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Significant Association of Matrix Metalloproteinase-9 Polymorphisms With Triple Negative Breast Cancer Risk

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Abstract

Background/Aim: Matrix metalloproteinase-9 (MMP-9) has been associated with the development and progression of breast cancer (BCa). However, the relationship between MMP-9 genetic variants and BCa susceptibility remains contentious and inconclusive. This study aimed to evaluate the association of MMP-9 rs3918242 promoter polymorphisms with BCa, with a particular focus on the risk of triple-negative breast cancer (TNBC).

Materials and Methods: A case-control study was conducted involving 1,232 BCa patients and 1,232 healthy controls. The MMP-9 rs3918242 genotypes were determined using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) analysis.

Results: The genotype distribution of MMP-9 rs3918242 among the control group adhered to Hardy-Weinberg equilibrium (p=0.3265). No statistically significant differences were observed in the genotype frequencies between BCa cases and controls (p for trend=0.2555). Although the homozygous variant genotype (TT) showed a potential risk-increasing effect, this was not statistically significant [odds ratio (OR)=1.43, 95% confidence interval (CI)=0.88-2.36, p=0.1869]. Similarly, allele frequency analysis indicated no significant association between the variant T allele and overall BCa risk (OR=1.13, 95%CI=0.97-1.33, p=0.1265). Additionally, no interaction was detected between MMP-9 rs3918242 genotypes and the age of BCa onset (both p>0.05). Notably, the TT genotype of MMP-9 rs3918242 was significantly associated with an increased risk of TNBC (OR=2.49, 95%CI=1.32-4.72, p=0.0072).

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Conclusion: The MMP-9 rs3918242 TT genotype may serve as a potential predictive biomarker for TNBC in the Taiwanese population.

Keywords: Breast cancer, matrix metalloproteinase-9, polymorphism, triple negative breast cancer, Taiwan.

Introduction

Breast cancer (BCa) is the most prevalent malignancy among women in 157 out of 185 countries, leading to 670,000 deaths globally in 2022 (1, 2). There are several indexes, including age, obesity, smoking, alcohol consumption, high-sugar diets, a sedentary lifestyle, and familial genetics, being recognized as BCa risk factors (3-5). Among the subtypes of BCa, triple-negative breast cancer (TNBC), comprising 15-20% of BCa cases, is characterized by the lack of estrogen receptor (ER+) and progesterone receptor (PR+), and human epidermal growth factor receptor-2 (HER-2+) expression (6). Among the BCa subtypes, TNBC is currently the most death threatening subtype without any effective drugs (7). The absence of precise biomarkers contributes to a relatively high recurrence rate of 50% among patients with stage I to stage III TNBC, accompanied by a 37% mortality rate within five years following surgical treatment (8). Despite significant efforts by translational scientists to identify potential biomarkers for BCa, particularly TNBC, the task remains incomplete and far from satisfactory (9-11).

Matrix metalloproteinases (MMPs), characterized by their collagenase activity, play a critical role in degrading connective tissue components and basement membranes, thereby promoting key processes such as angiogenesis and metastasis (12, 13). Increased expression of MMPs, particularly MMP-2 and MMP-9, has been linked to enhanced tumor proliferation and the onset of invasive and metastatic behaviors (14, 15). Numerous studies have established a connection between elevated MMP levels and the development and spread of BCa (16, 17).

