RESEARCH ARTICLE

The P275A Polymorphism in the Macrophage Scavenger Receptor 1 Gene and Prostate Cancer Risk: a Meta-Analysis

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Abstract

Background: Published data regarding associations between the P275A polymorphism in the macrophage scavenger receptor 1 (MSR1) gene and prostate cancer (PCa) risk are inconclusive. The aim of this study was to comprehensively evaluate the genetic risk of P275A polymorphism in MSR1 gene for PCa. Materials and Methods: A systematic literature search was carried out in Pubmed, Medline (Ovid), Embase, CBM, CNKI, Weipu, and Wanfang databases, covering all available publications (last search was performed on Apr 27, 2015). Statistical analysis was performed using Revman 5.2 and STATA 10.1 software. Results: A total of 5,017 cases and 4,869 controls in 12 case-control studies were included in this meta-analysis. When all groups were pooled, there was no evidence that the P275A polymorphism had a significant association with PCa under dominant (OR=0.93, 95%CI=0.81-1.06, and *p*=0.28), co-dominant (homogeneous OR=0.97, 95%CI=0.56-1.68, and *p*=0.92; heterogeneous OR=0.93, 95%CI=0.74-1.15, and *p*=0.49), recessive (OR=1.10, 95%CI=0.65-1.87, and *p*=0.73), over-dominant (OR=0.93, 95%CI=0.75-1.15, and *p*=0.50), and allelic (OR=0.95, 95%CI=0.77-1.16, and *p*=0.61) genetic models. For stratified analyses by ethnicity and study design, no significant associations were found in the white race, the yellow race, the black race and mixed ethnicity, and the population-based case-control (PCC) and hospital-based case-control (HCC) studies under all genetic models. Conclusions: Based on our meta-analysis, the P275A polymorphism in the MSR1 gene is unlikely to be a risk factor for PCa.

Keywords: Macrophage scavenger receptor 1 (MSR1) - prostate cancer - meta-analysis - polymorphism

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Introduction

Prostate cancer (PCa) is a commonly diagnosed noncutaneous cancer in men. Although the morbidity of PCa in Asia is lower than the places like Oceania, Europe and North America, it indeed has a rapid increasing (Wang et al., 2012; Matshela et al., 2014; Zhang et al., 2014). Despite the fact that the complex etiology of PCa remains obscure, various risk factors play important roles in PCa development such as genetic variations, advanced age and environmental exposures, which join hands in hands, triggering the disease. However, it was estimated that genetic influences contribute a lot (about 42%) to PCa risk (Lichtenstein et al., 2000), such as, individual and combined effects of rare, highly penetrant genes and more common polymorphisms with mild effects on androgen biosynthesis/metabolism, DNA repair and chronic inflammation pathways (Hsing and Chokkalingam, 2006; Chokkalingam et al., 2007). Therefore, numerous published studies have focused on the association of genetic variants with PCa susceptibility, and among which, the macrophage scavenger receptor 1 (MSR1) gene was comprehensively studied.

The MSR1 protein, a multidomain trimeric molecule composed of identical protein chains, plays a role in the innate immune response to pathogen infection, which may cause prostate cancer. While the MSR1 gene (MIM 153622) which is located at 8p22 region was reported as a candidate susceptibility gene for hereditary prostate cancer (HPC), but also a risk factor for sporadic disease based on independent genome wide linkage studies (Ostrander and Stanford, 2000; Xu et al., 2001; Xu et al., 2003; Chen et al., 2008). This gene is polymorphic, and a large number of single nucleotide polymorphisms (SNPs) have been already identified, such as Arg293X, Asp175Tyr, His441Arg, Val113Ala and Ile54Val, PRO3, INDEL1, I*vs*5-59, P275A and INDEL7. Among all of these polymorphisms, the P275A polymorphism was the most widely studied for its implication in prostate cancer. However, the results were inconsistent and inconclusive. Prior study suggested that MSR1 may play an important role in prostate carcinogenesis (Xu et al., 2003), but a subsequent literature shows the association is null (Chen et al., 2008). Considering that individual study may lack of persuasion to provide a reliable conclusion, we performed a meta-analysis to estimate these associations between PCa and MSR1 polymorphism, which refers in particular to P275A.

