Association of Long Non-Coding RNA MEG3 Polymorphisms and Risk of Prostate Cancer in Chinese Han Population

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Purpose: To explore the association between MEG3 polymorphisms and the risk of prostate cancer in the Chinese Han population.

Materials and Methods: Two MEG3 single-nucleotide polymorphisms (SNPs) (rs11627993 C >T rs7158663 A>G) were genotyped in a case-control study in which 165 prostate cancer patients and 200 healthy controls were recruited by a Real-Time Polymerase Chain Reaction (PCR) with the TaqMan assay. The odds ratios (ORs) and 95% confidence intervals (CIs) were used to estimate the strength of association.

Results: No statistically significant differences were found in the allele or genotype distributions of the MEG3 rs11627993 C >T and rs7158663 A > G polymorphisms among cases or healthy control subjects (rs11627993: CC vs CA: 95% CI = 0.54-1.95, ORs = 1.03; CC vs AA: 95% CI = 0.67-2.54, ORs = 1.30 ; CC/CA vs AA: 95% CI = 0.81-1.98, ORs = 1.26 , *P* = .29 ; C vs A: 95% CI = 0.85-1.57, ORs = 1.16, *P* = .35; rs7158663: AA vs AG: 95% CI = 0.76-5.08, ORs = 1.97, AA vs GG: 95% CI = 0.57-3.29, ORs = 1.37; AA/AG vs GG : 95% CI = 0.56-1.32, ORs = 0.86, *P* = .49; A vs G: 95% CI = 0.69-1.39, ORs = 0.98, *P* = .91) Further stratified analysis detected no significant association.

Conclusion: The MEG3 polymorphisms (rs11627993 C>T and rs7158663 A>G) does not influence the susceptibility to prostate cancer.

Keywords: maternal-expressed gene 3; polymorphism; susceptibility; prostate cancer; lncRNA

INTRODUCTION

According to recent reports, prostate cancer is the most common non-cutaneous malignancy and the second leading cause of cancer-related deaths of men in the developed world[1]. The incidence and mortality of prostate cancer in the Chinese Han population have also been increasing in the last several decades[2]. The 2019 China national cancer center reported that prostate cancer ranked sixth and tenth among male malignancies in terms of morbidity and mortality in 2015[2]. To date, the mechanisms of prostate cancer remains largely unknown.

LncRNAs are important for cancer initiation and progression with the development of advanced genomic methods[3]. The genome-wide association study have identified so many cancer risk SNPs which are located in noncoding regions[4]. SNPs may affect the normal function of genes through various mechanisms, thereby affecting individual tumor susceptibility[5].

MEG3 is abnormally expressed in various human cancers, such as hepatocellular carcinoma[6,7], bladder cancer[8], glioma[7], and gastric cancer[9]. Ribarska found low expression of MEG3 in prostate cancer[10]. Luo found that MEG3 can inhibit the proliferation of prostate cancer cells and promote apoptosis[11]. However, little is known about the association between SNPs in MEG3 and prostate cancer risk.

Based on the previous findings mentioned above, we hypothesized that genetic variants of MEG3 may influence the susceptibility of prostate cancer. To test the hypothesis, we carried out an association study between SNPs in MEG3 and prostate cancer risk in a hospital-based prostate cancer case-control study, in which 165 patients and 200 control subjects were recruited.

PATIENTS AND METHODS

Study subjects

This study recruited 165 prostate cancer cases and 200 control subjects from the Affiliated Zhongda Hospital of Southeast University. CaP patients were diagnosed be-

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Table 1. Demographic characteristics of CaP cases and controls characteristics.

