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The Association of Matrix Metalloproteinase-1 Promoter Polymorphisms with Prostate Cancer in Taiwanese Patients

CHENG-HSI LIAO[1,2,3], HSI-CHIN WU[4], PEI-SHIN HU[1,5], SHIH-WEI HSU[1,2,3], TE-CHUN SHEN[1,4], TE-CHUN HSIA[4], WEN-SHIN CHANG[4], CHIA-WEN TSAI[4] and DA-TIAN BAU[1,4,6]

[1]*Graduate Institute of Biomedical Sciences, China Medical University, Taichung, Taiwan, R.O.C.;*
[2]*Taichung Armed Forces General Hospital, Taichung, Taiwan, R.O.C.;*
[3]*National Defense Medical Center, Taipei, Taiwan, R.O.C.;*
[4]*Terry Fox Cancer Research Laboratory, Translational Medicine Research Center, China Medical University Hospital, Taichung, Taiwan, R.O.C.;*
[5]*Department of Ophthalmology, Changhua Christian Hospital, Changhua, Taiwan, R.O.C.;*
[6]*Department of Bioinformatics and Medical Engineering, Asia University, Taichung, Taiwan, R.O.C.*

Abstract. *Background/Aim: The family of matrix metalloproteinases (MMPs) is responsible for the maintenance of extracellular matrix component homeostasis and the association of MMP-1 genetic polymorphisms with personal susceptibility to prostate cancer has only been investigated in Turkish and Japan populations and never in Taiwan. In the current study, we aimed to examine the contribution of a polymorphism in the promoter region of MMP-1 to Taiwan prostate cancer. Materials and Methods: The MMP-1 rs1799705 polymorphic genotypes were genotyped among 218 prostate cancer patients and 436 healthy controls by the typical polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) methodology. Results: The percentages of 2G/2G, 1G/2G, and 1G/1G for MMP-1 -1607 genotypes were 36.2, 40.4 and 23.4% in the prostate cancer group and 33.7, 44.3, and 22.0% in the healthy control group (p trend=0.6362), respectively. The odds ratios (ORs) after adjusting for age and smoking status for those carrying 1G/2G and 1G/1G genotypes at MMP-1 -1607 were 0.84 (95%CI=0.55-1.21, p=0.3862) and 0.94 (95%CI=0.67-1.53, p=0.9586), respectively, compared to those carrying the wild-type 2G/2G genotype. Supporting these findings, the adjusted OR for those carrying the 1G allele at MMP-1 -1607 was 1.03 (95%CI=0.71-1.45, p=0.6910), compared to those carrying the wild-type 2G allele. Conclusion: Our findings suggest that the polymorphic genotypes at MMP-1 promoter -1607 may play a major role in determining personal cancer susceptibility for prostate cancer in Taiwan.*

Correspondence to: Da-Tian Bau, Chia-Wen Tsai and Wen-Shin Chang, Terry Fox Cancer Research Laboratory, Translational Medicine Research Center, China Medical University Hospital, 2 Yuh-Der Road, Taichung, 404 Taiwan, R.O.C. Tel: +886 422053366 Ext. 5805, e-mail: datian@mail.cmuh.org.tw; artbau2@gmail.com

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For many years, prostate cancer (MIM 176807) has been one of the most prevalent male cancers in western countries, such as USA, and its incidence is increasing in the Asia-Pacific countries (1). Although the rapid advances in surgical techniques and radiotherapy have improved the disease-free survival rates of prostate cancer patients with localized occurrences, the recurrence rate after radical prostatectomy, chemotherapy, or radiotherapy is still very high (2). In addition to some environmental and lifestyle-related factors, such as physical inactivity, obesity, and a high-fat diet, the most important risk factors for prostate cancer is having a family cancer history (3). Since, the prevalence rates of prostate cancer are both increasing in Taiwan and the world, to figure out feasible molecular markers for early detection and prognosis prediction of prostate cancer is one of the urgent missions for cancer genomic scientists (4).

