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The Relationship of *MMP-9* Gene Polymorphism rs3918242 (C-1562T) with Clinical-Pathological Features in Luminal Subtype Breast Cancer

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Abstract

Background: Breast cancer is a malignant tumor arising from the ductal or lobular epithelium. The Matrix Metalloproteinase-9 (*MMP-9*) rs3918242 polymorphism has been reported as a genetic factor influencing cancer cell proliferation and tumor progression. Therefore, this study aims to investigate the association between the *MMP-9* rs3918242 (C-1562T) gene polymorphism and the clinicopathology of luminal subtype breast cancer.

Methods: This study is a descriptive-analytic research with a cross-sectional design. The polymerase chain reaction (PCR) method was used to detect the *MMP-9* rs3918242 (C-1562T) gene polymorphism in patients' blood samples. Data were analyzed using SPSS version 26.0.

Results: The mean age of the participants, age at diagnosis, and age at menarche were 55.67±10.64, 53.29±10.28, and 13.48±1.60 years, respectively. Most participants had fewer than 2 childbirths (54.8%), and the majority were postmenopausal (64.5%). Regarding tumor characteristics, most cases were early-stage breast cancer (19 patients, 61.3%), while histological grading showed a predominance of high-grade tumors (23 patients, 74.2%). Bivariate analysis revealed a significant association between the *MMP-9* rs3918242 (C-1562T) gene polymorphism and the clinicopathological features of luminal subtype breast cancer, including stage and metastasis.

Conclusion: A significant association was identified between the *MMP-9* rs3918242 gene polymorphism and the clinicopathological characteristics of patients with luminal subtype breast cancer.

Keywords: luminal subtype breast cancer, clinicopathology *MMP-9* polymorphism

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Связь полиморфизма гена *MMP-9* rs3918242 (C-1562T) с клинико-патологическими особенностями при люминальном подтипе рака молочной железы

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Резюме

Актуальность: Рак молочной железы представляет собой злокачественное новообразование, развивающееся из протокового и дольного эпителия. Полиморфизм rs3918242 гена матриксной металлопротеиназы-9 (*MMP-9*) рассматривается как генетический фактор, влияющий на пролиферацию опухолевых клеток и прогрессирование опухоли. Целью настоящего исследования является изучение связи полиморфизма гена *MMP-9* rs3918242 (C-1562T) и клинико-патологических характеристик люминального подтипа рака молочной железы.

Методы: Данное исследование относится к категории описательно-аналитических исследований с поперечным дизайном. Для выявления полиморфизма гена *MMP-9* rs3918242 (C-1562T) в образцах крови пациентов использовали метод полимеразной цепной реакции. Статистическая обработка данных проводилась с использованием программного обеспечения SPSS версии 26.0.

Результаты: Средний возраст участников, возраст на момент постановки диагноза и возраст менархе составили 55,67±10,64, 53,29±10,28 и 13,48±1,60 года соответственно. У большинства пациентов число родов было менее двух (54,8%), при этом преобладали женщины в постменопаузе (19 пациентов, 64,5%). Большинство случаев относилось к ранним стадиям рака молочной железы (19 образцов 61,3%), при этом гистологический анализ выявил преобладание образцов высокой степени злокачественности (23 образца, 74,2%). Бивариантный анализ продемонстрировал статистически значимую связь между полиморфизмом гена *MMP-9* rs3918242 (C-1562T) и клинико-патологическими особенностями люминального подтипа рака молочной железы, включая стадию заболевания и наличие метастазов.
Заключение: Выявлена статистически значимая связь между полиморфизмом гена *MMP-9* rs3918242 и клинико-патологическими характеристиками пациентов с люминальным подтипом рака молочной железы.
Ключевые слова: люминальный подтип рака молочной железы, клинико-патология, полиморфизм *MMP-9*
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Introduction

Breast cancer is the malignant tumor arising from the ductal or lobular epithelium of the breast. In Indonesia, breast cancer is the most prevalent cancer among women, with an overall prevalence of 16.6% in 2020 and 30.8% among all female cancers. Luminal subtypes are the most common, accounting for 71% of cases as luminal A and 12% as luminal B, compared to 5% HER2-positive and 12% triple-negative breast cancer (TNBC). Studies have shown that patients with luminal subtypes have a high risk of recurrence and disease progression within 5 years. [1-8]

Matrix Metalloproteinase-9 (MMP-9) is a gene whose expression has been associated with breast cancer progression. Increased MMP-9 expression contributes to tumor cell migration, invasion, and metastasis, making it a potential marker for disease prognosis and therapeutic targeting.

