**INTRODUCTION**

Bladder cancer (BCa) was estimated to be the seventh most common type of cancer worldwide in 2009 [1]. In Poland, BCa was the third most frequent malignant tumor in men and thirteenth in women in 2009 [2]. Etiology of BCa includes environmental factors such as exposure to tobacco smoke, occupational exposure, and geography of selected infectious diseases like schistosomiasis [3]. The group of patients with non–muscle–invasive disease (NMIBC) covers 75% and muscle invasive disease (MIBC) covers 25% of BCa patients. About 20% of NMIBC occur as recurrences of MIBC and are related with an increased risk of metastases and low survival [4]. Therefore, more extensive studies are currently in progress to elucidate the importance of the various tumor characteristics or genetic factors in the areas of BCa risk, recurrence or progression [5, 6].

**MMPs** are implicated in various stages of physiological processes such as embryonic development, ovulation, wound healing, and pathophysiological processes like heart failure, arthritis, atherosclerosis, periodontal disease, bone remodeling, and carcinogenesis. MMPs can hydrolyze most of the extracellular matrix (ECM) components, a range of non–

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**MMP7 and MMP8 genetic polymorphisms in bladder cancer patients**

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**Key Words:** MMP ‹› genetic polymorphism ‹› case–control study ‹› bladder cancer

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**Introduction.** Breakdown of the extracellular matrix by matrix metalloproteinases (MMPs), as we know, is one of mechanisms involved and required in tumor invasion. MMP7 is a negative prognostic factor of various malignances, while MMP8 exhibits an inhibitory effect on tumorigenesis and metastasis. We evaluated the potential association of functional polymorphisms in the promoter of the MMP7 (rs11568818) and MMP8 (rs11225395) genes and bladder cancer (BCa) risk.

**Materials and methods.** The study included 241 BCa cases and 199 healthy population controls that were collected at the First Department of Urology, Medical University (Łódź, Poland) and at the Nofer Institute of Occupational Medicine (Łódź, Poland). Genomic DNA samples were isolated from venous blood and genetic polymorphisms were analyzed by real–time polymerase chain reaction using TaqMan fluorescent probes. Associations between genotype and allele status were estimated by logistic regression models adjusted for classic risk factors (e.g. age, gender and cigarette smoking).

**Results.** MMP7 and MMP8 genotypes were distributed similarly in BCa patients and in controls and at least one variant allele was not associated with BCa cancer risk (OR, 0.91; 95% CI, 0.60–1.39; p = 0.662 for MMP7 and OR, 0.96; 95% CI, 0.63–1.46; p = 0.836 for MMP8). We observed higher prevalence of MMP7 GG genotypes among BCa patients than in controls (OR, 1.54; 95% CI, 0.93–2.55; p = 0.093). Additionally, genetic polymorphisms in the MMP7 and MMP8 were not associated with the tumor grade or stage.

**Conclusions.** Our results suggest that genetic variations in two genes encoding members of the MMP7 and MMP8 are not associated with a risk of BCa in the Caucasian population.
matrix proteins, matrix substrates, and bioactive substrates. MMPs can also release from the ECM the signaling molecules important in tumor progression and metastasis [7]. MMPs are the enzymes that are able to organize the tissue architecture required in the process of carcinogenesis and contribute to cell adhesion, epithelial to mesenchymal transition, and tumor angiogenesis [8].

MMP7 also known as matrilysin–1 or PUMP–1, possesses broad substrate specificity, and can degrade collagen types: IV, V, IX, X, XI, aggrecan, entactin, laminin, vitronectin, fibrin/fibrinogen, tenascin, gelatin, fibronectin, and other substrates of the ECM components [7]. MMP7 expression can promote cancer cell growth and thus can be associated with tumor invasion, recurrence and poorer survival for various malignances [9–16]. MMP8, commonly known as collagenase–2 or neutrophil collagenase, hydrolyzes collagen types: I, II, III, VII, X, gelatin, entactin, tenascin, aggrecan, and other ECM components [7]. MMP8 is one of MMPs that has been found to produce anticancer effects due to its ability to inhibit tumorigenesis and metastasis [17, 18]. Cancer studies conducted over eight years have found an association between the development of specific cancer sites and functional polymorphisms that can alter gene expression located in the promoter regions of MMP7 (rs11568818) and MMP8 (rs11225395) [19–23]. However, there have been no association studies of MMP7 and MMP8 polymorphisms in BCa risk in the Caucasian population. Therefore, the objective of this association study was to evaluate polymorphisms in MMP7 and MMP8 and characterize their associations with BCa susceptibility in a population of healthy patients from Łódź.