MMP-9, also named as 92 kDa type IV collagenase, 92 kDa gelatinase, or gelatinase B, has been revealed to play a crucial role in the development and progress of various human malignancies, including non-small cell lung cancer (18), cervical cancer (19, 20), ovarian cancer (21), osteosarcoma (22), giant-cell tumor of bone (23), pancreatic cancer (24), hepatocellular carcinoma (25), and most of all, breast cancer (26, 27). MMP-9 contributes to carcinogenesis by remodeling the extracellular matrix and degrading membrane proteins, thereby regulating critical cancer cell behaviors such as proliferation, invasion, migration, and angiogenesis (28-30). The expression of MMP-9 was first detected in endothelial cells and stromal fibroblasts during the initial stages of stroma formation around intraductal and intralobular *in situ* carcinomas, and its expression was significantly up-regulated in the stroma of invasive ductal and lobular cancers (31). A significant correlation between MMP-9 gene expression and tumor differentiation grade has also been reported by Schveigert and his colleagues (32). These findings highlight MMP-9 as a crucial factor in BCa progression. Among the various genetic variants associated with *MMP-9*, the polymorphism *MMP-9* rs3918242 in the promoter region has been the most widely studied. This polymorphism has been explored in relation to several cancer types, including lung cancer (33), gastric (34), colorectal (35, 36), prostate (37), kidney cancer (38), and childhood leukemia (39). In the context of BCa, numerous studies have examined the potential role of *MMP-9* rs3918242 polymorphic genotypes in BCa risk, yielding contradictory results (40-55). In 2008, Decock *et al*. found that the T allele of *MMP-9* rs3918242 exhibited 1.5-fold higher promoter activity compared to the C allele (56). In 2014, it was reported that carriers of the *MMP-9* rs3918242 T allele had elevated MMP-9 levels (57). However, this conclusion was questioned in 2016 when Bargostavan *et al*. found no

