

## Association of Matrix Metalloproteinase-1 Genotypes With Bladder Cancer Risk

CHENG-HSI LIAO<sup>1,2,3\*</sup>, CHIA-WEN TSAI<sup>4\*</sup>, WEN-SHIN CHANG<sup>4\*</sup>, ZHI-HONG WANG<sup>5</sup>,  
CHI-LI GONG<sup>4</sup>, HSI-CHIN WU<sup>4</sup>, BO-REN WANG<sup>1,2,3</sup>, SHIH-WEI HSU<sup>1,2,3</sup>,  
WEN-CHIN HUANG<sup>1</sup>, TE-CHUN SHEN<sup>4</sup> and DA-TIAN BAU<sup>1,4,6</sup>

<sup>1</sup>Graduate Institute of Biomedical Sciences, China Medical University, Taichung, Taiwan, R.O.C.;

<sup>2</sup>Department of Surgery, Taichung Armed Forces General Hospital, Taichung, Taiwan, R.O.C.;

<sup>3</sup>National Defense Medical Center, Taipei, Taiwan, R.O.C.;

<sup>4</sup>Terry Fox Cancer Research Laboratory, Department of Medical Research,  
China Medical University Hospital, Taichung, Taiwan, R.O.C.;

<sup>5</sup>Department of Food Nutrition and Health Biotechnology, Asia University, Taichung, Taiwan, R.O.C.;

<sup>6</sup>Department of Bioinformatics and Medical Engineering, Asia University, Taichung, Taiwan, R.O.C.

**Abstract.** Aim: There is very little literature reporting the association of matrix metalloproteinase-1 (MMP1) with personal susceptibility to bladder cancer. In the current study, we carried out the first examination of the contribution of MMP1 rs1799750 to bladder cancer risk in Taiwanese. Materials and Methods: A total of 375 bladder cancer cases and 375 healthy controls were genotyped for MMP1 rs1799750 via polymerase chain reaction-restriction fragment length polymorphism methodology and this was evaluated for association with clinicopathological factors. Results: The frequencies of MMP1 rs1799750 2G/2G, 1G/2G, and 1G/1G genotypes were 35.7%, 44.8% and 19.5% in the group with bladder cancer and 32.5%, 46.4%, and 21.1% in the healthy control group ( $p$  for trend=0.6362). The odds ratios (ORs) for bladder cancer risk after adjusting for age and gender for those carrying 1G/2G and 1G/1G genotypes at MMP1 rs1799750 were 0.88 (95% CI=0.62-1.24,  $p$ =0.4357) and 0.83 (95% CI=0.61-1.26,  $p$ =0.3990), respectively, compared with the wild-type 2G/2G genotype. In allelic frequency analysis, the adjusted OR for those carrying the 1G allele at MMP1 rs1799750 was 0.87 (95% CI=0.71-1.23,  $p$ =0.3479)

compared to those people carrying a 2G allele. Conclusion: Our findings indicated that the genotypes at MMP1 rs1799750 appear to play little role in determining personal susceptibility to bladder cancer for Taiwanese.

Bladder cancer is the 11<sup>th</sup> most common cancer, accounting for about 3% of total cancer deaths globally estimated in 2018 (1). In Taiwan, although the incidence rates of bladder cancer have decreased in recent years, the rapid aging of the population means bladder cancer remains a serious public burden, which has an impact on patients and their relatives, resulting in a massive financial problem for society overall (2, 3). From the epidemiological viewpoint, tobacco smoking is believed to be the most critical risk factor for bladder cancer (4, 5), in addition to diabetes, exposure to chemicals, contamination in drinking water by arsenic, overuse of traditional Chinese herbs and genetic variations (6-9). A better understanding about genetic predictive markers of bladder cancer is useful for personalized medication and therapy, and reducing the incidence of and death rate by bladder cancer.

In literature, mounting evidence has shown that genetic polymorphisms of matrix metalloproteinases (MMPs) may contribute to the development of bladder cancer (10). MMPs, also named as matrixins, are a large protein family controlling metabolism of the extracellular matrix (11-13). MMPs are closely related to a series of cell behaviors such as proliferation, inflammation, apoptosis, invasion, migration and angiogenesis (12, 13). In literature, much evidence has shown that polymorphic variants of MMPs may be associated with personal susceptibility to several types of cancer (14-19).