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Materials and Methods

Selection of studies

A systematic literature search was carried out in Pubmed, Medline (Ovid), Embase, Chinese biomedical database (CBM), China national knowledge infrastructure (CNKI), Weipu and Wanfang database to identify studies involving association between the P275A polymorphism of MSR1 gene and PCa risk (last search was updated on Apr 27, 2015). The search terms were used as follows: (macrophage scavenger receptor 1 or MSR1) in combination with (polymorphism or variant or mutation) and (prostate cancer or prostate carcinoma or prostate neoplasm). The search results were limited to English and Chinese languages. Studies included in our meta-analysis met the following inclusion criteria: (1) evaluation of the P275A polymorphism of MSR1 gene and PCa risk, (2) the design had to be a case-control design published in a journal, (3) genotype distributions in both cases and controls were available for estimating an odds ratio with 95% confidence interval (CI) and *p* value, and (4) genotype distributions in control group should be consistent with Hardy-Weinberg equilibrium (HWE). Studies were excluded if one of the following existed: (1) no controls, (2) genotype frequencies or number not reported, and (3) abstracts, reviews. For duplication or overlapping publications, the studies with larger number of cases and controls or been published latest were included.

Data extraction

Two independent reviewers (QXZ and JQT) collected the data and reached a consensus on all items. In case of disagreement, a third author (FZ) would assess these articles. A standardized data form was used and included: first author's name, year of publication, original country, ethnicity, case age, study design, total number of cases and controls and genotyping method.

Statistical analysis

Odds ratios (OR) with 95%CI was used to assess the strength of association between P275A polymorphism and PCa risk. We first examined P275A genotypes using dominant model (GG+GC *vs* CC), recessive (GC+CC *vs* GG), over-dominant (GG+CC *vs* GC) and co-dominant (homogeneous co-dominant model: GG *vs* CC, heterogeneous co-dominant model: GC *vs* CC) genetic models. Then, the relationship between the allele and susceptibility to PCa was examined (allelic model). The pooled OR was calculated by a fixed-effect model or a random-effect model according to the heterogeneity. Heterogeneity was checked by a χ^2-based Q statistic and $p<0.10$ was considered statistically significant. A p-value$\geq$0.10 for the Q-test indicated the lack of heterogeneity among the studies, and so the summary OR estimate of each study was calculated by the fixed-effect model (Mantel and Haenszel, 1959). Otherwise, the random-effect model was used (DerSimonian and Laird, 1986). The statistical significance of OR was analyzed by Z test, and $p<0.05$ was considered as statistically significant. To evaluate the ethnicity-specific and study design-specific effects, we performed stratification analyses on both ethnicity and study design. For the subgroup analysis by ethnicity, the study populations were stratified into four groups: the white race, the yellow race, the black race and the mixed (if it was difficult to distinguish the ethnicity of participants according to the data presented, the study was termed "*mixed*"). Subjects were categorized into different classifications according to study design: population-based case-control study (PCC) and hospital-based case-control study (HCC). Sensitivity analysis was also performed by sequence excluding individual study to check the robustness of the result (Zhang et al., 2012; Zhao et al., 2014). The possible publication bias was examined visually in a Begg's funnel plot and the degree of asymmetry was tested by Egger's test ($p<0.05$ was considered representative of statistically significant publication bias) (Begg and Mazumdar, 1994; Sun et al., 2013). HWE was tested by Pearson's χ^2 test (Wigginton et al., 2005). Statistical analysis was performed using Revman5.2 and Stata 10.1 softwares.

Results

Study inclusion and characteristics

As shown in Figure 1, the initial search identified 107 results from the selected electronic databases. After reading the titles and abstracts, 57 potential articles were included for full-text view. After reading full texts, 44 studies were excluded for being irrelevant to PCa risk and P275A polymorphism of MSR1 gene. Therefore, 13 full-text articles remained for data extraction. 2 articles were excluded for not presenting usable data (Xu et al., 2002; Rennert et al., 2008), An additional article was excluded for repeating or overlapping (Cybulski, 2007). Finally, a total of 12 case-control studies published in 10 articles which met our inclusion criteria were identified, including 5017 cases and 4986 controls. The characteristics of each case-control study are listed in Table 1. Genotype and allele distributions for each case-control study are shown in Table 2. There were 8 case-controls of the white race (Seppala et al., 2003; Wang et al., 2003; Xu et al., 2003; Maier et al., 2006; Lindmark et al., 2004; Cybulski et al., 2007; Beuten et al., 2010), 1 of the yellow race (Hsing et