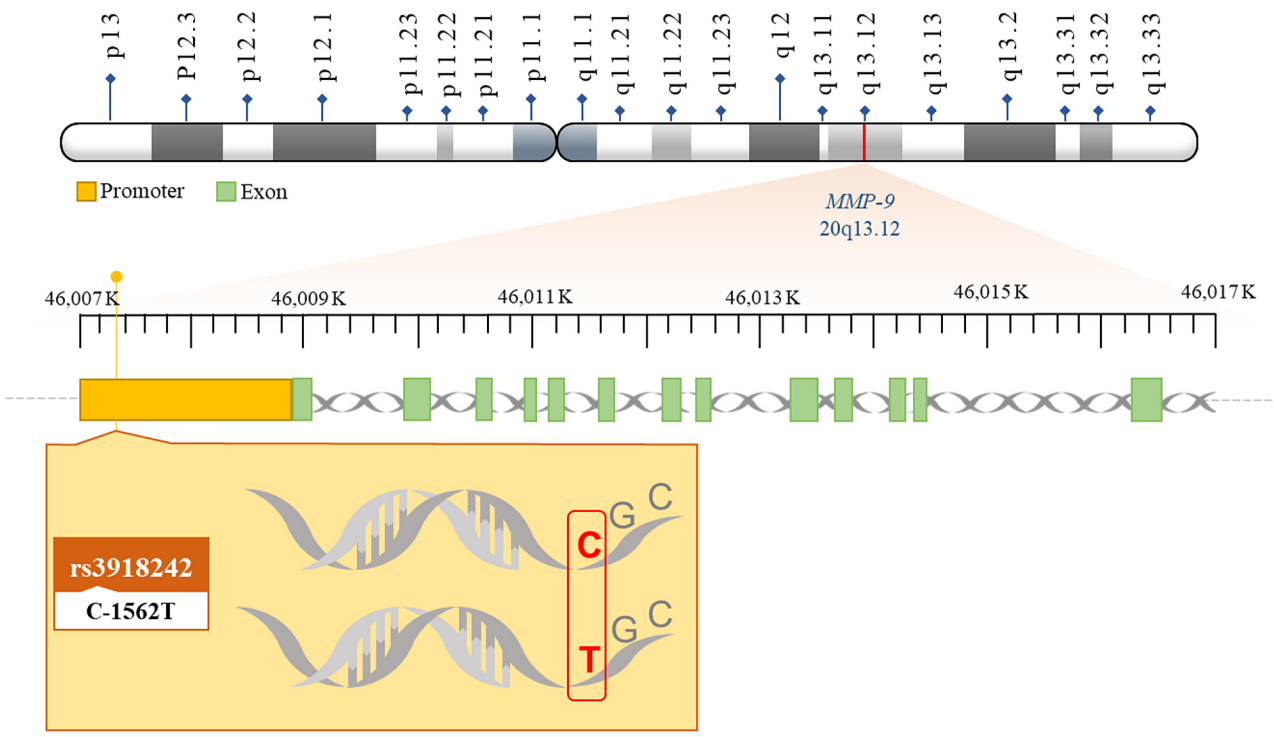

Figure 1. *A physical map of the MMP-9 rs3918242 promoter polymorphic site.*

effect of *MMP-9* rs3918242 genotypes on serum MMP-9 levels in BCa patients (49).

The findings, combined with the preceding reports, imply that the *MMP-9* genotype may contribute to BCa risk assessment. Consequently, this study aimed to investigate the impact of *MMP-9* rs3918242 promoter genotypes (Figure 1) on BCa susceptibility within a representative Taiwanese population consisting of 1,232 BCa cases and 1,232 non-cancerous controls. Notably, this is the first investigation to explore the potential predictive value of *MMP-9* genotypes specifically in relation to TNBC risk. Furthermore, the study includes a comparative analysis of the role of *MMP-9* rs3918242 genotypes in BCa across various populations.

Materials and Methods

Recruitment of BCa and non-cancerous control cohorts. This study included a cohort of 1,232 patients diagnosed with BCa, who were recruited from the outpatient clinics of the Department of General Surgery at China Medical University Hospital, Taiwan. All participants were Taiwanese, and the recruitment protocol, along with the criteria for inclusion and exclusion, has been described in our previous publications (10, 11). Clinical and pathological characteristics, including histological evaluations, were meticulously determined by experienced surgical nurses and doctors. Tissue samples were independently assessed and graded by at least two expert pathologists in the hospital. All participants provided informed consent, completed a structured questionnaire, and contributed peripheral blood samples.

For the control group, 1,232 healthy individuals matched for age were randomly selected from the hospital's Health Examination Cohort. Controls were excluded if they had a history of malignancies, metastatic cancers of unknown or other origins, or any hereditary or genetic disorders, such as endometriosis, leiomyoma,

or pterygium. Approval for this study was granted by the Institutional Review Board of China Medical University Hospital (DMR-99-IRB-108). Selected characteristics including age, age of first menarche, birth of first child, menopause, and TNBC status of the cohort are summarized in Table I.

Analysis of MMP-9 rs3918242 polymorphism status. Peripheral blood samples were obtained from all participants, and genomic DNA was isolated within 24 hours in accordance with established laboratory protocols (58-60). Genotyping for the *MMP-9* rs3918242 polymorphism was carried out using the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) technique. Specific primers targeting *MMP-9* sequences were developed and optimized by our laboratory (61, 62), with reaction parameters adhering to published methodologies (58, 63, 64). The amplified PCR products were digested using the restriction enzyme *Sph I* (New England Biolabs, Taipei, Taiwan, ROC), and genotyping results were resolved by electrophoresis on 3% agarose gels. Post-digestion, DNA fragments corresponding to the CC, CT, and TT genotypes for the *MMP-9* rs3918242 polymorphism were identified as 386 bp, 386+320+66 bp, and 320+66 bp, respectively. To ensure accuracy, each genotyping assay was independently repeated by two researchers blinded to participant identities. Concordance between the replicates was 100%, confirming the reliability of the results.

Methodologies for BCa MMP-9 statistical analysis. The Hardy-Weinberg equilibrium for the control population was evaluated using a chi-square goodness-of-fit test. Differences in age distribution between BCa patients and the control group were expressed as mean±standard deviation (SD) and analyzed using the unpaired Student's *t*-test. The distributions of *MMP-9* genotypes, as reported in both the current and prior studies (Table II, Table III, Table IV), were examined using Pearson's chi-square test with Yates' correction when expected cell counts exceeded 5, or Fisher's Exact test when any expected count was ≤5. The relationship between *MMP-9* genotypic variants and BCa susceptibility was quantified using odds ratios (ORs) with 95% confidence intervals (CIs), calculated under different stratification models. Statistical significance was defined as a p-value ≤0.05. All computations and analyses were conducted using SPSS software, version 16.0 (SPSS, Inc., Chicago, IL, USA).