Carcinoembryonic Antigen (CEA) is widely used as a marker for breast cancer progression; however, it lacks specificity. Another marker, Cancer Antigen (CA) 15-3, requires collaboration with CEA for effective use.[9] Due to the limitations of the aforementioned methods, there is a need for a marker that correlates closely with tumor grade, stage, and histological features in luminal subtype breast cancer.[10] Matrix Metalloproteinase-9 (MMP-9) emerges as a potential biomarker for detecting metastasis, especially in luminal subtype breast cancer.[11–13] Biologically, MMP-9 is involved in proteolytic degradation, cellular interactions, and extracellular matrix (ECM) breakdown. Increased MMP-9 expression plays a role in tumor development processes such as migration, invasion, metastasis, angiogenesis, inflammation, and proliferation. [14]

Studies exploring the association between MMP-9 gene polymorphism and breast cancer risk reveal that the MMP-9 variant rs3918242 (C-1562T) is a potential risk factor, with a P-value < 0.036 and Odds Ratio (OR) of 2.015, according to Rahimi et al. (2015). [15] Located in the gene's promoter region, MMP-9 rs3918242 can enhance enzyme expression and activity, leading to increased ECM degradation and influencing the progressiveness of breast cancer patients and their clinicopathological features.[16] Despite these findings, there is a gap in research specific to Indonesia, particularly on the role of the MMP-9 rs3918242 (C-1562T) gene polymorphism in luminal subtype breast cancer's clinicopathological features. Therefore, further studies are warranted to investigate this gap and explore the association of this gene polymorphism and the clinicopathological characteristics of luminal subtype breast cancer.

Materials and methods

Study Design and Subject Selection

This study employs a descriptive-analytic study with a cross-sectional design to investigate the correlation between MMP-9 rs3918242 (C-1562T) gene polymorphism and the clinicopathological features of luminal subtype breast cancer patients. The minimum required sample size was 28 individuals; accounting for a potential 10% dropout, the final target sample size was 31 participants. Sample collection was not performed, as the venous blood samples were already available through the Biological Material Department at the Faculty of Medicine, Udayana University.

Research Flow

The *MMP-9* rs3918242 (C-1562T) gene polymorphism was analyzed using the polymerase chain reaction (PCR) method. Before conducting PCR, DNA isolation is performed from the venous blood samples. Isolation involves placing 200µl of blood into a centrifugation tube and adding 200µl of BB buffer. Subsequently, 20 µl of Proteinase X is added, and the mixture is incubated at 65°C for 10 minutes. Then, 200µl of Absolute Alcohol is mixed, and the combination is transferred to a spin column. Centrifugation is carried out at 5000 x g for 1 minute, discarding the liquid passing through the spin column, and adding 500µl of wash buffer 1. The process is repeated, adding 500µl of Wash Buffer 2. After the final centrifugation at 12000 rpm for 3 minutes, the spin column is transferred to a new centrifugation tube. Subsequently, 100µl of preheated Elution Buffer at 65°C or H2O is added, left for 2 minutes, and centrifuged at 5000 x g for 1 minute. The purified DNA can be stored at 4°C or -20°C.

Following DNA purification, PCR amplification was performed in a 25 µL reaction mixture using a thermocycler. Initial denaturation was carried out at 94°C for 1 minute, followed by an initial extension at 72°C for 7 minutes. PCR was subsequently performed for 40 cycles, each consisting of 94°C for 30 seconds, 57°C for 30 seconds, and 72°C for 30 seconds. PCR products were visualized by agarose gel electrophoresis under ultraviolet (UV) light. DNA fragments were purified from the gel and subjected to sequencing.

