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HUMAN GENETICS

Associations of Polymorphic Loci of Matrix Metalloproteinase Genes with Breast Cancer in Women of the Central Black Earth Region of Russia

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Abstract—Polymorphic variants of matrix metalloproteinase (*MMP*) genes were tested for association with breast cancer (BC) in women of the Central Black Earth Region (CBER) of Russia with consideration to whether a patient has or does not have a family history of BC. The study included 358 BC patients (of which 68 had a family history of BC) and 746 control women. Genotyping was performed at ten polymorphic *MMP* loci: rs1799750 of *MMP1*; rs243865 of *MMP2*; rs679620 of *MMP3*; rs1940475 of *MMP8*; and rs17576, rs17577, rs3918242, rs2250889, rs3787268, and rs3918249 of *MMP9*. Logistic regression was performed to assess the associations of the *MMP* variants with BC in the patient subgroups with or without a family history of BC (the control group was the same for the two subgroups). Low risk of BC in women with a family history of BC was associated with *MMP2* rs243865 (OR 0.53–0.54, $p_{perm} \le 0.03$) and *MMP9* rs2250889 (OR 0.36–0.37, $p_{perm} \le 0.04$). Higher risk of BC in women without a family history of BC was associated with *MMP9* rs3787268 (OR = 2.16, $p_{perm} = 0.03$) and the following haplotypes at the *MMP9* polymorphisms ($p_{perm} \le 0.05$): CA at rs3918249–rs17576 (OR = 2.15), CCA at rs3918242–rs3918249–rs17576 (OR = 1.69), CCAG at rs3918242–rs3918249–rs17576–rs3787268 (OR = 1.69), and CAGCG at rs3918249–rs17576–rs3787268–rs2250889–rs17577 (OR = 3.06). Three haplotypes were associated with a low risk of BC in women without a family history of BC: GG at rs17576–rs3787268 (OR = 0.60), GGC at rs17576–rs3787268–rs2250889 (OR = 0.63), and CGG at rs3918249–rs17576–rs3787268 (OR = 0.62).

Keywords: breast cancer, matrix metalloproteinase genes, polymorphic loci, association, genetic burden

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INTRODUCTION

Breast cancer (BC) is a malignancy that originates from epithelial structures of the mammary gland [1]. According to the data that the International Agency for Research on Cancer published in 2020, BC is the most common cancer in women and accounts for 24.5% cancer cases; 2.3 million new BC cases are diagnosed annually in the global population [2]. BC accounts for 15.5% in the mortality structure of the female global population, causing deaths of 685 thousand women annually [3]. The number of patients newly diagnosed with BC in Russia has increased significantly (by 49%) over the past 15 years, from 49.5 thousand in 2005 to 73.9 thousand in 2019, according to the Federal State Statistics Service [4]. It should be noted that BC is both the most common cancer (20.9%) and the most common cause of cancer-related deaths (16.18%) in the female population of Russia [5]. Importantly, the BC incidence rate in the Central Black Earth Region (CBER, part of the Central Federal District) of Russia is higher than in the total Russian population [5]. In 2018, the BC incidence rate was 53.04 cases per 100000 females in the CBER (52.77 in Belgorod oblast, 53.64 in Kursk oblast, and 51.78 in Voronezh oblast, which are all CBER parts), while the rate was 51.64 in the general Russian population [5].

Genetic factors play an important role in BC; approximately 30% of all cases are thought to be hereditary [6]. However, particular genetic factors responsible for BC development are still poorly understood [6, 7]. Mutations found to date in high- and moderate-penetrance BC-susceptibility genes (*BRCA1/2*, *CHEK2*, *PALB2*, *ATM*, etc.) [6–8] account for approximately 5% of all BC cases and are detected in only one-third (30–40%) of the patients who have a family history of BC [6, 7]. Approximately 200 polymorphic loci have been associated with BC in numerous genome-wide association studies (GWASs) [9] and shown to determine together about 18% of BC heritability [10]. It should be noted that the BC heritability estimate based on the GWAS data (18%) is

more than 1.7 times higher than that derived from twin studies (31%) [11].

