ANTICANCER RESEARCH *37*: 4973-4977 (2017)
doi:10.21873/anticanres.11908

The Contribution of Matrix Metalloproteinase-7 Promoter Genotypes in Breast Cancer in Taiwan

AN-KUO CHOU[1,2*], CHIEH-LUN HSIAO[2,3,5*], TZU-CHING SHIH[4*], HWEI-CHUNG WANG[2], CHIA-WEN TSAI[2], WEN-SHIN CHANG[2], LIANG-CHIH LIU[2], TZONG-DER WAY[3], JING-GUNG CHUNG[3] and DA-TIAN BAU[2,3,5,6]

[1]*Department of Anesthesiology,* [2]*Terry Fox Cancer Research Laboratory, China Medical University Hospital, Taichung, Taiwan, R.O.C.;*
[3]*Ph.D. Program for Biotechnology Industry,* [4]*Department of Biomedical Imaging and Radiological Science, and* [5]*Graduate Institute of Biomedical Sciences, China Medical University, Taichung, Taiwan, R.O.C.;*
[6]*Department of Bioinformatics and Medical Engineering, Asia University, Taichung, Taiwan, R.O.C.*

Abstract. *Background/Aim: The matrix metalloproteinase (MMP) family of enzymes are in charge of degradation of various components of the extracellular matrix and their functional genetic polymorphisms may be associated with cancer susceptibility. The functional polymorphisms in the promoter region of MMP7 (A-181G and C-153T) have been reported to influence the binding capacity of nuclear proteins and may contribute to genetic susceptibility to cancer. In this study, we focused on investigating the contribution of the genotypes of MMP7 (A-181G and C-153T) to breast cancer in Taiwan. Materials and Methods: These two polymorphisms were genotyped in 1,232 patients with breast cancer and 1,232 controls by polymerase chain reaction-restriction fragment length polymorphism methodology. Results: The odds ratios (ORs) after adjusting for age, family history of cancer, smoking and alcohol drinking status for those carrying AG and GG genotypes at MMP7 promoter A-181G were 1.22 (95%CI=0.91-1.63, p=0.2235) and 2.84 (95%CI=1.64-7.48, p=0.0007) respectively, compared to those carrying the wild-type AA genotype. Supporting this finding, the adjusted OR for those carrying the G allele at MMP7 promoter A-181G was 1.57 (95%CI=1.29-1.93, p=0.0008), compared to those carrying the wild-type A allele. There was no polymorphic genotype at MMP7 C-153T found among any of the investigated individuals. Conclusion: Our findings suggest that the MMP7 A-181G polymorphisms may play a role in determining personal cancer susceptibility and GG genotype at MMP7 A-181G may serve as a biomarker for early detection and prediction of breast cancer in Taiwanese.*

Statistically, breast cancer is the most common malignancy and the leading cause of cancer mortality among females all worldwide (1). Current prognostication is mainly based on histological validation, consuming much manpower and time but of limited value. Therefore, molecular markers for early detection of breast cancer are urgently needed. The vast majority of deaths from breast cancer result from metastasis. Clinically, prognostic stratification of patients is carried out according to the tumor node-metastasis (TNM) staging system, which classifies breast cancer cases based on the extent of the tumor, spread to lymph nodes, and metastasis (2). Therefore, it is reasonable to elucidate useful genomic biomarkers from the aspect of TNM regulation for early detection and prediction of breast cancer.

The matrix metalloproteinases (MMPs) are a family of enzymes in charge of the degradation of a wide spectrum of extracellular matrix (ECM) and non-matrix proteins during both normal physiological processes and pathological states (3, 4). The most critical process in which MMPs are involved during carcinogenesis is the invasion of cancer into the surrounding ECM and penetration of local blood and lymph vessels, contributing to tumor metastasis (5). In the literature, there is mounting evidence indicating that functional polymorphisms of MMPs may contribute to inter-individual differences in susceptibility to several types of cancers (6-15). MMP7 has been detected in breast fibroadenomas and carcinomas (16-18), where it is thought to participate in tumor invasion, as is supported by both *in vitro* (19, 20) and *in vivo* experiments (21-24). MMP7 has also been shown to be produced constitutively by various

*These Authors contributed equally to this study.