Statistical Analysis

Univariate analysis was performed to describe variables including histopathological grade, cancer stage, and *MMP-9* rs3918242 (C-1562T) genotypes. Subsequently, normality of numeric data was assessed using the Shapiro-Wilk test, and bivariate inferential analysis, in the form of chi-square, is performed to ascertain the correlation between *MMP-9* gene polymorphism rs3918242 (C-1562T) and the clinical-pathological features of luminal subtype breast cancer. A significance level of $p<0.05$ is considered with SPSS version 26.0.

Ethical Approval

Ethical approval was obtained from the Research Ethics Committee of the Faculty of Medicine, Udayana University (approval number 1856/UN14.2.2. VII.14/LT/2022, dated July 11, 2022).

Results

Subject Characteristic

Based on the analysis results, the basic characteristics of the study sample were obtained, including the mean age of the sample, age at diagnosis, and age at menarche, which were 55.67±10.64, 53.29±10.28, and 13.48±1.60, respectively. Most participants had fewer than 2 parities (54.8%) and were post-menopausal (64.5%). The majority of cancer cases were categorized as early-stage, comprising 19 samples (61.3%), and histologically, high-grade samples dominated with 23 samples (74.2%). Tumors were more frequently located in the right breast (mamma dextra) than in the left (mamma sinistra), and most tumors were non-metastatic (18 samples, 58.1%). ER and PR receptors were mostly positive, whereas HER2 was predominantly negative (51.6%) (Table 1).

Genotype Distribution of MMP-9 rs3918242 Polymorphism in the Research Sample

Following sequencing, the distribution of *MMP-9* rs3918242 (C-1562T) genotypes was determined, classified as CC, CT, and TT. The polymorphic genotypes (CT and TT) combined accounted for 48.4%, whereas the CC genotype, representing the wild-type homozygote, accounted for 51.6% (Table 2).

Table 1
Baseline characteristics of the research samples
Таблица 1
Исходные характеристики исследуемых групп

Variable	Sample (N=31)	
	n	%
Mean Age (±SD)	55.67±10.64	
Mean Age at Diagnosis (±SD)	53.29±10.28	
Mean Age of Menarche (±SD)	13.48±1.60	
Parity		
• <2	17	54.8
• ≥2	14	45.2
Menstrual Status		
• Pre-Menopause	11	35.5
• Post-Menopause	20	64.5
Stadiums		
• Initial Stage	19	61.3
• Advanced Stage	12	38.7
Histological Grade		
• Low Grade (I-II)	8	25.8
• High Grade (III)	23	74.2
Tumor Location		
• Mammae Dextra	19	61.3
• Mammae Sinistra	12	38.7
Metastasis		
• Non-Metastatic	18	58.1
• Distant Metastasis	13	41.9
ER		
• Negative	1	3.2
• Positive	30	96.8
PR		
• Negative	8	25.8
• Positive	23	74.2
HER2		
• Negative	16	51.6
• Positive	15	48.4

Table 2
Distribution of the *MMP-9* rs3918242 gene polymorphism in research subjects
Таблица 2
Распределение полиморфизма гена *MMP-9* rs3918242 у участников исследования

MMP-9 Polymorphism rs-3918242 (C-1562T)	Samplel (n = 31)	
	n	%
CC	16	51.6
CT	7	22.6
TT	8	25.8
CT + TT	15	48.4

Association of MMP-9 rs3918242 Polymorphism with Clinicopathological features in Luminal Subtype Breast Cancer

Bivariate analysis was performed to examine associations between clinicopathological parameters, including stage, grade, and metastasis and *MMP-9* rs3918242 gene polymorphism genotypes. A significant association was observed, with carries of the CT + TT genotypes showing an increased risk of adverse clinicopathological features compared to the CC genotype (Table 3).