Characteristics		Cases (n=165)		Controls (n=200)		*P*-value[a]
		n	%	n	%	
Age(years)	≤ 70	76	46.10	101	50.50	0.39
	> 70	89	53.90	99	49.50	
Body mass index (kg/m^2)	≤ 23	56	33.90	68	34.00	0.99
	> 23	109	66.10	132	66.00	
Cigarette smoking	Never	98	59.40	102	51.00	0.11
	Ever	67	40.60	98	49.00	
Alcohol drinking	Never	100	60.60	132	66.00	0.29
	Ever	65	39.40	68	34.00	
Family history of cancers	No	118	71.50	168	84.00	$P < 0.01$
	Yes	47	28.50	32	16.00	

[a]Two-sided x^2 test for the distributions between the cases and controls.

tween July 2017 and July 2019 and were pathologically proven to have prostate adenocarcinoma after biopsy in the Affiliated Zhongda Hospital of Southeast University. The control group was age-matched, and the subjects were healthy checkup examinees without cancer history and were collected in the same period. All the patients were southern Chinese Han population. Controls were excluded if they had an abnormal prostate-specific antigen (PSA) level, or abnormal digital rectal examination (DRE). After informed consent was obtained, 2ml of peripheral blood sample was collected and each subject was asked to finish a questionnaire including age, race, tobacco use, alcohol use, family history of cancer, and so on. In the present research, smoking more than five cigarettes per day for more than 5 years was defined as smoking. Drinking habit was defined as drinking at least three times per week and lasting more than 10 years. Family history of cancer was defined as cancer in first-degree relatives (parents, siblings, or children). Disease stage was determined by pathologic findings, pelvic computed tomography, magnetic resonance image, and radio-nucleotide bone scans. The tumor stage was determined using TNM classification and graded according to WHO guidelines. Pathologic grade was recorded as the Gleason score.

All participants provided informed consent after the interview. This research protocol was approved by the Institutional Review Board of Affiliated Zhongda Hospital of Southeast University

SNPs selection and genotyping

We selected the SNPs of MEG3 with the minor allele frequency (MAF) > 0.05 in Han Chinese from the 1000 Genome Projects. As a result, rs11627993 and rs7158663 were selected. Genomic DNA was extracted from peripheral blood using the TIAN amp Blood DNA kit (Tian gen, China). Genotyping was performed by TaqMan SNP genotyping assay. Furthermore, about 3% of selected samples were blindly repeated for genotyping to confirm the results.

Statistical analysis

Tests for the Hardy-Weinberg equilibrium in cases and controls were performed by the good-of-fit χ^2 test. We estimated the association between genotypes and prostate cancer risk by odds ratios (ORs) and 95% confidence intervals (CIs) using the logistic regression. The ORs and 95%CIs were further adjusted for age, BMI (body mass index), and cigarette smoking, alcohol drinking, family history of cancers. All analyses were two-sided and $P < .05$ was considered significant. All statistical calculations were conducted with SPSS 13.0 software (SPSS Inc., Chicago, IL, USA).

Table 2. Genotypes in patients with CaP and controls.

SNPs		Genotypes	Cases ,n(%)	Controls ,n(%)	*P*-value[b]	Adjusted OR (95% CI)[c]
rs11627993a1	Total	165	200		0.62	
	CC	24(14.55)	27(13.50)			1.00(reference)
	CA	85(51.51)	94(47.00)			1.03(0.54-1.95)
	AA	56(33.94)	79(39.50)			1.30(0.667-2.54)
	CC/CA	109(66.06)	121(60.50)		0.29	1.00(reference)
	AA	56(33.94)	79(39.50)			1.26(0.81-1.98)
	Allele				0.35	
	C allele	133(40.30)	148(37.00)			1.00(reference)
	A allele	197(59.70)	252(63.00)			1.16(0.85-1.57)
rs7158663a2					0.34	
	AA	13(7.88)	11(5.50)			1.00(reference)
	AG	54(32.73)	78(39.00)			1.97(0.76-5.08)
	GG	98(59.39)	111(55.50)			1.37(0.57-3.29)
	AA/AG	67(40.61)	89(44.50)		0.49	1.00(reference)
	GG	98(59.39)	111(55.50)			0.86(0.56-1.32)
	Allele				0.91	
	A allele	80(24.20)	100(25.00)			1.00(reference)
	G allele	250(75.80)	300(75.00)			0.98(0.69-1.39)