Results

The demographic characteristics of the Taiwanese BCa population were compared with non-cancerous control subjects. Table I presents a summary of age, age at menarche, age at first childbirth, age at menopause, and TNBC status among 1,232 BCa patients and an equal number of non-cancer controls. No statistically significant differences were observed between the case and control groups for age, age at menarche, age at first childbirth, or age at menopause (all p>0.05). Noticeably, among the BCa cases, 194 were identified as TNBC (Table I).

The MMP-9 rs3918242 genotypic distributions among Taiwan BCa and non-cancerous control subjects. Table II displays the distribution of *MMP-9* rs3918242 genotypes among 1,232 non-cancer controls and 1,232 BCa cases. The genotype frequencies in the control group conformed to Hardy-Weinberg equilibrium (p=0.3265). No statistically significant differences in the distribution of *MMP-9* rs3918242 genotypes were observed between the BCa and control groups (p for trend=0.2555). Specifically, individuals carrying the heterozygous CT genotype exhibited a 1.09- and 1.43-fold elevated risk of BCa compared to those with the wild-type CC genotype, although this was not statistically significant (95%CI=0.91-1.32, p=0.3752). The TT homozygous variant genotype was associated with a 1.43-fold increased BCa risk; however, this result also failed to reach significance (95%CI=0.88-2.36, p=0.1869, Table II, top panel). When analyzed under a recessive model, individuals with the TT genotype had a 1.41-fold higher odds ratio for BCa compared to those with CC or CT

Table I. *Demographics of the 1,232 breast cancer patients and 1,232 healthy controls.*

Characteristic	Controls (n=1,232)			Patients (n=1,232)			*p*-Value
	n	%	Mean (SD)	n	%	Mean (SD)	
Age (yrs)							
<40	359	29.1%		362	29.4%		0.89[a]
40-55	558	45.3%		547	44.4%		
>55	315	25.6%		323	26.2%		
Age at menarche (yr)			12.4 (0.7)			12.1 (0.6)	0.79[b]
Age at birth of first child (yr)			29.4 (1.2)			29.8 (1.4)	0.63[b]
Age at menopause (yr)			48.8 (1.8)			49.3 (2.0)	0.59[b]
TNBC cases							
Yes				194	15.7%		
No				1038	84.3%		

[a]Chi-square or [b]unpaired Student's *t*-test; SD: standard deviation; yr: years; TNBC: triple-negative breast cancer.

Table II. *MMP-9 rs3918242 genotypes among the 1,232 patients with breast cancer and 1,232 non-cancerous healthy controls.*

Genotype	Frequency, n (%)		Odds ratio (95% Confidence internal)	*p*-Value[a]
	Cases (n=1,232)	Controls (n=1,232)		
rs3918242				
CC	889 (72.2)	917 (74.4)	1.00 (Reference)	
CT	304 (24.6)	287 (23.3)	1.09 (0.91-1.32)	0.3752
TT	39 (3.2)	28 (2.3)	1.43 (0.88-2.36)	0.1869
p_{trend}				0.2555
p_{HWE}				0.3265
Carrier comparison				
CC+CT	1193 (96.8)	1204 (97.7)	1.00 (Reference)	
TT	39 (3.2)	28 (2.3)	1.41 (0.86-2.30)	0.2155
CC	889 (72.2)	917 (74.4)	1.00 (Reference)	
CT+TT	343 (27.8)	315 (25.6)	1.12 (0.94-1.34)	0.2189

[a]Based on chi-square test with Yates' correction. p_{trend}: *p*-Value for trend analysis; p_{HWE}: *p*-Value for Hardy-Weinberg equilibrium.

genotypes, but the association was not statistically significant (95%CI=0.86-2.30, *p*=0.2155, Table II, middle panel). Similarly, the dominant model comparing carriers of the CT or TT genotypes to those with the CC genotype showed a non-significant increase in BCa risk (OR=1.12, 95%CI=0.94-1.34; *p*=0.2189, Table II, bottom panel).