Table 3

Association of the *MMP-9* rs3918242 gene polymorphism with clinicopathological breast cancer of the luminal subtype

Таблица 3

Связь полиморфизма гена *MMP-9* rs3918242 с клинико-патологическими характеристиками рака молочной железы люминального подтипа

Variable	Genotype		PR (95% CI)	p-value
	CT + TT	CC		
Stadiums • Initial Stadium • Advanced Stadium	9 6	3 13	3.200 (1.065 – 9.618)	0.018*
Histological Grade • High Grade • Low Grade	12 3	11 5	1.164 (-.768 – 1.764)	0.474
Metastasis • Distant • Non	10 5	3 13	3.556 (1.206 – 10.480)	0.007*

Note: *, statistically significant (p<0.05); PR, Prevalence ratio; CI, confidence interval

Прим.: * – статистическая значимость (p<0,05); PR – отношение распространённости; CI – доверительный интервал

Discussion

The present study demonstrates a significant relationship between the *MMP-9* rs3918242 (C-1562T) gene polymorphism and the stage of breast cancer in patients with the luminal subtype. These results are consistent with Caykara et al. (2020), who reported that *MMP-9* gene polymorphism is associated with higher cancer stage.[17] This association is attributed to the general function of the *MMP-9* gene, which mediates cancer cell spread, eliminating boundaries or adhesion between cancer cells and adjacent normal cells. This allows cells to invade other areas, including reaching the lymph nodes.[18] Furthermore, *MMP-9* rs3918242 (C-1562T) polymorphism may promote tumor growth, contributing to advanced cancer stage. Advanced cancer stage is associated with more severe clinical manifestations and poorer prognosis.[19]

The histopathological grade of luminal subtype breast cancer is an important predictor of prognosis, tumor behavior, and therapy response. Luminal A tumors are generally PR/ER-positive, HER2-negative, and have low Ki67, whereas Luminal B tumors are PR/ER-positive, HER2-negative, but exhibit high Ki67 expression.[20] Based on the sample characteristics, histological grade in luminal subtype breast cancer patients revealed 8 patients classified as low grade and 23 patients as high grade. No significant association was found between histological grade and *MMP-9* rs3918242 polymorphism (PR = 1.164, p = 0.474). According to a study by Fawziya et al., out of 121 samples, 74.7% were classified as grade 2, and 25.3% as grade III. This study found a significant relationship between polymorphism and the risk of breast cancer in the research sample. Significantly, *MMP-9* gene expression due to polymorphism increased (p=0.021), especially in the CC genotype, which exhibited higher expression compared to the CT genotype. Regarding histological grade and its relationship with the occurrence of the *MMP-9* rs3918242 gene polymorphism in the research sample, specifically for the CC genotype, a significant p-value of 0.005 was observed.[21]

Furthermore, based on research by Zahra et al. (2018), examining the association of *MMP-9* rs3918242 gene polymorphism with breast cancer and comparing it to *MMP-2* -1306C/T gene polymorphism, it was found that the *MMP-9* gene polymorphism could increase the risk of breast cancer by 4.83 times for the T allele.[22–26] In contrast, *MMP-2* -1306C/T polymorphism was not associated with breast cancer risk. In this study, 87% of tumors were <20 mm, and 13% were >20 mm. The majority of tumors were ductal (94.5%), with non-ductal tumors accounting for 5.5%.[27] Discrepancies in results between this study and others may be due to differences in the sampling techniques used or the sample size obtained. The limitation of this study is the relatively small sample size.

Conclusion

The present study demonstrates a significant association between *MMP-9* rs3918242 polymorphism and the clinicopathological features of luminal subtype breast cancer, particularly cancer stage, metastasis status, and histological grade.

Author contributions

Concept and design: Novianti, Adiputra, Supadmanaba
Acquisition, analysis, or interpretation of data: Novianti, Adiputra, Supadmanaba, Kusuma
Manuscript drafting and revising: Novianti, Adiputra, Supadmanaba, Sasmana
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