Correspondence to: Da-Tian Bau, Terry Fox Cancer Research Laboratory, China Medical University Hospital, 2 Yuh-Der Road, Taichung, 404 Taiwan, R.O.C. Tel: +886 422052121 Ext. 7534, e-mail: datian@mail.cmuh.org.tw; artbau2@gmail.com

Key Words: Breast cancer, genotype, MMP7, polymorphism, Taiwan.

exocrine glands, including the mammary and parotid glands, the pancreas, liver, prostate and peribronchial glands of the lung (25). Furthermore, other reports demonstrated that MMP7 is expressed in both non-neoplastic and neoplastic cells in human breast tissue (17, 18).

In a promoter assay, the basal promoter activity was higher in promoter constructs harboring the combination of the two rare alleles of *MMP7* at A-181G (rs11568818) and C-153T (rs11568819) (26), and the two polymorphisms were reported to influence the dimensions of the coronary artery (26). Among cancer genomic studies, the A-181G genotype of *MMP7* was reported to be associated with many types of cancer, including oral, esophageal, gastric, colorectal, lung, ovarian and renal cell carcinoma (27). For breast cancer, homozygosity for the G allele of *MMP7* A-181G, was positively associated with breast cancer risk in a population of Southeast China (28), but not in those of Western Iran (29) and Caucasian (30). The current study aimed to investigate the contribution of the two *MMP7* promoter polymorphisms, A-181G and C-153T, to susceptibility to breast cancer in Taiwan.

Materials and Methods

Patients and controls. A total of 1,232 female patients diagnosed with breast cancer were enrolled at the China Medical University Hospital, Taichung, Taiwan, R.O.C. At the same time, an equal number of healthy volunteers were selected as the controls for the study after initial random sampling. Exclusion criteria for the healthy controls included metastatic cancer from other or unknown origin, previous malignancy, and any hereditary or genetic disease. All the participants were volunteers, and completed a self-administered questionnaire and gave peripheral blood samples for our analyses. The content of the questionnaire included questions on medical history and the habits of alcohol consumption and cigarette smoking. These factors were recorded and are summarized in Table I. All the enrolled individuals provided their informed consent to participation in this study. Our study was evaluated and approved by the Institutional Review Board of China Medical University Hospital (DMR99-IRB-108). The selected characteristics of the control and patient groups are summarized and compared in Table I.

Methodology of MMP7 genotyping. The total genomic DNA of each participant was extracted from leukocytes from blood and stored as previously described (31-33). The genotyping methodology was the same as we previously published (27). Briefly, the polymerase chain reaction (PCR) cycling conditions were: one cycle at 94˚C for 5 min; 35 cycles of 94˚C for 30 s, 59˚C for 30 s and 72˚C for 30 s, and a final extension at 72˚C for 10 min. The PCR for *MMP7* A-181G was conducted using the forward primer 5'-TGGTACCATAATGTCCTGAATG-3', and the reverse primer 5'-TCGTTATTGGCAGGAAGCACACAATGAATT-3'. The obtained 150 bp PCR product was digested with *Eco*RI and resulted in two fragments of 120 and 30 bp when the G allele was present, while in the presence of the A allele, the 150 bp fragment remained intact. For *MMP7* C-153T, direct sequencing PCR was conducted with the same primers as for *MMP7* A-181G.

Statistical analyses. To ensure that the controls used were representative of the general population and to exclude the possibility of genotyping error, the deviation of the genotypic frequencies of *MMP7* polymorphisms in the controls from those expected under the Hardy–Weinberg equilibrium was assessed using the goodness-of-fit test. Pearson's chi-square test or Fisher's exact test (when the expected number in any cell was less than five) was used to compare the distribution of the *MMP7* genotypes between case and control groups. The associations between the *MMP7* polymorphisms and breast cancer risk were estimated by computing odds ratios (ORs) and their 95% confidence intervals (CIs) from unconditional logistic regression analysis with the adjustment for possible confounders.