Matrix metalloproteinase (*MMP*) genes are promising candidate genes potentially related to BC because their products, MMPs, play a substantial role in BC pathogenesis [12, 13]. MMPs are zinc-dependent endopeptidases; are produced in cancer and stromal cells; and are actively involved in degrading the extracellular matrix and basement membrane, thus affecting the tumor growth, angiogenesis, and metastasis [12, 13]. A far higher production of MMPs (MMP2, MMP9, etc.) has been observed in BC cells compared with normal breast cells [14, 15].

Associations of polymorphic loci of the *MPP* genes with BC in various ethnic or regional groups have been considered in many (>50) genetic epidemiological studies described in the literature (see [15–25], etc.). However, their results are often ambiguous and even discrepant in the case of certain loci. For example, rs243865 of *MMP2* has been tested for association with BC in 17 experimental studies and 3 meta-analyses. Only eight studies have reported a predisposing role of its allele *C* and a protective role of its allele *T*, while lack of association between *MMP2* rs243865 and BC has been observed in a substantial portion of the studies (see [16–20], etc.). Even more discrepant data are available for the association of *MMP9* rs3787268 with BC. Allele *A* of the locus has been identified as a risk factor for BC [21], while the polymorphism has shown no association with BC [22, 23] or its allele *A* has been associated with low risk of BC [24, 25] in other studies. It is therefore necessary in view of the data to continue relevant research in order to identify the *MMP* polymorphic loci that are important for BC development in particular populations, including those of Russia.

The objective of this work was to study the potential association with BC for polymorphic variants of the *MMP* genes in the female population of the CBER with consideration to whether a patient has or does not have a family history of BC.

MATERIALS AND METHODS

The study included 358 BC patients. Of these, 68 had a family history of BC (i.e., their first- or second-order relatives had BC (breast carcinoma)) and 290 patients had no family history of BC. Control subjects (746 women) also had no family history of BC. All women included in the study were ethnic Russians who were born and resided in the CBER of Russia [26, 27]. Patients were sampled at the Belgorod Regional Oncology Clinic from 2010 to 2016; patients newly diagnosed with breast carcinoma were only included in the sample. The diagnosis was confirmed by pathomorphological examination of intraoperative tumor tissue samples [1]. The control group was collected during occupational health checks, which were carried out at the Perinatal Center of the Belgorod Regional Clinical Hospital. The controls were of a similar age and had no clinical, instrumental, or history-related signs of BC. The mean ages were 54.7 ± 12.7 years (ranging from 25 to 84) in the patients and 55.3 ± 11.2 years (ranging from 27 to 82) in the controls ($p > 0.05$).

DNA preparations for genetic testing were derived from venous blood samples. The following criteria were used to select the polymorphic loci of the *MMP* genes for the study. First, literature data are available for comparisons [15–25; etc.]. Second, a polymorphism has a significant regulatory potential, being located in functionally active genomic regions (a promoter or an enhancer) or regions of binding sites for regulatory proteins, transcription factors, etc. The regulatory potentials of single nucleotide polymorphisms (SNPs) were assessed *in silico* with the use of the HaploReg bioinformatics database [28] as described previously [29]. Ten loci of five *MMP* genes were examined, including rs1799750 of *MMP1*; rs243865 of *MMP2*; rs679620 of *MMP3*; rs1940475 of *MMP8*; and rs17576, rs17577, rs3918242, rs2250889, rs3787268, and rs3918249 of *MMP9*. Genotyping at the polymorphic loci was performed by real-time PCR with TaqMan probes [30]; PCR was run using reagent kits from Test-Gen (Russia) and a CFX96 thermal cycler (Bio-Rad, United States). As a quality check, genotyping was repeated in a blind manner with approximately 5% of the DNA samples [31] and showed 100% reproducibility of the results.

Associations of the *MMP* polymorphisms with BC were evaluated using the PLINK program [32] and conventional logistic regression, by calculating the odds ratio (OR) and its 95% confidence interval (95%CI) [33] in the allelic, dominant, recessive, and additive genetic statistical models. Correction for multiple comparisons (false-positive associations) was performed using the adaptive permutation test [34] with a proper significance level ($p_{perm} < 0.05$). The *MMP* loci found to be significantly associated with BC were analyzed *in silico* with the use of the HaploReg bioinformatics database [28] and available literature data in terms their functional significance [35–37].