[a]The genotype frequencies among the control subjects were in agreement with the Hardy–Weinberg equilibrium (a1:x^2 =0.003 p=0.99 a2:x^2 =0.24 p = 0.89).
[b]Two-sided x^2test for the distributions or allele frequencies between the cases and controls.
[c]Odds ratios (ORs) were obtained from a logistic regression model with adjusting for age, BMI, cigarette smoking, alcohol drinking, family history of cancers.

Table3. MEG3 polymorphisms and clinicopathological characteristics in patients with CaP.

Variables		rs11627993 CC/CA,n(%)	AA,n(%)	*P*-value[a]	Adjusted OR (95% CI)[b]
Clinical stagec	Localized(84)	53(63.10)	31(36.90)	0.75	1.00(reference)
	Advanced(81)	56(69.14)	25(30.86)		0.91(0.51-1.62)
Gleason score	< 7(14)	13(92.86)	1(7.14)		1.00(reference)
	= 7(64)	39(60.94)	25(39.06)	0.05	8.33(1.03-67.71)
	> 7 (87)	57(65.52)	30(34.48)	0.07	6.84(0.85-54.85)
PSA	≤20 (74)	48(64.86)	26(35.14)	0.75	1.00(reference)
	> 29(91)	61(67.03)	30(32.97)		0.90(0.47-1.73)
	rs7158663 AA/AG,n(%)	GG,n(%)			
Clinical stagec	Localized(84)	33(39.29)	51(60.71)	0.67	1.00(reference)
	Advanced(81)	34(41.98)	47(58.02)		0.87(0.45-1.66)
Gleason score	< 7 (14)	5(35.71)	9(64.29)		1.00(reference)
	= 7 (64)	22(34.38)	42(65.62)	0.75	1.23(0.36-4.24)
	> 7 (87)	40(45.98)	47(54.02)	0.60	0.72(0.22-2.42)
PSA	≤ 20 (74)	27(36.49)	47(63.51)	0.32	1.00(reference)
	> 29(91)	40(43.96)	51(56.04)		0.72(0.38-1.36)

[a]Two-sided w2 test for the distributions or allele frequencies between the cases and controls.
[b]Odds ratios (ORs) were obtained from a logistic regression model with adjusting for age, BMI, cigarette smoking, alcohol drinking, family history of cancers.
cLocalized: T1–2N0M0; Advanced: T3–4NxMx or TxN1Mx or TxNxM1 [according to the international tumor–node–metastasis (TNM) staging system for CaP.]

RESULTS

Characteristics of the study population

The demographic characteristics of participants are described in **Table 1**. There was no significant difference in age ($P = .39$), BMI ($P = .99$), cigarette smoking ($P = .11$), and alcohol drinking distribution ($P = .29$). However, there was a significant difference in the family history of cancer between cases and controls ($P < .001$), which may suggest the incidence of prostate cancer is related to genetic factors.

Genotype distributions of MEG3 polymorphism and risk of CaP

Both of polymorphisms (rs11627993 C>T and

Table 4. Association and stratification analysis between MEG3 polymorphism and risk of CaP.