In 2010, Chuang and colleagues examined the expression of MMPs in 30 bladder neoplasms, finding all were MMP1-positive, while other MMPs such as MMP2 and MMP9 were

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\*These Authors contributed equally to this study.

Correspondence to: Da-Tian Bau, Terry Fox Cancer Research Laboratory, Department of Medical Research, 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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not so highly expressed (20). In addition, the overexpression of MMP1 was not correlated with tumor staging nor grading (20). The genomic role of *MMP1* remains unclear. In literature, the most commonly studied polymorphic site of *MMP1* is rs1799750 which located at -1,607 of the promoter of the *MMP1* gene. The variants at this polymorphic site consist of the insertion (2G) polymorphism, which in mice was reported to lead to higher transcriptional activity of *MMP1*, potentially higher levels or rates of collagen breakdown, and higher levels of MMP1 in serum than in mice with 1G/1G genotype (21). A meta-analysis published in 2012 investigating about 10,000 cancer cases concluded that those *MMP1* carrying the rs1799750 2G/2G genotype may have a slightly higher overall metastasis rate (22). In light of all the above, the aim of the current study was to examine the contribution of *MMP1* rs1799750 genotype at the promoter region to the risk of bladder cancer in Taiwanese.

## Materials and Methods

**Patients with bladder cancer and matched controls.** Totally, 375 cases diagnosed with bladder cancer were collected at the China Medical University Hospital in central Taiwan. At the same time, 375 controls matched for age and gender were selected from the Health Examination Cohort. The exclusion criteria for the controls were any previous malignancy, metastasized cancer, and any known familial or genetic diseases. The study design was approved by the Institutional Review Board of the China Medical University Hospital (DMR104-IRB-158). Selective demographic characteristics are summarized in Table I.

**Methodology for determination of *MMP1* rs1799750 genotype.** Genomic DNA from the blood of each participant was extracted, aliquoted and stored at -80°C as routinely conducted (23-25). The *MMP1* genotyping methodology was the same as in our recently published article (26). The polymerase chain reaction (PCR) conditions set at My Cycler (Biorad, Hercules, CA, USA) for *MMP1* genotyping were initially one cycle at 94°C for 5 min; followed by 35 cycles of 94°C for 30 s, 57°C for 30 s and 72°C for 30 s, and a final extension at 72°C for 10 min.

**Methodology for statistical analysis and determination of significance.** The descriptive statistics of bladder cancer cases and healthy controls are shown as the mean and standard deviation (SD) or as percentages. In Table I, Student's *t*-test was adopted for the comparison of ages between the two groups. In Tables I-III, Pearson's chi-square test without Yates' correction was used to compare the distribution of the subgroups. In addition, associations were evaluated using adjusted odds ratios (aORs) with their corresponding 95% confidence intervals (CIs) with adjustment for age, gender, and personal habits. Differences were identified as being significant when the *p*-value was less than 0.05.

## Results

**Comparison of characteristics among the patient and the healthy control groups.** Characteristics such as age, gender,

Table I. Basic characteristics of the 375 bladder cancer cases and 375 healthy controls.

Characteristic	Controls (n=375)	Cases (n=375)	<i>p</i> -Value
Age, years			
Mean±SD	62.9±9.8	61.4±10.3	0.7315 <sup>a</sup>
Age group			
≤55 Years	152 (40.5%)	158 (42.1%)	0.7108 <sup>b</sup>
>55 Years	223 (59.5%)	217 (57.9%)	
Gender			
Male	287 (76.5%)	279 (74.4%)	0.5525 <sup>b</sup>
Female	88 (23.5%)	96 (25.6%)	
Personal habit			
Cigarette smoking	186 (49.6%)	201 (53.6%)	0.3063 <sup>b</sup>
Alcohol drinking	176 (46.9%)	189 (50.4%)	0.3807 <sup>b</sup>
Stage			
Non-muscle-invasive		235 (62.7%)	
Muscle-invasive		140 (37.3%)	
Grade			
Low		151 (40.3%)	
High		224 (59.7%)	

SD: Standard deviation. <sup>a</sup>based on Student's *t*-test. <sup>b</sup>based on chi-squared test without Yates' correction.

personal habits, tumor stage and grades for the 375 control and 375 patients with bladder cancer are shown in Table I. Firstly, there was no difference found in the distribution of age and gender between the patient and healthy control groups since these frequencies were matched during recruiting of the non-cancer healthy controls. Secondly, neither smokers nor alcohol drinkers were found to be more frequent in the case group than in the control group (both *p*>0.05). It showed there was no difference in the frequency of smokers/drinkers between the two groups. Lastly, bladder cancer was mostly of non-muscle-invasive type (62.7%) and high clinical stage (59.7%).