RESULTS AND DISCUSSION

The observed genotype frequency distribution of each *MMP* polymorphic locus obeyed Hardy–Weinberg equilibrium in the subgroups of BC patients with or without a family history of BC and the control group (with the Bonferroni correction for multiple comparisons for $n = 10$ SNPs at the significance level $p_{bonferroni} > 0.005$ (0.05/10)) (Table 1).

A set of BC-associated polymorphisms of the *MMP* candidate genes was found to differ between the patients with or without a family history of BC. As is seen from Table 2, the subgroup with a family history of BC showed associations of the rs243865 (C>T)

Table 1. Allele and genotype frequency distributions of the *MMP* polymorphic loci in the BC patients and controls

Gene polymorphism	Genotype, rare allele	BC patients		Control group ($N = 746$), % (n)
		with family history of BC ($N = 68$), % (n)	without family history of BC ($N = 290$), % (n)	
rs1799750	*1G1G*	28.36 (19)	27.53 (79)	30.43 (220)
MMP1	*1G2G*	49.25 (33)	51.22 (147)	46.33 (335)
	2G2G	22.39 (15)	21.25 (61)	23.24 (168)
	2G	47.01	46.86	46.40
	p_{HWE}	1.00	0.72	0.07
rs243865	*CC*	71.21 (47)	54.58 (155)	57.24 (419)
MMP2	*CT*	27.27 (18)	39.79 (113)	35.66 (261)
	TT	1.52 (1)	5.63 (16)	7.10 (52)
	T	15.15	25.53	24.93
	p_{HWE}	1.00	0.53	0.20
rs679620	*CC*	22.73 (15)	27.93 (81)	25.71 (190)
MMP3	*CT*	60.61 (40)	49.31 (143)	48.85 (361)
	TT	16.66 (11)	22.76 (66)	25.44 (188)
	T	46.97	47.41	49.86
	p_{HWE}	0.14	0.90	0.55
rs1940475	*CC*	22.06 (15)	25.78 (74)	28.34 (210)
MMP8	*CT*	51.47 (35)	54.01 (155)	45.48 (337)
	TT	26.47 (18)	20.21 (58)	26.18 (194)
	T	52.21	47.21	48.92
	p_{HWE}	1.00	0.19	0.02
rs3918242	*CC*	66.18 (45)	71.33 (204)	69.12 (508)
MMP9	*CT*	30.88 (21)	24.13 (69)	28.43 (209)
	TT	2.94 (2)	4.54 (13)	2.45 (18)
	T	18.38	16.61	16.67
	p_{HWE}	1.00	0.03	0.60
rs3918249	*TT*	43.28 (29)	42.71 (120)	37.55 (276)
MMP9	*TC*	47.76 (32)	41.28 (116)	47.07 (346)
	CC	8.96 (6)	16.01 (45)	15.38 (113)
	C	32.84	36.65	38.91
	p_{HWE}	0.59	0.07	0.82
rs17576	*AA*	44.12 (30)	45.07 (128)	38.22 (284)
MMP9	*AG*	47.06 (32)	40.49 (115)	45.76 (340)
	GG	8.82 (6)	14.44 (41)	16.01 (119)
	G	32.35	34.68	38.90
	p_{HWE}	0.78	0.09	0.32

Table 1. (Contd.)

Gene polymorphism	Genotype, rare allele	BC patients		Control group ($N = 746$), % (n)
		with family history of BC ($N = 68$), % (n)	without family history of BC ($N = 290$), % (n)	
rs3787268 *MMP9*	*GG*	63.08 (41)	59.30 (169)	61.03 (451)
	GA	33.85 (22)	33.33 (95)	34.91 (258)
	AA	3.07 (2)	3.37 (21)	4.06 (30)
	A	20.00	24.04	21.52
	p_{HWE}	1.00	0.14	0.39
rs2250889 *MMP9*	*CC*	86.57 (58)	84.72 (244)	80.14 (589)
	CG	13.43 (9)	13.89 (40)	17.82 (131)
	GG	0.00 (0)	1.39 (4)	2.04 (15)
	G	6.72	8.33	10.95
	p_{HWE}	1.00	0.12	0.02
rs17577 *MMP9*	*GG*	62.79 (42)	72.73 (208)	68.73 (499)
	AG	34.33 (23)	23.08 (66)	28.51 (207)
	AA	2.98 (2)	4.19 (12)	2.76 (20)
	A	20.15	15.73	17.01
	p_{HWE}	1.00	0.04	0.89