			rs11627993(Cases/Controls)					
	N (Cases /Controls)		CC/CA		AA			
Variables			N	%	n	%	*P*-value[a]	Adjusted OR (95% CI)[b]
Total		165/200	109/121	66.06/60.50	56/79	33.94/39.50	0.29	1.27(0.82-1.98)
Age (years)	≤ 70	76/101	52/62	68.42/61.39	24/39	31.58/38.61	0.40	1.32(0.69-2.53)
	> 70	89/99	57/59	64.04/60.00	32/40	35.96/40.00	0.21	0.66(0.35-1.26)
Body mass index (kg/m^2)	≤ 23	56/68	35/42	62.50/61.76	21/26	37.50/38.24	0.86	1.07(0.51-2.24)
	> 23	109/132	74/79	67.89/59.85	35/53	32.11/40.15	0.17	1.49(0.85-2.62)
Cigarette smoking	Never	98/102	68/63	69.39/61.76	30/39	30.61/38.24	0.37	1.32(0.72-2.41)
	Ever	67/98	41/58	61.19/59.18	26/40	38.81/40.82	0.70	1.14(0.59-2.22)
Alcohol drinking	Never	100/132	68/83	0.68/62.88	32/49	0.32/37.12	0.71	1.12(0.63-1.98)
	Ever	65/68	41/38	63.08/55.88	24/30	36.92/44.12	0.32	1.44(0.70-2.93)
Family history of cancers	No	118/168	76/103	64.41/61.31	42/65	35.59/38.69	0.64	1.12(0.69-1.84)
	Yes	47/32	33/18	70.21/56.25	14/14	29.79/43.75	0.21	1.83(0.72-4.68)
			rs7158663(Cases/Controls)					
			AA/AG			GG		
			n	%		n		%
Total		165/200	67/89	40.61/44.50	98/111	59.39/55.50	0.51	0.87(0.56-1.33)
Age (years)	≤70	76/101	33/53	43.42/52.48	43/48	56.58/47.52	0.27	0.71(0.38-1.31)
	>70	89/99	34/36	38.20/36.36	55/63	61.80/63.64	0.87	1.05(0.57-1.93)
Body mass index (kg/m^2)	≤23	56/68	20/28	35.71/41.18	36/40	64.29/58.82	0.48	0.77(0.37-1.60)
	□23	109/132	47/61	43.12/46.21	62/71	56.88/53.79	0.86	0.95(0.56-1.64)
Cigarette smoking	Never	98/102	39/42	39.80/41.18	59/60	60.20/58.82	0.73	0.91(0.50-1.63)
	Ever	67/98	28/47	41.79/47.96	39/51	58.21/52.04	0.41	0.76(0.39-1.46)
Alcohol drinking	Never	100/132	38/58	38.00/43.94	62/74	62.00/56.06	0.60	0.86(0.49-1.51)
	Ever	65/68	29/31	44.62/45.59	36/37	55.38/54.41	0.71	0.87(0.43-1.78)
Family history of cancers	No	118/168	43/76	36.44/45.24	75/92	63.56/54.76	0.27	0.76(0.46-1.24)
	Yes	47/32	24/13	51.06/40.63	23/19	48.94/59.37	0.42	1.46(0.58-3.65)

[a] Two-sided w2 test for the distributions between the cases and controls.
[b] Odds ratios (ORs) were obtained from a logistic regression model with adjusting for age, BMI, cigarette smoking, alcohol drinking, family history of cancers.

rs7158663 A>G) were in accordance with Hardy-Weinberg equilibrium (HWE) in the control subjects (rs11627993:x^2 = 0.003 P = .99 rs7158663:x^2 = 0.24 P = .89). However, neither of the two MEG3 polymorphisms was associated with prostate cancer susceptibility, even after being adjusted for potential covariates (age, BMI, cigarette smoking, alcohol drinking, family history of cancers). We next evaluated the effects of combined risk genotypes on prostate cancer susceptibility. Similarly, no significant association was found (**Table 2**).

For rs11627993, after adjusting for potential covariates, compared with CC homozygotes, subjects carrying CA heterozygotes (95% CI = 0.54-1.95, ORs = 1.03) or AA homozygotes (95%CI = 0.67-2.54, ORs = 1.30) had a decreased risk of CaP. In addition, subjects carrying AA homozygotes had a 1.26-fold reduced risk (95%CI = 0.81–1.98 , P = .29) than these carrying CC/CA genotypes, and the A allele displayed a higher prevalence of CaP compared with the C allele (95%CI = 0.85–1.57, ORs = 1.16, P = 0.35). Similarly, for rs7158663, after adjusting for potential covariates, compared with AA homozygotes, subjects carrying AG heterozygotes (95%CI = 0.76-5.08, ORs = 1.97) or GG homozygotes (95%CI=0.57-3.29, ORs=1.37) had an increased risk of CaP (Table 3). The G allele displayed a lower prevalence of CaP compared with the A allele (95%CI = 0.69–1.39, ORs = 0.98, P = .91).