MATERIALS AND METHODS

Study population

BCa patients were recruited from the First Department of Urology, Medical University of Łódź and Nofer Institute of Occupational Medicine in Łódź from 2007 to 2013. The 241 BCa patients and 199 healthy population controls were recruited from an ethnically homogeneous Polish population. Data on histological cancer grades diagnosed at the First Department of Urology were not accessible for all cases. All of the BCa patients underwent transurethral resection and had histopathologically confirmed NMIBC or MIBC at various tumor (T) stage and grade (G) of neoplasm. The tumor stage (87.1% of diagnosed BCa patients), and tumor grade (89.2% of diagnosed patients) were included in the association analyses. To evaluate differences between MMP7 or MMP8 genotypes and tumor grade or stage, patients with BCa were divided into categories: group 1) with G1, and group 2) with G2 and G3 or group 1) with T1, and group 2) with T2–T4, respectively. All patients with missing data were excluded from these analyses. Additionally, to examine the joint effects of MMP7 or MMP8 genotypes and tobacco smoking status on BCa risk, we stratified cases and controls into three categories: 1) never smokers – persons who had never smoked in their lifetime, 2) ex–smokers – individuals who were abstinent for at least 1 year before the interview, 3) smokers – persons who stated they currently smoked cigarettes or who were abstinent for up to 1 year before the interview. The study was approved by the Local Ethical Committee of the Nofer Institute of Occupational Medicine.

DNA isolation and genotyping

The genomic DNA was isolated from the peripheral blood samples of the study subjects using commercial DNA kits QIAamp DNA Mini Kits (Qiagen) following the manufacturer’s protocol. The promoter single nucleotide polymorphisms (SNPs) in the MMP7 (rs11568818) and MMP8 (rs11225395) genes were genotyped using TaqMan fluorescent probes, assays on demand (Assay ID: C_27852953_10 and C_1366493_10, respectively) (Life Technologies). All patients and controls were genotyped using Real–Time PCR CFX96 System (BioRad).

Statistical analysis

Group characteristics were determined by the χ² (chi–square) test and Student’s t–test. Hardy–Weinberg equilibrium (HWE) was tested by comparing the observed and expected genotype frequencies in cases and controls at equilibrium based on the χ² test at a significant level of p <0.05. The strength of the association between genetic polymorphisms in the MMP and BCa susceptibility was measured by odds ratios (ORs) corresponding to 95% confidence interval (95% CI). ORs and 95% CI were determined by logistic regression analyses using additive models that included adjustment for age, gender, and cigarette smoking status. Major allele homozygotes served as the reference group, and heterozygotes and minor allele homozygotes were separately compared. The association between the MMPs genotype frequencies and characteristics was estimated by Fisher’s exact test using the Stata 11 (StataCorp LP, USA) software. All statistical tests presented in this paper are two–sided and p values were considered to be statistically significant when p ≤0.05.
RESULTS

Cohort characteristics

We analyzed genetic polymorphisms in the promoter region of MMP7 and MMP8 in 241 BCa patients and 199 controls from Poland. In Table 1 we summarized demographics, cigarette smoking status, and clinical characteristics of the patients. Statistically significant differences were observed between BCa cases and controls in terms of the distribution of gender ($p = 0.001$) and tobacco smoking status ($p = 0.001$). At the time of BCa diagnosis, patients were between ages 64.9 and 67.7 years (mean 66.1 ±10.4) and were at the same age as the controls (mean 66.3 ±10.6) ($p = 0.872$). The genotype distributions of both chosen polymorphisms were consistent with Hardy–Weinberg equilibrium (Table 2).

Analysis of association

For the genetic polymorphisms in the MMP7 (rs11568818) and MMP8 (rs11225395) genes, significant differences between genotyped BCa patients and controls were not observed. Prevalence of MMP7 $G/G$ genotype was only slightly different among patients (22.1%) and controls (16.1%), and BCa risk among MMP7 $G/G$ was estimated to OR, 1.54; 95% CI, 0.93–2.55; $p = 0.093$ (Table 3). Association of single MMP7 and MMP8 genotypes with BCa risk in groups stratified by tobacco smoking status was assessed. The statistical significance of additive effects was not observed among stratified groups (data not shown). We also studied MMP7 and MMP8 polymorphisms and their risk associated with different histology grade of BCa. None of the G and T–categorized groups of patients were associated with individual MMP7 or MMP8 polymorphisms (data not shown). In order to examine whether the effect of gene–gene interactions in MMP7 and MMP8 polymorphisms might change the BCa risk, we analyzed various combinations of genotypes. We observed that the combined effect of MMP7 and MMP8 genotypes did not provide statistically significant differences between cases and controls (Table 4), nor in any tobacco smoking status (data not shown).