Matrix metalloproteinases (MMPs) consist of a multigene family of zinc-dependent extracellular matrix (ECM) remodeling endopeptidases implicated in pathological processes, such as carcinogenesis (5, 6). In this regard, their activity plays a pivotal role in tumor growth and the multistep processes of invasion and metastasis, including proteolytic degradation of ECM, alteration of the cell-cell and cell-ECM interactions, migration and angiogenesis (7). In the literature, there are mounting few reports indicating that some *MMP* polymorphic genotypes, especially those implicated in the expression regulation, play a critical role in determining inter-individual differences of susceptibility to several types of cancer (8-16), while some others do not (17-24).

In the literature, the most commonly investigated *MMP-1* polymorphism is rs1799750 at its promoter region. The *MMP-1* rs1799750 located at -1,607 of the promoter of the *MMP-1* gene, consisting of an insertion ("2G/2G") polymorphism which is reported to lead to higher transcriptional activity of this gene, potentially to higher levels or rates of collagen breakdown, and higher levels of MMP-1 in their serum than those mice with 1G/1G genotypes (25). A meta-analysis investigating about 10,000 cancer cases, half of which metastasized, concluded that *MMP-1* rs1799750 2G/2G genotypes had a slightly higher overall risk of metastasis (26). As for prostate cancer, the reports from Weng H and his colleagues investigating three studies showed that overall analyses of *MMP-1*-1607 1G/2G polymorphism and risk of prostate cancer did not reach a statistical significant level (27). However, decreased risk of prostate cancer was observed in the Caucasians for *MMP-1*-1607 1G/2G polymorphism (27). The authors mentioned that the decreased risk of prostate cancer concerning *MMP-1*-1607 1G/2G polymorphism in Caucasians might be spurious results or false positives, and the significant differences were observed based on only two studies with limited participants (28, 29). Since there are no previous reports investigating the contribution of *MMP-1* rs1799750 in Taiwan, the current study aimed to examine the genetic frequencies of *MMP-1* rs1799750 promoter genotypes and evaluating the contribution of *MMP-1* genotypes to the susceptibility of prostate cancer in a representative Taiwanese population with 218 prostate cancer patients and 436 non-cancer healthy controls in central Taiwan.

Materials and Methods

Investigated prostate cancer and healthy control subjects. In this study, two hundred and eighteen patients diagnosed with prostate cancer were recruited at the outpatient clinics of general surgery and collected with the help of Tissuebank at the China Medical University Hospital, Taichung, Taiwan, Republic of China (30, 31). All patients participated voluntarily, completed a self-administered questionnaire and provided the peripheral blood samples. At the same period, a total of 436 non-prostate cancer healthy volunteers were recruited as controls, selected by matching for age, gender and habits after initial random sampling from the Health Examination Cohort of the hospital. The exclusion criteria of the control group included previous malignancy, metastasized cancer from other or unknown origin, and any familial or genetic diseases. All subjects in both groups have completed a short questionnaire which included questions about smoking and alcohol drinking habits. The study was approved by the Institutional Review Board of the China Medical University Hospital and written-informed consent was obtained from all participants.

MMP-1 genotyping methodology. The genomic DNA of the peripheral blood leukocytes of each participant was extracted, aliquoted and stored as previously described (32). The sequences of primer pairs for *MMP-1* rs1799750 polymorphism were designed by our team as previously published (20). Briefly, genotyping polymerase chain reaction (PCR) cycling conditions *via* My Cycler (Biorad, Hercules, CA, USA) for *MMP-1* were: one cycle at 94˚C for 5 min; 35 cycles of 94˚C for 30 sec, 57˚C for 30 sec and 72˚C for 30 sec and a final extension at 72˚C for 10 min (32).

Statistical methodology. The deviation of the genotypic frequencies of MMP-1 polymorphisms in the healthy controls from those expected under the Hardy–Weinberg equilibrium was assessed using the goodness-of-fit test to ensure that the controls used were representative of the general population and to exclude the possibility of genotyping error. The unpaired *t*-test and Pearson's chi-square test were used to compare the ages between case and control groups, and the distribution of the *MMP-1* genotypes between case and control groups, respectively. The associations between the *MMP-1* polymorphisms and prostate 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 when indicated.

