizes and integrating multi-omics approaches could deepen insight into MMP-7's multifaceted role in breast cancer biology and management.

4. Conclusion

The elevated expression of MMP7 in breast carcinoma is a hallmark of its invasive phenotype. It is structurally necessitated by the need to break down tissue boundaries and is molecularly driven by a convergence of deregulated oncogenic pathways (especially Wnt/β-catenin) and pro-inflammatory signals from the tumor microenvironment. In contrast, the benign, non-invasive, and genetically stable nature of a fibroadenoma means these powerful inductive signals are absent, resulting in minimal MMP7 expression. Therefore, detecting high levels of MMP7 serves as a molecular marker distinguishing a dangerous, invasive cancer from a harmless, self-limited benign tumor. Although most studied MMP-7 SNPs were monomorphic in this Iraqi population, the rs11225307 polymorphism is present and requires further evaluation. MMP-7 represents a promising molecular biomarker and potential therapeutic target for breast cancer management. Future studies should explore the functional impact of rs11225307 and expanded cohorts for validation.

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Conflict of interest

The authors declare that there is no conflict of interest.

Ethical approval

The study was approved by the University of Basrah College of Medicine and Basrah Health Directorate ethics committees. Participants provided informed consent.

Data availability

The datasets generated during and/or analyzed during the current study are available from the cor responding author on reasonable request

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Author contributions

Conception: wijdan Nazar, Mazin Hawaz, collection of samples by Hiba Jassam Rafid adel and Karam Basil, writing and statistical analysis by Wijdan Nazar and Hiba Jassam, Proff reading by wijdan Nazar, Mazin Hawaz And Hiba Jassam. All authors reviewed and approved the final manuscript for publication.

References

1. Chou AK, Hsiao CL, Shih TC, Wang HC, Tsai CW, Chang WS, Liu LC, Way TD, Chung JG, Bau DT. The contribution of matrix metalloproteinase-7 promoter genotypes in breast cancer in taiwan. *Anticancer Res*. 2017 Sep;37(9):4973–4977.
2. Ministry of Health, Iraq. Cancer Registry of Iraq Annual Report 2023 [Internet]. Baghdad: Ministry of Health; 2024. Available from: https://storage.moh.gov.iq/2024/11/24/2024_11_24_12127028949_4299728097670824.pdf.
3. Mohsin RN, Mohamad BJ. Clinical and histopathological features of breast cancer in Iraqi patients between 2018–2021. *Iraqi Journal of Science*. 2024;65(1):90–107. doi:10.24996/ij.
4. Alih, HH, Abd SY, Al-Kaseer E, Al-Diwan J. Cancer in Iraq, general view of annual report 2022. *Journal of Contemporary Medical Sciences*. 2025;10(6). https://doi.org/10.22317/jcms.v10i6.1676.
5. Al-Askari BW, Abdelkefi MS. Risk factors for breast cancer in Iraqi women. *Onkologia i Radioterapia*. 2023;17(9). Available from: https://www.oncologyradiotherapy.com/articles/risk-factors-for-breast-cancer-in-iraqi-women-104062.html.
6. Yari K, Rahimi Z, Payandeh M, Rahimi Z. MMP-7 A-181G Polymorphism in breast cancer patients from western iran. *Breast Care*. 2015;10(6):398–402.
7. Abood RA. Breast cancer in basra oncology center: A Clinico- Epidemiological Analysis. *Asian Pac J Cancer Prev*. 2018;19(10):2943–2946. Published 2018 Oct 26. doi:10.22034/APJCP.2018.19.10.2943.
8. Liao HY, Da CM, Liao B, Zhang HH. Roles of matrix metalloproteinase-7 (MMP-7) in cancer. *Clin Biochem*. 2021;92:9–18. doi:10.1016/j.clinbiochem.2021.03.003.
9. Mustafa S, Koran S, AlOmair L. Insights into the role of matrix metalloproteinases in cancer and its various therapeutic aspects: a review. *Front Mol Biosci*. 2022;9:896099. doi:10.3389/fmolb.2022.896099.
10. Morla S, Kumar A, Kumar, S. Newcastle disease virus mediated apoptosis and migration inhibition of human oral cancer cells: A probable role of β-catenin and matrix metalloproteinase-7. *Sci Rep*. 2019;9:10882. https://doi.org/10.1038/s41598-019-47244-y.
11. Loh CY, Chai JY, Tang TF, Wong WF, Sethi G, Shanmugam MK. The E-Cadherin and N-Cadherin Switch in Epithelial-to-Mesenchymal Transition: Signaling, Therapeutic Implications, and Challenges. *Cells*. 2019 Oct 20;8(10):1118. doi:10.3390/cells8101118.
12. Heuberger J, Birchmeier W. Interplay of cadherin-mediated cell adhesion and canonical Wnt signaling. *Cold Spring Harb Perspect Biol*. 2010;2(2):a002915. doi:10.1101/cshperspect.a002915.
13. Beeghly-Fadiel A, Long JR, Gao YT, *et al.* Common MMP-7 polymorphisms and breast cancer susceptibility: a multistage study of association and functionality. *Cancer Res*. 2008; 68(15):6453–6459. doi:10.1158/0008-5472.CAN-08-0636.
14. Nosho K, Yoshida M, Yamamoto H, *et al.* Association of Ets-related transcriptional factor E1AF expression with overexpression of matrix metalloproteinases, COX-2 and iNOS in the early stage of colorectal carcinogenesis. *Carcinogenesis*. 2005;26:892–899. doi: 10.1093/carcin/bgi029.
15. Han JC, *et al.* Elevated matrix metalloproteinase-7 expression promotes metastasis in human lung carcinoma. *World J Surg Oncol*. 2015;13:1–10.
16. Liu D, Nakano J, Ishikawa S, Yokomise H, Ueno M, Kadota K, Urushihara M, Huang CL. Overexpression of matrix metalloproteinase-7 (MMP-7) correlates with tumor proliferation, and a poor prognosis in non-small cell lung cancer. *Lung Cancer*. 2007;58(3):384–391.