polymorphism of *MMP2* in the allelic (*T* vs. *C*, OR = 0.54, 95%CI 0.33–0.88, $p_{perm} = 0.01$), additive (*TT* vs. *CT* vs. *CC*, OR = 0.54, 95%CI 0.34–0.90, $p_{perm} = 0.01$), and dominant (*TT* and *CT* vs. *CC*, OR = 0.53, 95%CI 0.30–0.92, $p_{perm} = 0.03$) genetic statistical models and the rs2250889 (C>G) polymorphism of *MMP9* in the additive (*GG* vs. *CG* vs. *CC*, OR = 0.37, 95%CI 0.15–0.94, $p_{perm} = 0.04$) and dominant (*GG* and *CG* vs. *CC*, OR = 0.36 95%CI 0.14–0.96, $p_{perm} = 0.04$) genetic statistical models. BC in the patients without a family history of the disease was associated with rs3787268 (G>A) of *MMP9* in the recessive genetic statistical model (*AA* vs. *GA* and *GG*, OR = 2.16, 95%CI 1.08–4.32, $p_{perm} = 0.04$).

Haplotypes were analyzed for the six *MMP9* polymorphisms, which are relatively close together (approximately 7 kb apart) in chromosome 20. Sporadic BC was associated with seven haplotypes, which included all of the six *MMP9* polymorphisms examined in this work. The majority (four out of seven) haplotypes increased the BC risk. The set included haplotypes CA at rs3918249–rs17576 (OR = 2.15, $p = 0.009$), CCA at rs3918242–rs3918249–rs17576 (OR = 1.69, $p = 0.004$), CCAG at rs3918242–rs3918249–rs17576–rs3787268 (OR = 1.69, $p = 0.005$), and CAGCG rs3918249–rs17576–rs3787268–rs2250889–rs17577 (OR = 3.06, $p = 0.009$). The three following haplotypes were associated with low risk of BC: GG at rs17576–rs3787268 (OR = 0.60, $p = 0.005$), GGC at rs17576–rs3787268–rs2250889 (OR = 0.63, $p = 0.01$), and CGG at rs3918249–rs17576–rs3787268 (OR = 0.62, $p = 0.01$). Note that the p_{perm} values established for the above seven haplotypes obeyed the significance requirement $p_{perm} < 0.05$. The BC patients with a family history of BC did not display a significant association of any haplotype at the *MMP9* SNPs with BC risk ($p_{perm} > 0.05$).

To summarize, we found that allele *T* of rs243865 (C>T) of *MMP2* (OR 0.53–0.54) and allele *G* of rs2250889 (C>G) of *MMP9* (OR 0.36–0.37, $p_{perm} \leq 0.04$) play a protective role in female BC patients with a family history of BC in the CBER of Russia. In female BC patients without a family history of BC, higher risk of the disease is associated with genotype *AA* at rs3787268 (G>A) of *MMP9* (OR = 2.16) and certain *MMP9* haplotypes, which are various combinations of alleles at the six *MMP9* polymorphisms (rs3918242, rs3918249, rs17576, rs3787268, rs2250889, and rs17577).