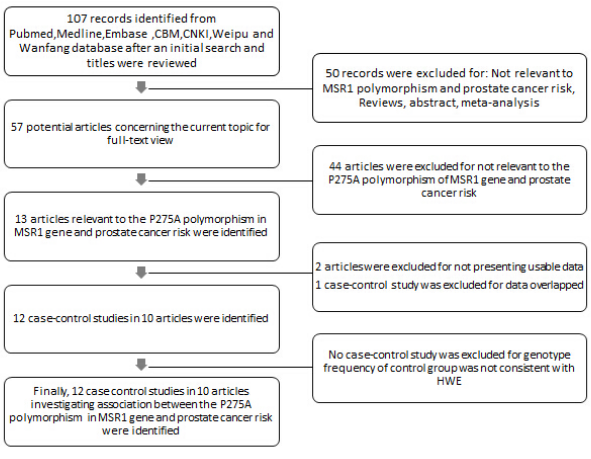

Figure 1. Flow Diagram of Included/Excluded Studies. MSR1, Macrophage Scavenger Receptor 1; HWE, Hardy-Weinberg equilibrium

Table 1. Characteristics ofthe Studies Included in Meta-analysis

First author	Year	Country	Ethnicity	Case age (year)	Study design	No. (Cases/Controls)	Genotyping method
Beuten et al	2010	USA	the white race (Caucasian)	65.5±8.5†	PCC	596/840	NM
			the white race (Hispanic)			194/454	
			the black race (African-American)			82/188	
Chen et al	2008	USA	the mixed (70%Caucasion)	NM	PCC	679/691	PCR
Cybulski et al	2007	Poland	the white race (Polish)	67.3	HCC	737/511	RFLP-PCR
Lindmark et al	2003	Sweden	the white race (Swedish)	63	PCC	205/408	PCR
Maier et al	2006	Germany	the white race (Caucasian)	64.1	PCC	506/197	PCR
Miller et al	2003	USA	the black race (African-American)	NM	PCC	131/333	NM
Seppa¨la et al	2003	Finland	the white race (Finnish)	68.6	HCC	537/480	PCR
W.Hsing et al	2007	China	the yellow race (Chinese)	NM	PCC	124/146	QuickStep PCR
Wang et al	2003	USA	the white race (Caucasian)	65 (median age)	HCC	926/488	RT-PCR
Xu et al	2003	USA	the white race (Caucasian)	59.3	HCC	300/250	PCR

HCC, hospital-based case-control study; PCC, population-based case-control study; NM, not mentioned; †Mean ± SD,the mean age is calculated for the overall cases(Caucasians, African-American and Hispanic), not stratified by race; PCR, polymerase chain reaction; RT-PCR, reverse transcription polymerase chain reaction; RFLP-PCR, polymerase chain reaction-restriction fragment length polymorphism

Table 2. Distribution of P275A Genotype and Allele among Prostate Cancers and Controls

Author	Cases(n)			Controls(n)			Cases(n)		Controls(n)		HWE[a] for
	CC	GC	GG	CC	GC	GG	C	G	C	G	control *p*
Beuten et al-AA[b]	76	6*	NA	174	14*	NA	NA	NA	NA	NA	0.96
Beuten et al-Ca[b]	568	28*	NA	791	49*	NA	NA	NA	NA	NA	0.22
Beuten et al-Hi[b]	166	28*	NA	373	81*	NA	NA	NA	NA	NA	0.10
Chen et al	603	68	8	622	67	2	1274	84	1311	71	0.89
Cybulski et al	663	74	0	474	37	0	1400	74	985	37	0.39
Lindmark et al	190	15	0	385	21	2	395	15	791	25	0.07
Maier et al	446	58	2	168	28	1	950	62	364	30	0.89
Miller et al	118	12	1	287	43	3	248	14	617	49	0.33
Seppa¨la et al	516	21	0	460	20	0	1053	21	940	20	0.64
W.Hsing et al	61	48	15	56	72	18	170	78	184	108	0.48
Wang et al	822	101	3	438	49	1	1745	107	925	51	0.76
Xu et al	271	28	1	209	38	3	570	30	456	44	0.40