Results

Comparison of demographics and lifestyles between the prostate cancer patient and control groups. The distributions of frequencies of the ages and smoking status of the 218 prostate cancer patients and 436 healthy controls are summarized in Table I. Statistically, there was no difference between the two groups as for their ages (p=0.58). Regarding personal smoking habits, it was found that more cancer patients (81.2%) than healthy controls (77.0%) were smokers (p<0.05) during their life time in this selected cohort population (Table I).

Association of MMP-1 promoter genotypes and prostate cancer risk. The distributions of genetic frequencies for the investigated *MMP-1* -1607 polymorphisms among the prostate cancer patients and healthy controls are presented and compared in Table II. Compared to the wild-type genotype (2G/2G) sub-group, there was no significant altered risk for the hetero-variant 1G/2G or homo-variant 1G/1G genotypes, even after adjustment for the confounding factors including age and smoking status (adjusted OR=0.84 and 0.94, 95%CI=0.55-1.21 and 0.67-1.53, p=0.3862 and 0.9586; respectively). The results of recessive (2G/2G+1G/2G *versus* 1G/1G) and dominant (2G/2G *versus* 1G/1G+1G/2G) model analysis in the carrier comparison also showed a non-significant level for the variant 1G allele to behave as a determinant of personal prostate cancer susceptibility in Taiwan (Table II).

Association of MMP-1 allelic subtypes and prostate cancer risk. The frequencies of the *MMP-1* promoter -1607 alleles among prostate cancer patient and healthy control subjects are presented in Table III. Supporting the findings shown in Table II, the variant 1G allele at *MMP-1* -1607 was not significantly associated with prostate cancer risk (adjusted OR=0.98, 95%CI=0.79-1.21, p=0.8439) (Table III).

Table I. *Demographics and life styles of the 218 prostate cancer patients and the 436 healthy control subjects in Taiwan.*

Characteristic	Controls (n=436)			Patients (n=218)			*p*-Value
	n	%	Mean (SD)	n	%	Mean (SD)	
Age (years)			63.9 (6.6)			63.6 (6.9)	0.58[a]
<50	275	63.1%		142	65.1%		0.67[b]
≥55	161	36.9%		76	34.9%		
Family history							
First degree (Father, brother, and son)				17	7.8%		
Second degree				4	1.8%		
No history				197	90.4%		
Smoking Habit							
Ever smoker	336	77.0%		177	81.2%		0.27[b]
Non-smoker	100	23.0%		41	18.8%		

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

Table II. *Distributions of matrix metalloproteinase-1 (MMP-1) -1607 genotypic frequencies among 218 prostate cancer cases and 436 healthy controls in Taiwan.*

	Cases (%)	Controls (%)	Adjusted OR (95%CI)[a]	*p*-Value[b]
MMP-1 -1607				
2G/2G (wild-type)	79 (36.2)	147 (33.7)	1.00 (reference)	
1G/2G	88 (40.4)	193 (44.3)	0.84 (0.55-1.21)	0.3862
1G/1G	51 (23.4)	96 (22.0)	0.94 (0.67-1.53)	0.9586
p for trend				0.6362
Carrier comparison				
2G/2G+1G/2G	167 (76.6)	340 (78.0)	1.00 (reference)	
1G/1G	51 (23.4)	96 (22.0)	1.03 (0.71-1.45)	0.6910
2G/2G	79 (36.2)	147 (33.7)	1.00 (reference)	
1G/1G+1G/2G	139 (63.8)	289 (66.3)	0.83 (0.64-1.23)	0.5224

OR: Odds ratio; CI: confidence interval. [a]Data has been adjusted with confounding factors include age and smoking status; [b]Based on Chi-square test without Yates' correction test.