**Association of *MMP1* rs1799750 genotypes and bladder cancer risk.** The genotypic analysis for the *MMP1* rs1799750 among the controls and the patients with bladder cancer is shown in Table II. The *MMP1* rs1799750 genotypic frequency distributions were not significantly different between the control and the case groups (*p* for trend=0.6362) (Table II). In detail, 1G/2G and 1G/1G variants at *MMP1* rs1799750 seemed not to be associated with an elevated bladder cancer risk [aOR=0.88 (95% CI=0.62-1.24) and 0.83 (95% CI=0.61-1.26); *p*=0.4357 and 0.3990, respectively; Table II]. Compared with those carrying a 2G allele (2G/2G+1G/2G), homozygosity for the 1G allele at *MMP1* rs1799750 conferred no risk for bladder cancer (aOR=0.88, 95% CI=0.62-1.27; *p*=0.5857) (Table II). Lastly, compared with those homozygous for the 2G allele, the analytic results still showed that carrying a 1G allele (1G/1G+1G/2G) at *MMP1* rs1799750 did not alter bladder cancer risk

Table II. Distributions of matrix metalloproteinase-1 (MMP1) rs1799750 genotypic frequencies among patients with bladder cancer and healthy controls.

MMP1	Bladder cancer, n (%)	Controls, n (%)	Adjusted OR (95% CI) <sup>a</sup>	p-Value <sup>b</sup>
rs1799750				
2G/2G	134 (35.7)	122 (32.5)	1.00 (Reference)	
1G/2G	168 (44.8)	174 (46.4)	0.88 (0.62-1.24)	0.4357
1G/1G	73 (19.5)	79 (21.1)	0.83 (0.61-1.26)	0.3990
P <sub>trend</sub>				0.6362
P <sub>HWE</sub>				0.2482
Carrier comparison				
2G/2G+1G/2G	302 (80.5)	296 (78.9)	1.00 (Reference)	
1G/1G	73 (19.5)	79 (21.1)	0.88 (0.62-1.27)	0.5857
2G/2G	134 (35.7)	122 (32.5)	1.00 (Reference)	
1G/1G +1G/2G	241 (64.3)	253 (67.5)	0.86 (0.65-1.18)	0.3554

CI: Confidence interval; OR: odds ratio; P<sub>HWE</sub>: p-value under Hardy-Weinberg equilibrium <sup>a</sup>Data were adjusted for age, gender, and personal habits.

<sup>b</sup>Based on chi-square test without Yates' correction.

Table III. Allelic frequencies for matrix metalloproteinase-1 (MMP1) rs1799750 polymorphism among patients with bladder cancer and healthy controls.

MMP1 Allele	Bladder cancer, n (%)	Controls, n (%)	Adjusted OR (95% CI) <sup>a</sup>	p-Value <sup>b</sup>
2G	436 (58.1)	418 (55.7)	1.00 (Reference)	
1G	314 (41.9)	332 (44.3)	0.87 (0.71-1.23)	0.3479

CI: Confidence interval; OR: odds ratio. <sup>a</sup>Data were adjusted for age gender, and personal habits. <sup>b</sup>Based on chi-square test without Yates' correction.

(aOR=0.86, 95% CI=0.65-1.18; p=0.3554) (Table II). Overall, *MMP1* rs1799750 seemed to have no direct contribution to the risk of bladder cancer.

**Bladder cancer risk according to *MMP1* promoter allelic frequencies.** The distributions of alleles for *MMP1* rs1799750 among the patients with bladder cancer and healthy controls are shown in Table III. Consistent with the findings in Table II, analysis of allelic frequencies showed that the 1G allele at *MMP1* rs1799750 was not significantly associated with the risk of bladder cancer in Taiwan (p=0.3479, adjusted OR=0.87, 95% CI=0.71-1.23) (Table III). In detail, the percentages of variant allelic frequencies in the groups of cases and controls were 41.9% and 44.3%, respectively (Table III). The results of analysis of *MMP1* rs1799750 genotypes after stratifying by age, gender, smoking and alcohol consumption status showed no associations at all (all p>0.05, data not shown). Clinically, there was no significant difference in distributions between different stages and grades (both p>0.05, data not shown).