[a]HWE, Hardy-Weinberg equilibrium; [b]-AA, Arican-American; [b]-Ca, Caucasian; [b]-Hi, Hispanic; *Numbers of GC+GG; NA, not available

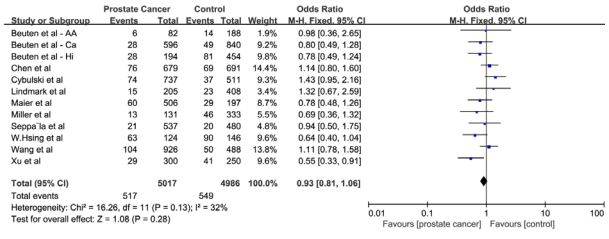

Figure 2. Meta-analysis with a Fixed-Effect Model for the Association between Prostate Cancer Risk and the P275A Polymorphism in the MSR1 Gene (GG+GC *vs* CC). CI=confidence interval; OR, odds ratio

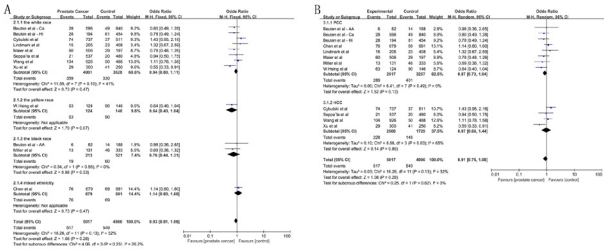

Figure 3. Meta-analysis for the Association between Prostate Cancer Risk and the P275A polymorphism in the MSR1 Gene (GG+GC *vs* CC): A, Subgroup Analysis by Ethnicity; B, Subgroup Analysis by Study design. CI=confidence interval; OR, odds ratio

al., 2007), 2 of the black race (Miller et al., 2003; Beuten et al., 2010) and 1 of mixed ethnicity (70% Caucasions) (Chen et al., 2008). All the included 10 eligible reports were written in English.

Quantitative data synthesis

All studies: As shown in Figure 2, the heterogeneity of (GG+GC *vs* CC) for all 12 studies was assessed and the value of χ^2 was 16.26 with 11 degrees of freedom and p=0.13 in a fixed-effect model. Additionally, the I-square, which is another index of the test of heterogeneity, was 32%, suggesting a moderate heterogeneity. Thus, we chose the fixed-effect model to synthesize the data. Overall, OR was 0.93 (95%CI=0.81-1.06), and the test for overall effect Z value was 1.08 (p=0.28) in dominant (GG+GC *vs* CC) model. The results suggested no significant association between P275A polymorphism of MSR1 gene and PCa risk under dominant (GG+GC *vs* CC) model. Summary results for all comparisons are presented in Table 3.

Subgroup analyses: Subgroup analyses by ethnicity and study design were performed. For ethnicity (GG+GC *vs* CC, Figure 3A), the analysis was stratified into four

Table 3. Meta-Analysis of the P275A Polymorphism in the MSR1 Gene on Prostate Cancer Risk