**Table 1. Selected characteristics of the BCa patients and healthy controls at the time of diagnosis**

| Variable                  | Controls n (%) | Cases n (%) | $p$–value$^b$ |
|---------------------------|----------------|-------------|--------------|
| Gender                    |                |             |              |
| Female                    | 23 (11.6)      | 59 (24.5)   |              |
| Male                      | 176 (88.4)     | 182 (75.5)  | 0.001        |
| Mean age (years) ±SD      | 66.1 ±10.4     | 66.3 ±10.6  | 0.872        |
| Smoking status$^c$        |                |             |              |
| Never–smokers$^e$         | 70 (35.4)      | 64 (27.0)   |              |
| Ex–smokers$^e$            | 91 (45.9)      | 92 (38.8)   |              |
| Smokers$^e$               | 32 (18.7)      | 81 (34.2)   | 0.001        |
| Tumor grade$^d$           |                |             |              |
| G1                        | –              | 113 (46.9)  |              |
| G2                        | –              | 64 (26.6)   |              |
| G3                        | –              | 38 (15.8)   |              |
| G2 and G3                 | –              | 102 (42.3)  |              |
| Unknown                   | –              | 26 (10.7)   | –            |
| Tumor stage$^f$           |                |             |              |
| NMIBC (T1)                | –              | 169 (70.1)  |              |
| MIBC (T2–T4)              | –              | 41 (17.0)   |              |
| Unknown                   | –              | 31 (12.9)   | –            |

$^a$ the number of cases and controls may vary because of some missing data; $^b$ chi–square test was used to determine $p$–value; $^c$t–test was used to determine $p$–value; $^e$ never smokers – persons who had never smoked; $^d$ex–smokers – individuals who were abstinent for at least 1 year; $^f$sMokers – individuals who currently smoke or who were abstinent for up to 1 years before the interview; NMIBC – non–muscle–invasive bladder cancer; MIBC–muscle–invasive bladder cancer

**Table 2. Summary of the genetic polymorphisms in the MMP analyzed in this study**

| Gene                        | MMP7 | MMP8 |
|-----------------------------|------|------|
| MMPs exert cancer effects   | Supporting | Inhibiting |
| dbSNP ID                    | rs11568818 | rs11225395 |
| Nucleotide position$^a$     | −181 | −799 |
| Type of region              | Promoter | Promoter |
| Chromosome                  | 11q22.2a | 11q22.2b |
| RefSNP Alleles$^b$          | A/G  | C/T  |
| Allele with greater transcriptional activity | G allele | T allele |
| Alleles frequency of BCa patients$^c$ | B  | 0.45 | 0.44 |
| Alleles frequency of controls$^c$ | B  | 0.42 | 0.44 |

$^a$ minus indicates promoter region; $^b$ major/minor alleles and frequencies, as determined by the distribution among the case and controls; $^c$ A major allele, B minor allele; $^d$ Hardy–Weinberg equilibrium $p$–value

DISCUSSION

It is generally believed that the development of the invasive phenotype (advanced metastatic stage of cancer) and further poor prognosis may be associated with increased expression of MMPs [22, 24, 25]. Furthermore, we know that MMPs regulatory effect may be related to MMP promoter SNPs. It is
Expression of the A allele compared to the G allele is transcriptionally more effective on carcinogenesis, while MMP8 possesses inhibitory effect [16, 17, 26]. Genetic polymorphism in the MMP7 and MMP8 may play different roles in cancer risk and cancer progression. MMP7 over-expression is associated with risk of developing malignant melanoma [37]. In analyzed individuals from Central Poland, the frequency of MMP7 G alleles was 0.42, while for MMP8 T it was 0.44. To compare, in control individuals from Łódź, the frequency of MMP7 G alleles was 0.45 [38], while in individuals from Szczecin, the frequency was 0.39 [37].

Recent studies on the metastatic potential of breast cancer cells show that over-expression of MMP8 protein provides a protective effect in the metastatic process [32]. Also, in studies of the squamous cell carcinoma of the tongue it has been found that MMP8 protein expression is correlated with improved survival of patients [34]. However, there are only a few case-control studies regarding MMP8 rs11225395 impact on cancer development. In vitro data has suggested that promoter MMP8 polymorphism has putative functional significance and higher transcription activity for minor MMP8 T allele compared with MMP8 C allele [33]. Indeed, breast cancer risk (OR, 0.7; 95% CI, 0.5–0.9) and survival (OR, 0.4; 95% CI, 0.2–0.8) was significantly reduced for women carrying the MMP8 allele T [35, 36]. However, a study of Polish individuals reported that allele T was associated with risk of developing malignant melanoma [37].