We compared out findings with the literature data and observed the following. The association of the rs243865 (C>T) polymorphism of *MMP2* with BC has been studied in various ethnic and regional populations worldwide in many works. Results from 20 stud-

Table 2. Associations of the *MMP* polymorphisms with BC in patients with or without a family history of BC

Gene polymorphism	Rare allele	*N*	Allelic model				Additive model				Dominant model				Recessive model			
			OR	95%CI		*p*	OR	95%CI		*p*	OR	95%CI		*p*	OR	95%CI		*p*
				L95	U95			L95	U95			L95	U95			L95	U95	
Patients with a family history of BC																		
rs1799750, *MMP1*	*2G*	790	1.03	0.72	1.46	0.89	0.96	0.65	1.42	0.85	0.95	0.51	1.76	0.87	0.95	0.47	1.89	0.88
rs243865, *MMP2*	*T*	**798**	**0.54**	**0.33**	**0.88**	**0.01**	**0.54**	**0.34**	**0.90**	**0.01**	**0.53**	**0.30**	**0.92**	**0.03**	0.27	0.04	2.03	0.20
rs679620, *MMP3*	*T*	805	0.89	0.62	1.27	0.52	0.86	0.57	1.30	0.47	1.06	0.53	2.10	0.87	0.60	0.28	1.28	0.18
rs1940475, *MMP8*	*T*	809	1.14	0.80	1.62	0.46	1.15	0.77	1.72	0.49	1.16	0.60	2.24	0.67	1.27	0.67	2.40	0.47
rs3918242, *MMP9*	*T*	803	1.13	0.71	1.78	0.61	1.05	0.62	1.77	0.86	1.04	0.56	1.92	0.90	1.17	0.25	5.44	0.84
rs3918249, *MMP9*	*C*	802	0.77	0.53	1.12	0.17	0.82	0.54	1.25	0.36	0.80	0.45	1.43	0.45	0.71	0.29	1.73	0.45
rs17576, *MMP9*	*G*	811	0.75	0.52	1.09	0.13	0.80	0.52	1.22	0.30	0.76	0.42	1.35	0.34	0.73	0.30	1.76	0.48
rs3787268, *MMP9*	*A*	804	0.91	0.58	1.43	0.69	1.03	0.61	1.73	0.92	1.01	0.55	1.85	0.98	1.20	0.27	5.33	0.81
rs2250889, *MMP9*	*G*	802	0.59	0.29	1.17	0.13	**0.37**	**0.15**	**0.94**	**0.04**	**0.36**	**0.14**	**0.96**	**0.04**	0.00	0.00	–	1.00
rs17577, *MMP9*	*A*	793	1.23	0.79	1.92	0.36	1.19	0.72	1.98	0.50	1.26	0.69	2.30	0.46	1.10	0.24	5.00	0.91
Patients without a family history of BC																		
rs1799750, *MMP1*	*2G*	1002	1.02	0.84	1.24	0.85	1.12	0.88	1.41	0.36	1.40	0.95	2.07	0.09	0.94	0.62	1.41	0.76
rs243865, *MMP2*	*T*	1005	1.03	0.83	1.29	0.78	0.93	0.70	1.22	0.59	1.01	0.72	1.43	0.94	0.53	0.23	1.21	0.13
rs679620, *MMP3*	*T*	1018	0.91	0.75	1.10	0.32	0.86	0.67	1.09	0.20	0.80	0.55	1.17	0.25	0.83	0.56	1.23	0.35
rs1940475, *MMP8*	*T*	1017	0.93	0.77	1.13	0.49	1.01	0.80	1.27	0.94	0.91	0.63	1.32	0.63	1.13	0.77	1.66	0.52
rs3918242, *MMP9*	*T*	1010	1.00	0.77	1.29	0.97	1.03	0.75	1.41	0.86	0.99	0.69	1.43	0.97	1.37	0.54	3.48	0.50
rs3918249, *MMP9*	*C*	1005	0.91	0.74	1.11	0.35	0.97	0.76	1.23	0.80	0.91	0.64	1.29	0.60	1.05	0.66	1.66	0.84
rs17576, *MMP9*	*G*	1016	0.83	0.68	1.02	0.08	0.81	0.63	1.04	0.09	0.80	0.57	1.12	0.19	0.68	0.41	1.13	0.13
rs3787268, *MMP9*	*A*	1013	1.15	0.92	1.45	0.22	1.17	0.88	1.56	0.27	1.06	0.76	1.50	0.72	**2.16**	**1.08**	**4.32**	**0.03**
rs2250889, *MMP9*	*G*	1012	0.74	0.53	1.04	0.08	0.71	0.47	1.06	0.09	0.65	0.41	1.04	0.07	0.79	0.22	2.84	0.71
rs17577, *MMP9*	*A*	1001	0.91	0.70	1.19	0.49	0.90	0.65	1.24	0.50	0.88	0.60	1.27	0.48	0.90	0.34	2.37	0.83