Genetic model	Sample size		Analysis	Test of association		P value for	Test for heterogeneity	
(No. of studies)	cases	controls	model	OR (95% CI)	*p*	Egger's test	*p*	I^2
Total (12)								
GG+GC *vs* CC (12)	5017	4986	F	0.93 [0.81, 1.06]	0.28	0.324	0.13	32%
GC+CC *vs* GG (9)	4145	3504	F	1.10 [0.65, 1.87]	0.73	0.111	0.55	0%
GG+CC *vs* GC (9)	4145	3504	R	0.93 [0.75, 1.15]	0.50	0.323	0.09	41%
GG *vs* CC (9)	3720	3129	F	0.97 [0.56, 1.68]	0.92	0.128	0.47	0%
GC *vs* CC (9)	4115	3474	R	0.93 [0.74, 1.15]	0.49	0.368	0.07	44%
G *vs* C (9)	8290	7008	R	0.95 [0.77, 1.16]	0.61	0.160	0.06	46%
Subgroup by ethnicity								
the white race (8)								
GG+GC *vs* CC (8)	4001	3628	F	0.94 [0.80, 1.11]	0.47		0.10	41%
GC+CC *vs* GG (6)	3211	2334	F	0.62 [0.20, 1.90]	0.40		0.74	0%
GG+CC *vs* GC (6)	3211	2334	R	1.00 [0.75, 1.32]	0.98		0.08	48%
GG *vs* CC (6)	2914	2141	F	0.61 [0.20, 1.86]	0.38		0.72	0%
GC *vs* CC (6)	3205	2327	R	0.99 [0.75, 1.32]	0.96		0.08	49%
G *vs* C (6)	6422	4668	R	0.96 [0.73, 1.27]	0.79		0.06	53%
the black race (2)								
GG+GC *vs* CC (2)	213	521	F	0.76 [0.44, 1.31]	0.33		0.56	0%
Subgroup by study design								
HCC (4)								
GG+GC *vs* CC (4)	2500	1729	R	0.97 [0.66, 1.44]	0.89		0.03	65%
GC+CC *vs* GG (4)	2500	1729	F	0.65 [0.16, 2.71]	0.55		0.29	13%
GG+CC *vs* GC (4)	2500	1729	R	0.99 [0.68, 1.43]	0.94		0.06	60%
GG *vs* CC (4)	2276	1585	F	0.63 [0.15, 2.62]	0.53		0.26	20%
GC *vs* CC (4)	2496	1725	R	0.98 [0.68, 1.43]	0.93		0.05	61%
G *vs* C (4)	5000	3458	R	0.97 [0.65, 1.43]	0.86		0.03	68%
PCC (8)								
GG+GC *vs* CC (8)	2517	3257	R	0.87 [0.73, 1.04]	0.13		0.49	0%
GC+CC *vs* GG (5)	1645	1775	F	1.20 [0.67, 2.13]	0.54		0.49	0%
GG+CC *vs* GC (5)	1645	1775	R	0.87 [0.68, 1.13]	0.30		0.27	23%
GG *vs* CC (5)	1444	1544	F	1.05 [0.58, 1.89]	0.88		0.39	3%
GC *vs* CC (5)	1619	1749	R	0.87 [0.66, 1.14]	0.31		0.23	29%
G *vs* C (5)	3290	3550	R	0.93 [0.74, 1.17]	0.53		0.25	25%

OR, odds ratio; CI, confidence interval; F, fixed-effect model; R, random-effect model

Table 4. Sensitivity Analysis of the P275A Polymorphism in the MSR1 Gene on Prostate Cancer Risk under (GG+GC *vs* CC) Genetic Model

Excluded study	Cases/controls[#]	OR (95%CI)	*p**
Beuten et al - AA	4935/4798	0.93 [0.81, 1.06]	0.28
Beuten et al - Ca	4421/4146	0.94 [0.81, 1.09]	0.40
Beuten et al - Hi	4823/4532	0.94 [0.82, 1.09]	0.43
Chen et al	4338/4295	0.89 [0.77, 1.04]	0.13
Cybulski et al	4280/4475	0.88 [0.76, 1.01]	0.07
Seppa¨la et al	4480/4506	0.93 [0.80, 1.07]	0.29
Lindmark et al	4812/4578	0.91 [0.79, 1.05]	0.20
Maier et al	4511/4789	0.94 [0.82, 1.09]	0.40
Miller et al	4886/4653	0.94 [0.82, 1.08]	0.40
W.Hsing et al	4893/4840	0.96 [0.83, 1.10]	0.55
Wang et al	4091/4498	0.90 [0.77, 1.04]	0.16
Xu et al	4717/4736	0.97 [0.84, 1.12]	0.65

[#]The number of cases/controls is caculated by sequentially excluded each case-control study; OR, odds ratio; CI, confidence interval; *vs*, versus; **p* value for Q-test