The MMP-9 rs3918242 allelic frequency distributions among Taiwan BCa and non-cancerous control subjects. Allelic frequency analyses were performed to corroborate the genotyping results for *MMP-9* rs3918242 presented in Table II. Similarly, the presence of the variant T allele was not significantly associated with a modified risk of BCa (OR=1.13, 95%CI=0.97-1.33, *p*=0.1265, Table III). Collectively, the genotypes of *MMP-9* rs3918242 may not serve as a predictive biomarker for BCa risk in Taiwan.

The correlation of MMP-9 rs3918242 genotypes with onset ages in determining BCa risk. The *MMP-9* rs3918242 genotyping data were further analyzed by stratifying participants based on age to examine the potential interaction between *MMP-9* rs3918242 genotypes and age in BCa risk (Table IV). Among individuals younger or older than 55 years, the heterozygous and homozygous

Table III. *Allelic frequencies of MMP-9 rs3918242 among the 1,232 patients with breast cancer and 1,232 non-cancerous healthy controls.*

Genotypes	Controls, n (%)	Cases, n (%)	Odds ratio (95% Confidence internal)	*p*-Value[a]
rs3918242				
Allele C	2082 (84.5)	2121 (86.1)	1.00 (Reference)	
Allele T	382 (15.5)	343 (13.9)	1.13 (0.97-1.33)	0.1265

[a]Data based on Chi-square test with Yates' correction.

Table IV. *The association between MMP-9 rs3918242 genotypes and breast cancer risk after stratification by age.*

Genotype	Younger (≤55), n		OR (95%CI)[a]	*p*-Value	Elder (>55), n		OR (95%CI)	*p*-Value[a]
	Controls	Cases			Controls	Cases		
CC	686	658	1.00 (ref)		231	231	1.00 (ref)	
CT	211	224	1.11 (0.89-1.37)	0.3874	76	80	1.05 (0.73-1.51)	0.8538
TT	20	27	1.41 (0.78-2.53)	0.3194	8	12	1.50 (0.60-3.74)	0.5174
Total	917	909			315	323		
P_{trend}				0.3717				0.6695

OR: Odds ratio; CI: confidence interval; TNBC: triple-negative breast cancer; Ref: reference; *P*trend: *p*-value for trend analysis; [a]data based on Chi-square test with Yates' correction (n≥5) or Fisher's exact test (n<5).

Table V. *Association of MMP-9 genotypes with breast cancer risk after stratification into triple-negative breast cancer (TNBC), non-TNBC, and healthy controls.*

Genotype	Control	Non-TNBC	OR, 95%CI	*p*-Value[a]	TNBC	OR, 95%CI	*p*-Value[a]
CC	889	761	1.00 (Ref)		128	1.00 (Ref)	
CT	304	252	0.97 (0.80-1.17)	0.7817	52	1.19 (0.84-1.68)	0.3783
TT	39	25	0.75 (0.45-1.25)	0.3251	14	2.49 (1.32-4.72)	0.0072*
Total	1232	1038			194		
P_{trend}				0.5259			0.0011*

OR: Odds ratio; CI: confidence interval; Ref: reference; *P*trend: *p*-value for trend analysis; [a]data based on Chi-square test with Yates' correction; *statistically significant.

variant genotypes did not show a statistically significant correlation with BCa susceptibility (OR=1.11, 1.41, 1.05, and 1.50; 95%CI=0.89-1.37, 0.78-2.53, 0.73-1.51, and 0.60-3.74; *p*=0.3874, 0.3194, 0.8538, and 0.5174, respectively, Table IV).