## Discussion

One of the major components of the extracellular matrix is collagen, the enzymatic substrate of MMP1. In esophageal and

colorectal cancer tissues, MMP1 has been shown to be overexpressed and associated with higher risk of death (27, 28). As early as 1979, a pilot study showed that muscle-invasive bladder cancer tissues have higher collagenase activity as their non-invasive counterparts (29). Later MMP1 was detected in the urine of patients with bladder cancer for the first time, and its concentration was found to be significantly increased in urine from patients with higher stage and grade (30). Elevated MMP1 has also been associated with poor survival of patients with bladder cancer (31). Notably, it has been reported that MMP1 was overexpressed in all tissues of fresh-prepared samples from patients with bladder cancer (n=30), while the overexpression of MMP1 was not correlated with tumor staging nor grading (20). It is hypothesized that inherited genomic variations may determine personal susceptibility to bladder cancer initiation, progression, invasion and metastasis.

In the literature, associations of *MMP1* genotypes have been examined among many types of cancer, such as lung (32, 33), breast (34-36), oral (37), colorectal (38, 39), gastric (40-42), endometrial (43), cervical (44, 45), prostate (17, 46), and ovarian (47, 48), in addition to bladder cancer (49-52). Although there were several studies investigating the association of *MMP1* genotypes with bladder cancer, the results were inconclusive and the total sample size is far from convincing, which we discuss later.

Table IV. A concise summary of literature regarding the association of matrix metalloproteinase-1 (*MMP1*) rs1799750 genotype with bladder cancer risk.

Authors (Ref)	Year published	Population	Controls, n	Cases, n	Highlighted findings
Kader <i>et al.</i> (50)	2006	Caucasian	560	560	<i>MMP1</i> rs1799750 genotype is not associated with bladder cancer risk
Tasci <i>et al.</i> (49)	2007	Turkish	94	102	2G Allele is associated with increased bladder cancer risk, especially among smokers
Srivastava <i>et al.</i> (51)	2010	Indian	200	200	2G Allele is associated with increased bladder cancer risk, especially among smokers
Wieczorek <i>et al.</i> (52)	2013	Polish	199	241	2G Allele is associated with increased bladder cancer risk, especially among smokers
Current		Taiwanese	375	375	<i>MMP1</i> rs1799750 genotype is not associated with bladder cancer risk, and no increased risk among smokers

In the present study, it was found that the 1G allele of *MMP1* rs1799750 was not significantly associated with risk of bladder cancer (Tables II and III). In addition, *MMP1* rs1799750 genotypes were not associated with age, gender, nor smoking and alcohol consumption behaviors (data not shown). Compared with previous studies, our samples are more genetically conserved (all Taiwanese) and representative (375 patients with bladder cancer and 375 healthy controls). We have summarized previous articles on *MMP1* in bladder cancer in Table IV. Our findings are consistent with that reported by Kader and colleagues (50) but not with others with relatively limited samples (49-52). There may be ethnic variations among the reports, and more investigations are needed. Another limitation of the study is that we did not measure the phenotypic status of the participants, and have no understanding the correlation of 1G allele at *MMP1* rs1799750 and transcriptional activity. In addition, the associations between the expression level of *MMP1* with other parameters, such as age, gender, smoking or alcohol consumption status, or tumor stage and grade, are not available. Chuang and colleagues analyzed 30 samples, finding that *MMP2* was correlated with high-grade tumors and *MMP9* was correlated with advanced tumor stage. However, the expression of *MMP1*, *MMP3*, and tissue inhibitor of metalloproteinase-1 and -2 was not correlated with either tumor staging or grading (20). Their data are valuable, however, there is no genotype-phenotype correlation.

In conclusion, this study examined the genotypic patterns of *MMP1* rs1799750 among Taiwanese people. Neither *MMP1* 1G nor 2G allele appeared to contribute to susceptibility of bladder cancer. Some other markers, for instance single nucleotide polymorphisms on other *MMPs* may play more critical roles than *MMP1*, and further investigations are needed to elucidate their role in bladder cancer etiology.

### Conflicts of Interest

The Authors have declared no conflicts of interest.

### Authors' Contributions

Research design: Liao CH, Tsai CW and Chang WS; patient and questionnaire summaries: Liao CH, Wu HC and Wang BR; experimental work: Gong CL, Chang WS and Wang ZH; statistical analysis: Hsu SW, Huang WC and Shen TC; article writing: Tsai CW and Bau DT; review and revision: Bau DT.

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