Stratified analyses

We next evaluated the stratified association of rs11627993 and rs7158663 with prostate cancer risk by clinical stage (Localized: T1–2N0M0; Advanced: T3–4NxMx or TxN1Mx or TxNxM1), pathologic grade (Gleason score <7, 7, and >7) and serum PSA level (≤ 20 and >20) (**Table3**), potential covariates(**Table 4**). No association with rs11627993 or rs7158663 and prostate cancer was found.

DISCUSSION

It is well known that environmental and genetic factors such as genetic mutations and polymorphisms contribute to prostate cancer carcinogenesis[12,13]. Long non-coding RNAs are molecules larger than 200 nucleotides, which do not code protein[14]. It has been reported that lncRNAs affect not only biologic processes such as metabolism, proliferation, tissue differentiation, cell type identity maintenance, apoptosis, cell signal regulation, organ development, and aging but also tumorigenesis[15,16]. Maternally expressed gene 3 (MEG3) is a lncRNA which is expressed in many normal tissues, and located on chromosome 14q32.3[17]. It is the first lncRNA identified as a tumor suppressor, preventing cancer initiation and development[18]. Recent studies demonstrated decreased MEG3 levels in a variety of primary human cancer[19]. MEG3 expression level is decreased in lung cancer[20]. The downregulation of MEG3 usually led to more aggressive cancers and MEG3 expression level correlated with tumor grade and prognosis in colorectal cancer, and gastric cancer[21,22]. Yin et al. analyzed 62 CRC cases and demonstrated that a lower MEG3 level correlates with lower pathological grade, deeper tumor invasion, and advanced TNM stage[23]. Sun et al. reported that downregulated MEG3 is associated with poor prognosis and promotes cell proliferation in gastric cancer[24]. Li et al. found MEG3 expression level is significantly lower in invasive NFPAs compared to noninvasive NFPAs[25]. SNPs play important roles in carcinogenesis by affecting gene expression and function[26]. Some polymorphisms may affect the expression and secondary structure of lncRNA, which contribute to the development of cancer[27-29]. Cao et al. genotyped five tagSNPs in the MEG3(rs3087918, rs11160608, rs4081134, rs10144253, and rs7158663) to investigate their role in colorectal cancer risk in a case-control study. They demonstrated that rs7158663 may be associated with colorectal cancer risk[23]. Another study reported that MEG3 rs4081134 was associated with the risk of neuroblastoma in Chinese children[30]. However, no studies on the association between MEG3 polymorphisms and the risk of the prostate cancer have been conducted until now.

This is the first study to explore the correlation between the MEG3 polymorphisms and prostate cancer susceptibility in China. The results showed that a family history of cancer increases the risk of prostate cancer. But no significant association was found between MEG3 polymorphisms and the risk of prostate cancer. Our study had several limitations. The primary limitation was a small sample size, which may impair the strength of the statistical power, especially for the stratification analysis. Secondly, only two MEG3 polymorphisms were genotyped. More potentially functionally polymorphisms in MEG3 needed to be studied

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CONCLUSIONS

In conclusion, our study showed that the MEG3 polymorphisms (rs11627993 and rs7158663) have no impacts on the risk of prostate cancer. A study based on multi-hospitals with larger sample should be conducted. Moreover, in vitro and in vivo functional analysis to reveal the mechanism how the genetic polymorphisms in MEG3 affect the prostate cancer risk also need to be studied.

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CONFLICT OF INTEREST

The authors report no conflicts of interest in this work.

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