The novel finding of the MMP-9 rs3918242 genotypic profile can serve as a marker for TNBC risk prediction. Although the *MMP-9* rs3918242 genotypes were not associated with overall BCa risk, their potential as predictive biomarkers for TNBC was investigated. BCa cases were categorized into TNBC and non-TNBC subgroups for this analysis. The results showed no significant correlation between *MMP-9* rs3918242 genotypes and non-TNBC (*p*=0.5259). However, among TNBC cases, the homozygous variant genotype of *MMP-9* rs3918242, but not the heterozygous genotype, exhibited a statistically significant difference in distribution compared to the control group (*p*=0.0072). This significant finding was further supported by trend analysis (*p* for trend=0.0011, Table V).

Discussion

The genetic contribution of MMP-9 to BCa, an inherited disease, remains inadequately understood. Since 2007, several research groups have investigated the relationship between *MMP-9* rs3918242 genotypes and BCa risk (Table VI), but results have been inconsistent and inconclusive. In 2007, Holliday and Roeche's teams explored the role of *MMP-9* rs3918242 genotypes in BCa risk using cohorts from the UK and Brazil, respectively. Both studies were limited by small sample sizes and did not find significant associations (40, 41). The same year, Lei's group studied a cohort of over a thousand individuals from Sweden but also found no notable associations (42). In 2009, Sadeghi and his colleagues conducted a similar investigation in an Iranian BCa cohort and identified an association between the CT and TT genotypes of *MMP-9* rs3918242 and an increased BCa risk (p=0.0001 and 0.0099, respectively) (43). However, their study was limited by a small sample size of fewer than 100 participants in both case and control groups. In 2014, the research team studying BCa cohorts from China reported a negative association, though their sample size did not exceed one hundred participants either (44). In almost the same period, researchers from the former Russia also found no significant link between *MMP-9* rs3918242 genotypes and BCa risk (45). Notably, a study in India revealed an association between the TT genotype and an increased risk of BCa (46). In 2015, Rahimi's group in Iran reported another negative association with a relatively small sample size, including 101 BCa patients and 104 healthy controls, although they suggested that T variants of *MMP-9* rs3918242 might be linked to a higher BCa risk (47). In 2016, AbdRaboh and colleagues studied a mixed-population cohort in Dubai and similarly found no significant relationship between *MMP-9* rs3918242 genotypes and BCa incidence. Their sample size was also under 100 participants (48). The same year, Bargostavan's team in Iran reported similar findings of no significant association (49). Despite the crucial role of MMP-9 in protein expression, scientists continued to investigate the potential link between *MMP-9* genotypes and BCa. In 2017, Padala's team in India and Toroghi's team in Iran presented evidence suggesting that the homozygous TT and heterozygous CT genotypes of *MMP-9* rs3918242 were associated with an increased incidence of BCa (50, 51). The following year, Manshadi and his colleagues in Iran expanded the sample size, and provided additional evidence showing that both the homozygous TT and heterozygous CT genotypes of *MMP-9* rs3918242 were associated with an elevated risk of BCa (52). Subsequently, Felizi's team and Pavlova's group in Iran, in 2018 and 2022 respectively, also investigated *MMP-9* rs3918242 genotypes in Brazilian and Soviet cohorts but found no significant association. While their sample sizes exceeded one hundred participants, they did not provide precise genotype data in their publications (53, 54). In parallel, an Egyptian study by Ibrahim *et al.* also found no significant association (55). In the present study, our primary goal was to assess the effects of *MMP-9* rs3918242 genotypes on BCa risk within a representative Taiwanese cohort. Although no significant associations were identified between the genotypes of this polymorphism and the risk of BCa (Table II and Table III), encouragingly, due to our large sample size and comprehensive clinical data, we were capable of providing the first direct evidence linking the *MMP-9* rs3918242 TT genotype with TNBC (Table V). In other words, our team is the first to investigate the association between *MMP-9* rs3918242 genotypes and TNBC, identifying its significant role in disease pathogenesis.