Table III. *Allele frequencies of matrix metalloproteinase-1 (MMP-1) -1607 1G/2G among 218 prostate cancer cases and 436 healthy controls in Taiwan.*

Allele	Cases (%) n=436	Controls (%) n=872	Adjusted OR (95%CI)[a]	*p*-Value[b]
MMP-1 -1607				
Allele 2G	246 (56.4)	487 (55.8)	1.00 (reference)	0.8439
Allele 1G	190 (43.6)	385 (44.2)	0.98 (0.79-1.21)	

OR: Odds ratio; CI: confidence interval. [a]Data has been adjusted with confounding factors include age and smoking status; [b]Based on Chi-square test without Yates' correction test.

To sum up, the findings in Tables II and III are consistently supporting each other in that *MMP-1* -1607 genotypic or allelic variants were not determinant factors for prostate cancer risk in Taiwan.

Discussion

A peculiarity of tumor cells is their enhanced ability to migrate and invade into adjacent tissues. The interaction of cells and extracellular matrix is dynamically regulated and plays a role in tumor migration, while the MMPs are critically responsible for maintaining the homeostasis of the components of extracellular matrix (33, 34). MMPs were frequently shown to be accumulated at the leading edge of elongated tumor cells during metastasis, and the up-regulation of MMPs in several types of cancer from their normal conditions was often associated with poor prognosis of the cancer patients (35-39). Among breast cancer cells of different tumorigenicities, it is found that more malignant cells had increased levels of MMPs than the less malignant ones (40). Noticeably, more malignant cells do express higher levels of MMP-3, -9, -13, and the key player of the current study, MMP-1 (41, 42).

The investigations regarding the genotypic contribution of MMP-1 to prostate cancer are very few (28, 29), while there are numerous attempts to obtain molecular antagonists of integrins inhibiting signal pathways from these proteins which lead to MMP or FAK activation or stimulate vessel development in tumors (43). The promoter polymorphic site of *MMP-1*, -1607, may determine the levels of MMP-1 and influence the personal susceptibility to prostate cancer. In the current study, it was demonstrated that the genotypes of *MMP-1* -1607 were non-significantly associated with prostate cancer in the investigated population in Taiwan

(Tables II and III). This negative association is similar to those findings in Turkish and Japanese populations, respectively (28, 29). In 2017, Weng and his colleagues conducted a meta-analysis, and concluded that no significant association was observed between *MMP-1* -1607 1G/2G polymorphism and the risk of prostate cancer (27). Although the sample size of the current study (control:case=436:218) is more representative than the previous studies in Turkish (control:case=43:55) and Japan (control:case=251:283) populations (28, 29), the contribution of *MMP-1* polymorphic genotypes to prostate cancer still needs further validation in multi-center and multi-population studies.

It is well acknowledged that prostate cancer is a multifactorial and complicated disease involving both gene and environment factors, and the contribution of smoking to prostate cancer is also of high interest. In 2010, smoking has been identified as a risk factor for prostate cancer with a meta-analysis pooling together the data from 24 individual investigations enrolling more than 26,000 participants with prostate cancer all over the world (44). We have conducted the analysis of the interaction of smoking behavior and *MMP-1* -1607 1G/2G polymorphic genotypes, finding that there is no differential distribution of the *MMP-1* -1607 1G/2G polymorphic genotypes among smokers or non-smokers (data not shown). We have to conservatively take into consideration the following two points when interpreting the results of this gene-environment interaction: a) the smoking prevalence in prostate cancer patients (81.2%) is much higher in the cohort study than the average in Taiwan; 2) when matching the controls with the cases, the colleagues have also matched the percentages of smoking behaviors (77.0%), therefore, the smoking percentage for the non-cancer subjects is also much higher in the cohort study than the average of Taiwan.

In conclusion, our results suggest that the *MMP-1* -1607 1G/2G polymorphic genotypes did not significantly predispose Taiwanese males and could not serve as good predictors for prostate cancer susceptibility. Further phenotypic studies, such as the determination of MMP-1 levels in the serum of prostate cancer patients and genotype-phenotype correlations are warranted.

Conflicts of Interest

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

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