OR, odds ratio; 95%CI, 95% confidence ratio of OR (L95, lower limit; U95, upper limit), *p,* significance level. The results significant by the permutation test (1000 permutations) are in bold.

ies in the field have been reported in the literature from 2004 to 2022. It should be noted that the results obtained in different populations are discrepant. Certain studies have associated rs243865 (C>T) of *MMP2* with BC and its particular clinical features (metastasis, survival, histological type of the tumor, etc.) both as an individual polymorphism and as a component of combinations with other polymorphic loci of the *MMP* genes [17, 20, 38–42]. Allele *T* of rs243865 has been identified as protective in BC in the above studies, like in our work, while allele *C* of the locus has been associated with higher risk of BC. For example, genotype *CC* has been found to be a genetic factor associated with higher BC risk in studies performed in Mexico (90 BC patients and 96 controls) [20] and Saudi Arabia (90 BC patients and 92 controls) [39]: OR has been estimated at 2.15 and 2.02, respectively. A meta-analysis has shown that BC patients have a higher frequency of genotype *CC* (OR = 1.27) and a lower frequency of genotype *CT* (OR = 0.78) of *MMP2* rs243865 (C>T) as compared with control subjects [17]. Another meta-analysis (9858 BC patients and 10871 controls) has associated genotype *CC* at rs243865 with higher BC risk in the Latin American population, but not in the European and Asian populations [40]. Studies in China (462 BC patients and 509 controls) [38] and Tunisia (210 BC patients and 250 controls) [41] have demonstrated that allele *T* plays a protective role in BC (OR = 0.46 and 0.49, respectively).

No association of the *MMP2* rs243865 (C>T) polymorphism with BC has been observed in a number of studies carried out in various (Polish, Greek, Brazilian, Swedish, Chinese, Iranian, etc.) populations ($p > 0.05$) [19, 21, 43–49]. Likewise, the rs243865 (C>T) locus of *MMP2* has not been associated with BC in Russian women (395 patients with infiltrating BC and 329 controls) [50]. Note that a deviation from Hardy–Weinberg equilibrium has been observed in the patient group ($p = 0.0089$), presumably suggesting the effect of a factor related to the neoplastic processes [50]. Two meta-analyses have also not associated the *MMP2* rs243865 (C>T) locus with BC or BC metastasis [16, 18]. It should be noted that our group of BC patients without a family history of BC similarly displayed no association of the *MMP2* rs243865 (C>T) polymorphism with BC ($p > 0.05$). Our findings and the literature data make it possible to assume that differences in proportion of BC patients with a family history of the disease are one of the factors that may explain the discrepancies in the results obtained in association studies of the *MMP2* rs243865 (C>T) locus in various populations, in addition to differences in the genetic structure and environmental and individual risk factors between the human populations examined. The *MMP2* rs243865 (C>T) polymorphism determines predisposition to BC in women with a family history of the disease according to our findings, but is not associated with BC in women without a family history of BC.

As earlier experimental studies have shown, the rs243865 (–1306C>T) polymorphic locus is in the *MMP2* promoter region (CCACC box) in the vicinity of a binding site for the SP-1 transcription factor and the C>T nucleotide substitution decreases expression of the MMP2 protein [51]. *In silico* evaluation of the functional potential of the *MMP2* rs243865 polymorphism point to its important regulatory role in the human genome. The genome region that harbors the polymorphism is subject to the epigenetic regulation of gene expression via posttranslational modification of histone proteins, is associated with expression of the *AYTL1* gene and the long noncoding RNA *RP11-212I21.2* (*MMP2-AS1*), is an open chromatin region (a DNase hypersensitivity region), etc. [52, 53]. According to the HaploReg epigenetic database, the genome region of the rs243865 polymorphism acts as an enhancer regulatory region of the gene (and is marked by the H3K4me1 methylated variant of histone H3) in breast myoepithelial primary cells (Epigenome ID: E028, Mnemonic: BRST.MYO).