Results

Comparison of demographics and lifestyles between the breast cancer case and control groups. The frequency distributions of the demographics and lifestyles for the healthy controls and breast cancer cases are summarized in Table I. Statistically, there were no difference between the two groups for age, age at menarche, age at birth of first child, or age at menopause ($p>0.05$). Regarding smoking and alcohol drinking status, more patients (13.8 and 13.1%) than controls (7.0 and 7.4%) had these habits ($p<0.05$) (Table I).

Association of MMP7 promoter genotypes and breast cancer risk. The distributions of genetic frequencies for *MMP7* A-181G and C-153T polymorphisms in the breast cancer cases and controls are presented and compared in Table II. Firstly, there was no polymorphic genotype at *MMP7* C-153T found among the cases nor the controls (Table II, lower panel). Secondly, the ORs after adjusting for possible confounding factors (age, family history, smoking and alcohol drinking status) for those carrying AG and GG genotypes at *MMP7* promoter A-181G were 1.22 (95%CI=0.91-1.63, $p=0.2235$) and 2.84 (95%CI=1.64-7.48, $p=0.0007$), respectively, compared to those carrying the wild-type AA genotype (Table II, upper panel). The p for trend was significant ($p=0.0018$) (Table II). In the dominant model (AG plus GG *versus* AA), the association between *MMP7* promoter A-181G polymorphism and the risk for breast cancer was also statistically significant (OR=1.39, 95%CI=1.08-2.06, $p=0.0185$) (Table II). To sum up, these data indicate that the GG genotype at *MMP7* A-181G may be a useful biomarker for determining the risk of breast cancer in Taiwan (Table II).

Association of MMP7 allelic subtypes and breast cancer risk. The adjusted OR for those carrying the G allele at *MMP7* promoter A-181G was 1.57 (95%CI=1.29-1.93, $p=0.0008$) compared to those carrying the wild-type A allele (Table III). Consistent with the findings in Table II, there was a statistically differential distribution of allelic frequencies between breast cancer cases and healthy controls for the *MMP7* promoter A-181G (Table III).

Table I. *Demographics and lifestyles of the investigated breast cancer patients and the control healthy females in a Taiwanese population.*

Characteristic	Controls (n=1,232)			Patients (n=1,232)			*p*-Value
	n	%	Mean (SD)	n	%	Mean (SD)	
Age (years)							
<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 (years)			12.4 (0.7)			12.1 (0.6)	0.79[b]
Age at birth of first child (years)			29.4 (1.2)			29.8 (1.4)	0.63[b]
Age at menopause (years)			48.8 (1.8)			49.3 (2.0)	0.59[b]
Tumor site							
Unilateral				1198	97.2%		
Bilateral				34	2.8%		
Family history							
First degree (Mother, sister, and daughter)				55	4.5%		
Second degree				6	0.5%		
No history				1171	95%		
Habit							
Cigarette smoker	86	7.0%		170	13.8%		<0.0001[a]
Alcohol drinker	91	7.4%		162	13.1%		<0.0001[a]

[a]Chi-square or [b]unpaired Student's *t*-test.

Table II. *Distributions of matrix metalloproteinas-7 (MMP7) A-181G and C-153T genotypic frequencies among breast cancer cases and controls in a Taiwanese population.*

	Cancer cases, n (%)	Controls, n (%)	Adjusted OR (95% CI)[a]	*p*-Value[b]
A-181G				
AA	1065 (86.4)	1103 (89.5)	1.00 (Reference)	
AG	134 (10.9)	118 (9.6)	1.22 (0.91-1.63)	0.2235
GG	33 (2.7)	11 (0.9)	2.84 (1.64-7.48)	0.0007*
AG+GG	167 (13.6)	129 (10.5)	1.39 (1.08-2.06)	0.0185*
p_{trend}				0.0018*
C-153T				
CC	1232 (100.0)	1232 (100.0)	1.00 (Reference)	
CT	0 (0.0)	0 (0.0)	--	
TT	0 (0.0)	0 (0.0)	--	
p_{trend}				

OR, Odds ratio; CI, confidence interval. [a]Data have been adjusted for confounding factors include age, family history, smoking and alcohol drinking status. [b]Based on chi-square test without Yates' correction. *Statistically significant.