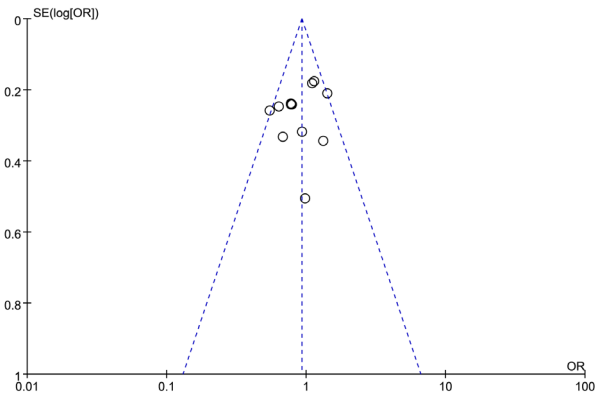

Figure 4. Begg's Funnel Plot for Publication Bias in Selection of Studies on the P275A Polymorphism in the MSR1 Gene (GG+GC *vs* CC). OR, odds ratio

subgroups: the white race (4001 cases and 3628 controls), the yellow race (124 cases and 146 controls), the black race (213 cases and 521 controls) and mixed ethnicity (679 cases and 691 controls). The data suggested that P275A was not associated with PCa risk under dominant model in overall population (OR=0.93, 95%CI=0.81-1.06, *p*=0.28; Figure 1). In addition, we did not detect the obvious association between P275A polymorphism and PCa risk in overall population when examining the contrast of (GG *vs* CC) (OR=0.97, 95%CI=0.56-1.68, *p*=0.92); (GC *vs* CC) (OR=0.93, 95%CI=0.74-1.15, *p*=0.49); (GC+CC *vs* GG) (OR=1.10, 95%CI=0.65-1.87, *p*=0.73); (GG+CC *vs* GC) (OR=0.93, 95%CI=0.75-1.15, *p*=0.50); and (G allele *vs* C allele) (OR=0.95, 95%CI=0.77-1.16, *p*=0.61).

No significantly increased risks were found among the white race (OR=0.94, 95%CI=0.80-1.11, and p=0.47), the yellow race (OR=0.64, 95%CI=0.40-1.04, and p=0.07), the black race (OR=0.76, 95%CI=0.44-1.31, and p=0.33) and the mixed ethnicity (OR=1.14, 95%CI=0.80-1.60, and p=0.47) under dominant model. Similarly, in the subgroup analysis by study design status (GG+GC *vs* CC, Figure 3B), the analysis was stratified into two subgroups: population-based case-control study (PCC) and hospital-based case-control study (HCC), no obviously increased risk was identified among PCC (OR=0.87, 95%CI=0.73-1.04, and p=0.13) and HCC (OR=0.97, 95%CI=0.66-1.44, and p=0.89). Summary results of other comparisons are listed in Table 3.

Sensitivity analysis

The one-way sensitivity analyses were performed to assess the stability of the results, namely, a single study in the meta-analysis was deleted each time to reflect the influence of the individual data set to the pooled OR. After sequentially excluding each case-control study, statistically similar results were obtained for (GG+GC *vs* CC) (all p values were >0.05), confirming the stability of this meta-analysis. The detailed data were presented in Table 4.

Publication bias

We assessed publication bias by Begg's funnel plot and Egger's test. The shape of funnel plots (Figure 4) did not reveal any evidence of obvious asymmetry in all comparison models, and the Egger's test was used to provide statistical evidence of funnel plot symmetry. The results did not show any evidence of publication bias (p>0.05). The detailed data were present in Table 3.

Discussion

In many developed countries, PCa is the most frequently diagnosed malignancy in men (Hu et al., 2013). One of the risk factors of PCa is chronic inflammation, which is associated with macrophage scavenger receptor 1 (MSR1). As an important component in the inflammation pathway, MSR1 may link chronic inflammation and prostate cancer by altering inflammation responses upon the binding of a wide range of ligands (Krieger and Herz, 1994; Platt and Gordon, 2001; Xu et al., 2003; Sun et al., 2006). Given the important roles of MSR1 in prostate cancer etiology makes it possible that genetic variations of the MSR1 gene may affect the susceptibility to the development of PCa. Genetic variants, such as SNPs in the Exon6 region of the MSR1 encoding gene, is the most extensively studied polymorphism, which features cytosine (C) converting to guanine (G) at position -823 bp of the Exon6 region, affecting transcription activity of P275A polymorphism of MSR1 gene and its functional activity (Chen et al., 2008). To date, conclusions of the association of P275A polymorphism in the MSR1 gene with prostate cancer is still indeterminate; thus, we performed a meta-analysis of 12 case-control studies, including 5017 cases and 4986 controls, to evaluate the associations between P275A polymorphism and PCa risk. Considering the genetic background and study design may affect the results of meta-analysis, subgroup analyses were performed by ethnicity and study design.