Although most of the studies mentioned above involved sample sizes of fewer than a thousand participants, some cohorts had notably insufficient sample sizes that failed to meet Hardy-Weinberg equilibrium assumptions. Furthermore, as these studies were conducted in diverse populations with distinct genetic backgrounds, comparing and referencing the findings across them proves to be challenging. This variability also prevented the research teams from exploring the relationship between these genotypes and TNBC. Nevertheless, each of these studies provides valuable data with both academic and clinical significance. Therefore, we have compiled a summary of

Table VI. *Literature reporting the genotypes of matrix metalloproteinase 9 rs3918242 among various breast cancer populations.*

First author	Year	Ethnicity	CC, CT, TT genotype # of the controls	CC, CT, TT genotype # of the cases	Highlights of the study	Ref #
Hung	2024	Taiwan	889:304:39	917:287:28 (128:52:14 for triple negative breast cancer)	TT genotypes contributed to increased triple-negative breast cancer risk (p=0.0072) instead of breast cancer risk (p=0.1869)	Current
Pavlova	2022	Russia	Not available	Not available	No specific genotype significantly contributed to altered breast cancer risk	(54)
Ibrahim	2020	Egypt	130:16:0	137:27:0	No specific genotype significantly contributed to altered breast cancer risk	(55)
Felizi	2018	Brazil	CC:CT+TT=186:45	CC:CT+TT=115:24	No specific genotype significantly contributed to altered breast cancer risk	(53)
Manshadi	2018	Iran	189:11:0	156:36: 6	CT and TT genotypes contributed to increased breast cancer risk (p=0.0001 and 0.0092, respectively)	(52)
Toroghi	2017	Iran	53:51:0	70:42:0	CT genotype contributed to decreased breast cancer risk (p=0.0413)	(51)
Padala	2017	India	150:101:49	121:107:72	TT genotypes contributed to increased breast cancer risk (p=0.0091)	(50)
Bargostavan	2017	Iran	72:27:1	67:34:4	No specific genotype significantly contributed to altered breast cancer risk	(49)
AbdRaboh	2016	Dubai	51: 25:1	28:29:2	No specific genotype significantly contributed to altered breast cancer risk	(48)
Rahimi	2015	Iran	84:19:1	68:31:2	No specific genotype significantly contributed to altered breast cancer risk	(47)
Shevchenko	2014	Russia	329:229:85	390:280:106	No specific genotype significantly contributed to altered breast cancer risk	(45)
Chiranjeevi	2014	India	86:68: 37	73:66:61	TT genotypes contributed to increased breast cancer risk (p=0.0156)	(46)
Wang	2014	China	38:34:18	46:30:14	No specific genotype significantly contributed to altered breast cancer risk	(44)
Sadeghi	2009	Iran	91:9:0	57:28:5	CT and TT genotypes contributed to increased breast cancer risk (p=0.0001 and 0.0099, respectively)	(43)
Lei	2007	Sweden	692:240:14	682:239:25	No specific genotype significantly contributed to altered breast cancer risk	(42)
Roehe	2007	Brazil	83:15:2	76:20:0	No specific genotype significantly contributed to altered breast cancer risk	(41)
Holliday	2007	UK	15:4: 0	10:3: 0	No specific genotype significantly contributed to altered breast cancer risk	(40)

all the literature examining the association between *MMP-9* rs3918242 genotypes and BCa in Table IV, and succinctly highlighted their key findings (Table IV). Our study benefits from the largest sample size to date, but further validation in diverse populations with varying ethnic backgrounds is necessary. We tentatively conclude that the TT genotype of *MMP-9* rs3918242 is significantly associated with an increased BCa risk.