Table III. *Allelic frequencies for matrix metalloproteinas-7 (MMP7) A-181G and C-153T polymorphisms in the breast cancer case and control groups in a Taiwanese population.*

Polymorphic site, allele	Cancer cases, n (%) N=1232	Controls, n (%) N=1232	Adjusted OR (95% CI)[a]	*p*-Value[b]
A-181G				
Allele A	2264 (91.9)	2324 (94.3)	1.00 (Reference)	0.0008*
Allele G	200 (8.1)	140 (5.7)	1.57 (1.29-1.93)	
C-153T				
Allele C	2464 (100.0)	2464 (100.0)	1.00 (Reference)	
Allele T	0 (0.0)	0 (0.0)	--	

OR, Odds ratio; CI, confidence interval. [a]Data have been adjusted for confounding factors including age, smoking, drinking status, family cancer history. [b]Based on chi-square test without Yates' correction. *Statistically significant.

Discussion

MMP7, located on chromosome 11q21–q22 with 13 exons, is an important member of the MMP gene family, while the MMP7 protein is of broad substrate specificity for both ECM and non-ECM components (34). In the present study, we examined the genotypes of *MMP7* among a Taiwanese breast cancer population, and assessed whether there was an association between the genotypes of *MMP7* A-181G and *MMP7* C-153T with breast cancer risk. The results show that there was a significant association between the presence of the G allele (GG genotype) at *MMP7* A-181G and breast cancer risk in this Taiwanese cohort. Our findings suggest that the GG genotype at *MMP7* A-181G may play a determinant role in increasing susceptibility to breast cancer.

Molecularly, the A-181G polymorphism in the promoter region of *MMP7* gene modulates gene transcription through affecting the binding of nuclear proteins (35, 36). Nuclear proteins bind to the *MMP7* -181G allele with higher affinity than to the -181A allele. Hence, in the presence of the -181G allele, the transient transfection-investigated promoter activity is about 2- to 3-fold higher compared to the -181A allele (35).

Elevated expression of MMP7 may serve as a promising serum marker for the detection of metastasis and prediction of poor survival in gastric (37), colorectal (38, 39) and ovarian cancer (40), but not in lung cancer (41), or breast cancer in our population (data not shown). In an animal model, overexpression of MMP7 contributed to tumorigenicity but did not enhance the invasion and metastasis capacities of tumors (42). In the future, the genotype–phenotype correlation of MMP7 at breast cancer tumor sites should be determined, as should whether the elevated expression of MMP7 at mRNA or protein levels contributes to lymph node metastasis of breast cancer. Importantly, since the status of invasion and metastasis are usually determined at the time of diagnosis, no firm conclusion regarding the contribution of the *MMP7* −181A/G polymorphism to tumor metastasis can be drawn until the long-term follow-up of patients with breast cancer has been completed.

In conclusion, our results suggest that the promoter polymorphisms of *MMP7*, namely -181G, significantly confers higher susceptibility to breast cancer in Taiwanese than does *MMP7* -181A. Multi-centered and well-designed epidemiological studies are needed to validate our findings. Further signaling network studies are warranted before the contribution of *MMP7* to breast cancer can be fully ascertained.

Acknowledgements

The Authors are grateful to Hsin-Ting Li and Shiou-Ting Yen for their excellent technical assistance. The clinical team of Dr. Su, Wang and Liu in sample collection and all the participants in this study are appreciated. This study was supported partially by a research grant from Taiwan Ministry of Health and Welfare Clinical Trial and Research Center of Excellence (MOHW106-TDU-B-212-113004). The funders had no role in study design, data collection and analysis, decision to publish or preparation of the article.

Conflicts of Interest

The Authors declare no conflict of interest in regard to this study.

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Received July 9, 2017
Revised July 27, 2017
Accepted August 1, 2017