17. Chakraborti S, Mandal M, Das S, Mandal A, Chakraborti T. Regulation of matrix metalloproteinases: an overview. *Mol Cell Biochem*. 2003;253:269–285. doi: 10.1023/a:1026028303196.
18. Bartnykaitė A, Savukaitytė A, Bekampytė J, Ugenskienė R, Laukaitienė D, Korobeinikova E, Gudaitienė J, Juozaitytė E. The role of matrix metalloproteinase single-nucleotide polymorphisms in the clinicopathological properties of breast cancer. *Biomedicines*. 2022;10(8):1891.
19. Gao YT. Genetic polymorphisms in the MMP-7 gene and breast cancer survival. *Int J Cancer*. 2009. doi:10.1002/IJC.23859.
20. Ramala SR Jr, Chandak S, Chandak MS, Annareddy S. A comprehensive review of breast fibroadenoma: Correlating clinical and pathological findings. *Cureus*. 2023;15(12):e49948. Published 2023 Dec 5. doi:10.7759/cureus.49948.
21. Shabani S, Maleki A. Advanced bioinformatics analyses in breast cancer molecular subtype prediction. In: Modeling and Analysis of Breast Cancer Data. *IGI Global*. 2025:63–82. doi: 10.4018/979-8-3373-5137-7.ch003.
22. Kaur G, Singh S, Kumar S, *et al.* Genomic alterations and immunogenicity in HER2-positive breast cancer: recent advances. *J Transl Med*. 2023;21:1311. doi: 10.1186/s13048-023-01311-1.
23. Kumar P, Siripini S, Sreedhar AS. The matrix metalloproteinase 7 (MMP7) links Hsp90 chaperone with acquired drug resistance and tumor metastasis. *Cancer Rep (Hoboken)*. 2022;5(12):e1261. doi:10.1002/cnr2.1261.
24. Livak KJ, Schmittgen TD. Analysis of relative gene expression data using real-time quantitative PCR and the 2(-Delta Delta C(T)) Method. *Methods*. 2001;25(4):402–408. doi:10.1006/meth.2001.1262.
25. Xu Y, Zhao Y, Wang J, *et al.* Novel nanocarrier for HER2-positive breast cancer therapeutic targeting. *Int J Pharm*. 2025;125937. doi: 10.1016/j.ijpharm.2025.125937.
26. Beeghly-Fadiel A, Shu XO, Long J, *et al.* Genetic polymorphisms in the MMP-7 gene and breast cancer survival. *Int J Cancer*. 2009;124(1):208–214. doi:10.1002/ijc.23859.
27. Beeghly-Fadiel A, Xiang YB, Deming SL, Long JR, Xu WH, Cai Q, Zheng W, Shu XO. No association between matrix metalloproteinase (MMP)-1, MMP-3, and MMP-7 SNPs and endometrial cancer risk. *Cancer Epidemiol Biomarkers Prev*. 2009 Jun;18(6):1925–8. doi: 10.1158/1055-9965.EPI-09-0244. Epub 2009 May 12. PMID: 19435861.
28. Luo HZ, Zhou ZG, Yang L, Yu YY, Tian C, Zhou B, Zheng XL, Xia QJ, Li Y, Wang R. Clinicopathologic and prognostic significance of MMP-7 [Matrilysin] expression in human rectal cancer. *Jpn J Clin Oncol*. 2005;35(12):739–744
29. Jiang WG, Davies G, Martin TA, Parr CH, Watkins G, Mason MD, Mokbel K, Mansel RE. Targeting matrilysin and its impact on tumor growth in vivo: the potential implications in breast cancer therapy. *Clinical Cancer Res*. 2005;11:6012–6019.
30. Vizoso FJ, González LO, Corte MD, Rodríguez JC, Vázquez J, Lamelas ML, Junquera S, Merino AM, García-Muñiz JL. Study of matrix metalloproteinases and their inhibitors in breast cancer. *Br J Cancer*. 2007;26;96(6):903–11.