MMP2 (also known as gelatinase A) exerts collagen-degrading activity toward type IV collagen and is expressed in connective tissue cells [54]. Type IV collagen is a component of the basement membrane, and, consequently, proteolytic activity of MMP2 eventually increases the remodeling of the extracellular matrix in membrane-containing structures [19]. Literature data demonstrate that MMP2 is among the most important factors that determine tumor invasion and metastasis. MMP2 expression in BC lesions is far higher than in normal breast cells, which express MMP2 to a minimal level [14]. It is important to emphasize that allele *T* of rs243865 exerts a protective effect (OR < 1) in BC according to our and literature data [17, 20, 38–41] and that MMP2 expression decreases as a result of the C>T nucleotide substitution in the binding region of the SP-1 transcription factor [51]. The data fully agree with the above finding that MMP2 expression is minimal in noncancer breast cells (fibroblasts, etc.) compared with BC cells [14].

The rs2250889 (C>G) polymorphism of *MMP9* proved to significantly contribute to the predisposition to BC in women with a family history of BC from the CBER of Russia. Its allele *G* acts as a protective factor in BC (OR < 1). Scarce fragmentary data on the role of *MMP9* rs2250889 in BC are available in the literature. Only four relevant experimental studies have been reported in the literature to date, including two studies performed in the Chinese population (1056 patients and 1063 controls in one study [55] and 249 patients and 255 controls in the other [56]), one study in the Malaysian population (80 patients and 80 controls) [57], and one study in the Jordanian population (230 patients and 225 controls) [58]. A significant association of the *MMP9* rs2250889 (C>G) locus with BC has been observed only in the small-scale study of the Malaysian population; genotype *GG* has been identified as a genetic factor associated with higher

risk of BC (OR = 10.84) [57]. Three meta-analyses have considered the problem [22–24]. One was based on the results from three out of the four above studies and associated the *MMP9* rs2250889 (C>G) locus with BC (allele *G* is a BC risk factor, OR = 2.53) [23]. The two other meta-analyses (of which one was based on the same three out of the four studies and the other included two studies) did not detect the association at a statistically significant level ($p > 0.05$) [22, 24].

Thus, the rs2250889 (C>G) polymorphism of *MMP9* was associated with BC in only two (including this work) out of the five relevant studies according to our and published data. Genotype *GG* at the *MMP9* rs2250889 (C>G) locus is a genetic factor associated with higher risk of BC in an Asian (Malaysian) population, while allele *G* of the polymorphism protects against BC (OR 0.36–0.37) in a Caucasian population (the population of the CBER of Russia). The available experimental data are certainly not ample enough for making ultimate or even preliminary decisions about ethnic specifics of the association of the *MMP9* rs2250889 (C>G) locus with BC. The issue needs further investigation, and the data should be refined. Note that there is convincing evidence in the literature that distinct interethnic differences are characteristic of the associations of several candidate genes with multifactorial phenotypes (e.g., bone mass, glaucoma, etc.) (see [59–61], etc.).

A significant functional role is played by the *MMP9* rs2250889 (C>G) locus according to published data [62, 63] and the HaploReg online database. First, the polymorphism is in *MMP9* exon 6. The C>G substitution in position c.1721 is nonsynonymous and leads to a substitution of proline for arginine in position 574 of the MMP9 protein. Second, the genome region that harbors rs2250889 is an evolutionarily conserved open chromatin region and acts as an enhancer regulatory region (marked with the H3K4me1 methylated variant of histone H3) in more than 20 tissues and organs, including various epithelial and myoepithelial mammary primary cell cultures: human mammary epithelial cells (HMEC) (Epigenome ID: E119, Mnemonic: BRST.HMEC), breast variant human mammary epithelial cells (vHMEC) (Epigenome ID: E028, Mnemonic: BRST.HMEC.35), and breast myoepithelial primary cells (Epigenome ID: E027, Mnemonic: BRST.MYO). Third, the DNA region of rs2250889 provides binding sites for the CTCF regulatory protein and NRSF transcription factor. The C>G nucleotide substitution (rs2250889) decreases affinity of the regulatory DNA motif for the NRSF transcription factor.