By analyzing our results, no noteworthy associations between P275A polymorphism of MSR1 gene and PCa risk were detected in the dominant (GG+GC *vs* CC) genetic model. In addition, in the other genetic models, the statistic data also showed that this polymorphism was not significantly associated with prostate cancer. These results demonstrated that P275A polymorphism may not have obviously elevated or lowered risk for prostate cancer in overall population. Considering the different property of genetic background might contribute to the possible presence of heterogeneity between the studies and affect the results of genetic association studies, we further performed subgroup analyses by ethnicity and study design. In the stratified analysis by ethnicity, we found that the variant G allele carriers (GG+GC) had not influenced the risk of prostate cancer in the white race, the yellow race, the black race or the mixed group. There may be many factors influencing the result, such as differences in populations, selection factors and so on. Thus, further studies are demanded to validate our findings. However, according to one case-control study made by Xu et al., the carriers of the G allele had almost a 45% decreased risk of PCa in the white race, suggesting that P275A polymorphism might play a role in the pathogenesis of PCa (Xu et al., 2003). Possible explanation to this different result may be that the sample size of cases and controls in this study is relatively small, and controls may not always be truly representative for the general population, leading to the underpowered result. Therefore, a methodologically preferable design such as a representative population-based study is needed to avoid selection bias and to increase the statistical power. In addition, subgroup analysis was also performed by study design, no significant association between P275A polymorphism and PCa risk was found among HCC and PCC subjects under all genetic models. Considering the limited studies of the yellow race and the black race included in our meta-analysis, this may increase the risk of false negative findings, any conclusions at overall population level should be interpreted with great caution.

Heterogeneity is a potential problem when interpreting the results of the present meta-analysis. In overall analysis, we found that moderate heterogeneity between studies existed in dominant model, heterogeneous co-dominant model, over-dominant model and allelic model comparisons. After subgroup analyses by ethnicity and study design, the heterogeneity was effectively removed under dominant model among the black race and PCC group, or decreased under over-dominant, heterogeneous co-dominant and allelic model in PCC group, whereas increased heterogeneity were observed under all genetic models in the white race and HCC group. The possible explanations for the heterogeneity may be considerable genetic heterogeneity between the samples that were drawn from geographically diverse populations. Another important factor contributing to heterogeneity was that homogeneity in either the case or control groups was uncertain. In addition, we attempted to determine if the

heterogeneity might also be explained by other variables such as stages of PCa, smoking status, and environmental factors included in the different studies, but are unable to provide a reliable answer to this question because of insufficient information for these variables.

We have to mention a previously published study by Sun et al (Sun et al., 2006). They also investigated the association between P275A polymorphism and PCa risk. There were some differences between these two studies. Firstly, the current meta-analysis included more case-control studies compared with Sun's study. And then, some issues that might influence the results of meta-analysis were assessed in our study, such as HWE analysis, sensitivity analysis and publication bias. In addition, the current study was a meta-analysis only focused on P275A polymorphism, while Sun's study was more devoted with the other polymorphisms. Despite of these differences, we also found no significant sign of associations between P275A polymorphism and PCa risk, which is consistent with Sun's study, strongly suggesting that this polymorphism might not contribute to PCa pathogenesis.

Some limitations of this meta-analysis should be acknowledged when explaining our results. Firstly, the overall outcomes were based on individual unadjusted ORs, while a more precise estimation should be conducted adjusted by confounding factors such as smoking status, age, and environmental factors. Secondly, the results should be cautiously interpreted because controls were not uniformly defined. Thirdly, in our meta-analysis, as only certain published studies written in English were included, which indicates that some potential published studies in other languages or unpublished studies could be missed, publication bias is very likely to occur although it was not shown in the statistical test. And the last, the sample sizes in this analysis were not adequate, especially the yellow race populations; therefore, more subjects of different ethnicities would be required to accurately clarify whether ethnicity has a biological influence on cancer susceptibility.

In conclusion, our meta-analysis suggests that the P275A polymorphism in the MSR1 gene is unlikely to be a risk factor for prostate cancer. Due to limitations showed above in this analysis, it is critical that more large-scale and well-designed multicenter studies are needed to clarify the role of P275A polymorphism in prostate cancer.

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