In the present association study we tested the hypothesis whether the functional genetic polymorphisms in the MMP7 and MMP8 genes contributed to BCa risk. To our knowledge, this is the first study investigating the relationship between MMP7 (rs11568818) and MMP8 (rs11225395) polymorphisms and BCa risk in Caucasian population. Two studies conducted by Srivastava et al. in North India population showed significantly higher risk of BCa among MMP7 G/G (rs11568818) individuals (OR, 2.38; 95% CI, 1.43–2.51), but no consistent results for other types of cancer [27]. MMP7 genetic polymorphism affects the transcriptional activity of that gene and leads to changes in its expression. Namely, the G allele compared to the A allele is transcriptionally more active [28]. Expression of MMP7 has been detected in various cancers [16, 26]. Studies which investigated serum and plasma levels of MMP7, identified high levels of MMP7 as predictors of BCa outcomes. Moreover, MMP7 protein expression can correlate with pathologic parameters like tumor stage, tumor grade, and metastasis in BCa [29, 30, 31].

**Table 3. Distribution of the genetic polymorphisms in the MMP7 and MMP8 among controls and BCa patients**

| Gene dbSNP | Genotypes | Controls | Cases | BCA risk (95% CI), \( p \)-value |
|------------|----------|----------|-------|---------------------------------|
|            | \( n (\%) \) | \( n (\%) \) |       | Crude Adjusted<sup>d</sup> | Unadjusted<sup>d</sup> |
| **MMP7**   |          |          |       |                               |                        |
| (rs11568818)|          |          |       |                               |                        |
| A/A        | 63 (31.6) | 76 (31.7) |       |                               |                        |
| A/G        | 104 (52.3) | 111 (46.3) |       |                               |                        |
| G/G        | 32 (16.1) | 53 (22.1) |       |                               |                        |
| A/G+G/G    | 136 (68.3) | 164 (68.3) |       |                               |                        |
| **MMP8**   |          |          |       |                               |                        |
| (rs11225395)|          |          |       |                               |                        |
| C/C        | 60 (30.2) | 72 (29.9) |       |                               |                        |
| C/T        | 101 (50.8) | 125 (51.9) |       |                               |                        |
| T/T        | 38 (19.1) | 44 (18.2) |       |                               |                        |
| C/T+T/T    | 139 (69.9) | 169 (70.1) |       |                               |                        |

<sup>a</sup>Genotypes and frequencies, as determined by the distribution among the cases and controls; <sup>b</sup>the number of cases and control may vary because of some missing data; <sup>c</sup>OR, odds ratio, CI, 95% confidence interval; <sup>d</sup>odds ratio adjusted for age, gender and cigarette smoking status.

**Table 4. Risk of BCa associated with the gene-gene interactions in MMP7 and MMP8 polymorphisms**

| Genotype | Genotype | Controls | Cases | OR (95% CI)<sup>b</sup>, \( p \)-value |
|----------|----------|----------|-------|---------------------------------|
| MMP7     | MMP8     |          |       | Crude | Adjusted<sup>d</sup> |
| A/A      | C/C      | 16 (25.4) | 15 (19.7) | Ref<sup>b</sup> |                        |
|          | C/T+T/T  | 47 (74.6) | 61 (80.3) | 1.38 (0.62–3.08), 0.540 |                        |
| A/G+G/G  | C/C      | 44 (32.4) | 57 (34.8) | 1.38 (0.62–3.10), 0.537 |                        |
|          | C/T+T/T  | 92 (67.6) | 107 (65.2) | 1.24 (0.58–2.65), 0.699 |                        |

<sup>a</sup>OR, odds ratio, CI, 95% confidence interval; <sup>b</sup>major allele homozygotes (reference group)

The analysis of SNPs in MMPs as prognostic biomarkers, might identify BCa patients at an increased risk of lymph node metastasis even before surgery. MMP gene variants may influence their transcriptional activity and protein expression, function, and activity. Therefore, they may be associated with cancer risk, prognosis, and responses to treatment.
CI, 1.30–4.34), while MMP8 C/T+T/T (rs11225395) genotype carriers possessed reduced BCa risk (OR, 0.27; 95% CI, 0.10–0.69) [19, 23]. Nevertheless, we found that these genetic polymorphisms do not contribute to risk of BCa and cancer grade. However, we observed that individuals with MMP7 G/G genotype were at statistically borderline risk of BCa (OR, 1.54; 95% CI, 0.93–2.55; p = 0.093). We found no additive effect of smoking and genetic polymorphisms in the MMP7 and MMP8 among never-smokers, ex-smokers, and smokers. Additionally, our investigation of the potential combined effect of gene–gene interaction between genetic polymorphisms, reported no correlation with BCa risk and cancer grade.

CONCLUSIONS

In this study, the results show no association between the genetic polymorphisms in biologically Relevant candidate genes such as MMP7 (rs11568818) and MMP8 (rs11225395) and BCa risk in the Caucasian population. It should be noted that our study was encumbered with a limitation. Due to the small number of cases studied, some associations were not evident. The search for new biomarkers of cancer is still required and more extensive research on genetic polymorphisms of MMP in BCa should be undertaken in the future.

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