The relationship between *MMP-9* rs3918242 genotypes and clinical outcomes in BCa has been infrequently explored. For example, the *MMP-9* rs3918242 CT genotype has been linked to an increased risk of lymph node metastasis in a mixed-ethnicity Caucasian BCa cohort (65). Over-expression of MMP-9, driven by promoter polymorphisms, along with elevated MMP-9 levels, may enhance tumor cell migration and

cancer progression through the breakdown of the extracellular matrix. Furthermore, variability in individual susceptibility to BCa and its prognosis may be attributed to the influence of MMP variants on the tumor microenvironment (65). In 2013, Slattery *et al*. found an association between *MMP-9* rs3787268 and survival outcomes in BCa patients with ER-/PR- tumors (66). The presence of the *MMP-9* rs3918242 C allele was associated with a reduced likelihood of HER2-positive BCa (67). This evidence suggests that *MMP-9* rs3918242 genotypes may serve as promising biomarkers for predicting BCa aggressiveness.

Simultaneously, the potential effects of other polymorphic sites within the *MMP-9* gene on BCa risk should not be overlooked. Several frequently studied polymorphisms, such as *MMP-9* rs17576 (68-73), rs2250889 (68, 69, 73, 74), and rs3787268 (66, 69, 75), have been examined for their potential roles in influencing individual BCa susceptibility. Further research is necessary to confirm their contributions to BCa pathogenesis.

The dysregulation of MMP-9 is a key factor in the pathogenesis of TNBC, although the precise mechanisms remain to be further elucidated. For example, the expression level of MMP-9 has been shown to correlate with a lack of response to neoadjuvant chemotherapy in TNBC patients (76). The down-regulation of MMP-9 *via* tyrosine kinase Src has been reported to inhibit the growth and metastasis of MDA-MB-231 cells, a well-established TNBC cell line (77). Additionally, TNFα-induced invasion and migration of TNBC cells may involve not only the up-regulation of CDKN1A/p21 but also the increased expression of MMP-9 (78). Therefore, the presence of *MMP-9* rs3918242 TT genotypes may serve not only as a diagnostic marker but also as a prognostic indicator for targeting metastatic behavior in TNBC therapy in the future.

Despite the inclusion of an extremely large sample size in this case-control study, several limitations warrant our consideration. First, extended follow-up periods are required to assess the role of *MMP-9* rs3918242 genotypes in BCa prognosis, particularly in terms of survival, metastasis, and recurrence. Second, the absence of measurements for MMP-9 expression at the RNA or protein levels restricts the ability to perform genotype-phenotype correlation analyses. Third, it is important to note that other *MMP-9* polymorphisms, such as those mentioned above, may also contribute to BCa risk and should not be disregarded. Finally, similar to the point, the potential impact of genotypes from other MMP and/or TIMP family members on BCa risk should be further explored. In 2023, we reported that *TIMP-2* rs8179090 genotypes were significantly associated with an increased risk of BCa in younger women (≤55 years old) but not in older women (>55 years old) (11). Moreover, the study was the first to establish a link between *TIMP-2* rs8179090 genotypes and the risk of TNBC (11). Other studies have reported positive associations between BCa risk and *MMP* genotypes, including *MMP-7* A-181G (79), and *TIMP-1* rs4898 (80). Additional researches on other MMPs and/or TIMPs, from proteomic, transcriptomic and/or genomic angles, are essential to gain a comprehensive understanding of BCa, especially TNBC, development and its underlying etiology.

To the best of our knowledge, our findings represent the first evidence suggesting that the *MMP-9* rs3918242 genotypic profile could serve as a novel predictive biomarker for TNBC. Even more compelling is the observed association between the *MMP-9* rs3918242 TT genotype and an elevated risk of TNBC, underscoring the potential clinical value of this genotype. These results highlight the importance of further research to translate these insights into meaningful advancements in clinical practice.

Conflicts of Interest

The Authors declare no conflicts of interest with any company or person.

Authors' Contributions

Research design: Hung CC, Shih HY and Wang YC; patient and questionnaire summaries: Liu CH, Hung CC and Su CH;

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