We found that genotype *AA* of the *MML9* rs3787268 (G>A) polymorphism is associated with higher risk of BC in women without a family history of BC from the CBER of Russia (OR = 2.16). In agreement with our finding, Slattery et al. [21] have associated higher risk of BC with genotypes *AA* + *GA* compared with genotype *GG* (OR = 1.52) in women from the United States. Genotypes *AA* + *GA* have been associated with the survival of BC patients in the southeast Chinese population [56]. At the same time, the *MMP9* rs3787268 (G>A) locus has not been associated with BC in three studies, including an experimental work [55] and two meta-analyses [22, 23]. Allele *A* of rs3787268 has been found to exert a protective effect in BC (OR = 0.82) in an experimental study of the Han Chinese population [25] and a meta-analysis [24]. Discrepant data are therefore available on the association of the MMP9 rs3787268 (G>A) locus with BC. The issue needs further genetic epidemiological studies.

Based on the HaploReg epigenetic database and published data [63], the rs3787268 polymorphism is in a *MMP9* intron (c.1331–163G>A), which is a functionally active genome region (an open chromatin region) and plays an important regulatory role by acting as a *MMP9* enhancer (marked with methylated histone H3K4me1) in various tissues and organs, including epithelial and myoepithelial breast primary cells: breast myoepithelial primary cells (Epigenome ID: E027, Mnemonic: BRST.MYO) and breast variant human mammary epithelial cells (vHMEC) (Epigenome ID: E028, Mnemonic: BRST.HMEC.35). The DNA region of the rs3787268 locus provides binding sites for six transcription factors: Sox, HDAC2, p300, Pou1f1, Mef2, and Zfp105. It should be noted that the G>A nucleotide substitution in position c.1331–163 (rs3787268) increases affinity for all of the six transcription factors.

MMP9 (also known as gelatinase 9) is a type IV collagenase. The enzyme degrades type IV collagen and denatured collagens and thus destroys the basement membranes, playing an important role in the pathophysiology of BC. MMP9 is involved in BC progression and metastasis [22, 64]. Literature data indicate that MMP9 expression is upregulated in BC [18] and that higher MMP9 concentrations are observed in cancer tissue compared with normal breast tissue [15]. MMP9 expression is of prognostic significance for the overall and relapse-free survival of BC patients [22]. A meta-analysis of data on 2344 BC patients from 15 earlier studies has shown that high levels of MMP9 expression increase the relapse risk and decrease the survival in BC patients [65].

It should be noted that the *MMP* genetic variants that determine susceptibility to BC in women of the CBER of Russia exert pleiotropic effects because the respective MMPs perform numerous functions in many biomedical processes. MMPs proteolytically cleave various components of the connective-tissue matrix and modulate the production of laminin, fibronectin, etc., thus playing a key role in extracellular matrix remodeling. MMPs are involved in the pathophysiology of a broad range of common human disorders, such as arterial hypertension, cerebrovascular events, primary open-angle glaucoma, and peptic

ulcer disease, on evidence of earlier studies performed in the CBER population (the same population was examined in this work) (see [52, 53, 62, 63, 66], etc). The data indicate that the MMP genes play a crucial role in both normal and pathological conditions. Genetic epidemiological studies in the field make it possible to identify the syntropic and specific genetic *MMP* variants that determine susceptibility to various human disorders.

Our study showed that associations of the polymorphic loci of the *MMP* candidate genes with BC differ between women with and without a family history of the disease. In women with a family history of BC, lower risk of the disease is associated with the polymorphic loci rs243865 of *MMP2* (OR 0.53–0.54 for allele *T*) and rs2250889 of *MMP9* (OR 0.36–0.37 for allele *G*). In women without a family history of BC, higher risk of BC is associated with rs3787268 of *MMP9* (OR = 2.16 for allele *A*) and haplotypes at the six *MMP9* polymorphic loci: rs3918242, rs3918249, rs17576, rs3787268, rs2250889, and rs17577 ($p_{perm} \leq 0.05$).

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COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interests. The authors declare that they have no conflict of interest.

Statement of compliance with standards of research involving humans as subjects. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants involved in the study.

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