31. Chou AK, Hsiao CL, Shih TC, Wang HC, Tsai CW, Chang WS, Liu LC, Way TD, Chung JG, Bau DT. The contribution of matrix metalloproteinase-7 promoter genotypes in breast cancer in Taiwan. *Anticancer Res*. 2017;37(9):4973–4977.
32. Muhammad HH, Hussein AG, Qasim BJ. Immunohistochemical expression of matrix metalloproteinase-7 (MMP-7) in human breast lesions. *New Iraqi J Med*. 2012 Aug;8(2): 7–12.
33. Sun X, Hu X. Unveiling Matrix Metalloproteinase 13's Dynamic Role in Breast Cancer: A Link to Physical Changes and Prognostic Modulation. *International Journal of Molecular Sciences*. 2025;26(7):3083. https://doi.org/10.3390/ijms26073083.
34. Aroner SA, Rosner BA, Tamimi RM, *et al.* Plasma matrix metalloproteinase 1, 3, and 7 levels and breast cancer risk in the Nurses' Health study. *Cancer Causes Control*. 2014;25(12):1717–1723. doi:10.1007/s10552-014-0462-7.
35. Stamos JL, Weis WI. The β-catenin destruction complex. *Cold Spring Harb Perspect Biol*. 2013;5(1):a007898. Published 2013 Jan 1. doi:10.1101/cshperspect.a007898.
36. Issa H, Singh L, Lai KS, Parusheva-Borsitzky T, Ansari S. Dynamics of inflammatory signals within the tumor microenvironment. *World J Exp Med*. 2025;15(2):102285. Published 2025 Jun 20. doi:10.5493/wjem.v15.i2.102285.
37. Guo YJ, Pan WW, Liu SB, Shen ZF, Xu Y, Hu LL. ERK/MAPK signalling pathway and tumorigenesis. *Exp Ther Med*. 2020;19(3):1997–2007. doi:10.3892/etm.2020.8454.
38. Kwon MJ. Matrix metalloproteinases as therapeutic targets in breast cancer. *Front Oncol*. 2023;12:1108695. Published 2023 Jan 19. doi:10.3389/fonc.2022.1108695.
39. Kessenbrock K, Plaks V, Werb Z. Matrix metalloproteinases: regulators of the tumor microenvironment. *Cell*. 2010 Apr 2;141(1):52–67. doi: 10.1016/j.cell.2010.03.015.
40. Mavrommatis J, Markaki S, Kerammopoulos A, Nakopoulou L. Immunohistochemical expression of MMP-7 in invasive breast cancer. *APMIS*. 2005;115:246–55
41. Mylona E, Kapranou A, Mavrommatis J, Markaki S, Keramopoulos A, Nakopoulou L. The multifunctional role of the immunohistochemical expression of MMP-7 in invasive breast cancer. *APMIS*. 2005;113(4):246–55.
42. Gacuta E, Ławicki M, Kulesza M, *et al.* Plasma Levels of Matrilysins (MMP-7 and MMP-26) and Stromelysins (MMP-3 and MMP-10) in Diagnosis of Endometrial Cancer Patients. *Int J Mol Sci*. 2025;26(8):3824. Published 2025 Apr 18. doi:10.3390/ijms26083824.
43. Buiar P, Szezech JD Jr, Sales MR, Favero GM. Time to focus again on matrix metalloproteinases? Results of complex network analysis involving the pathophysiology of HER2-positive breast cancer. *ecancermedicalscience*. 2025 Feb;19. doi: 10.3332/ecancer.2025.1850.
44. Buiar P, Szezech JD Jr, Sales MR, Favero GM. Time to focus again on matrix metalloproteinases? Results of complex network analysis involving the pathophysiology of HER2-positive breast cancer. *J Cancer Res*. 2025 Feb;19. doi: 10.3332/ecancer.2025.1850.