Association between the 8q24 rs6983267 T/G polymorphism and prostate cancer risk: a meta-analysis

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ABSTRACT. Recent studies have indicated that single nucleotide polymorphisms (SNPs) within the 8q24 region may be a risk factor for prostate cancer (PCa). Here, we performed a meta-analysis to evaluate the association between the 8q24 rs6983267 T/G polymorphism and PCa risk. A systematic literature search was carried out in multiple electronic databases independently by two investigators. Pooled odds ratios (ORs) and 95% confidence intervals for 8q24 rs6983267 T/G and PCa were calculated using a fixed-effect model (the Mantel-Haenszel method). In total, 24 case-control studies from 19 articles were included in our meta-analysis. Our analysis indicated that there is a significant PCa risk associated with the rs6983267 polymorphism in a dominant model (GG *vs* GT+TT, pooled OR = 1.298, P < 0.001); recessive model (GG+GT *vs* TT, pooled OR = 1.302, P < 0.001); and homozygote comparison (GG *vs* TT, pooled OR = 1.494, P < 0.001). Similarly, in a subgroup analysis of European and Asian descent, our results revealed that there are associations between

rs6983267 T/G polymorphism and PCa susceptibility with the dominant model (GG *vs* GT+TT), recessive model (GG+GT *vs* TT), and homozygote comparison (GG *vs* TT). To investigate the association between rs6983267 and risk of PCa under different clinical conditions, further analyses were conducted regarding different clinical characteristics including the Gleason score, tumor stage, and PSA level to provide a more comprehensive view of PCa risk and this SNP. Publication bias was assed using the Begg test and the Egger test, and none was detected.

Key words: Prostate cancer; Meta-analysis; Polymorphism

INTRODUCTION

Prostate cancer (PCa) is the most common cancer and third leading cause of cancer-related deaths among males in developed countries (Crawford, 2003). Approximately 233,000 new cases were expected to be diagnosed with 29,480 estimated deaths in the USA in 2014 (Siegel et al., 2014). Despite this, the underlying etiology of PCa is poorly understood. The most recognized factors associated with PCa risk include age, ethnicity, cigarette smoking, and alcohol consumption. Additionally, it has been suggested that several genetic polymorphisms could influence susceptibility to PCa (Wang et al., 2010; Shao et al., 2012).

Identifying genetic variants that increase the risk of disease development and progression is important for improving screening regimens, diagnosis, and treatment of PCa (Cheng et al., 2008). A region on chromosome 8q24 was first shown to confer PCa risk in a genome-wide linkage scan of 871 Icelandic men (Amundadottir et al., 2006). Subsequently, multiple independent studies have provided compelling evidence that has demonstrated that the risk of PCa is influenced by genetic variations in the 8q24 region (Haiman et al., 2007; Cheng et al., 2008). One promoter polymorphism rs6983267 T/G in the 8q24 region has been reported in genome-wide association studies (GWAS) to be significantly associated with PCa risk (Yeager et al., 2007; Zheng et al., 2007). While there have been numerous studies that have investigated associations between this polymorphism and the risk of PCa, the results have been inconsistent and inconclusive.

For these reasons, we performed a meta-analysis to offer a more comprehensive estimation of the association between rs6983267 and PCa susceptibility in two groups: Asian descent and European descent. Other than using the odds ratio (OR) derived from a corresponding pooling model, we evaluated the association between rs6983267 and PCa risk for cases with different clinical characteristics including the Gleason score, tumor stage, and prostate specific antigen (PSA) level.

MATERIAL AND METHODS

Literature search and data extraction

We searched for related articles in six databases including PubMed, ScienceDirect, Karger, Web of Science, Wiley Online Library, and Springer. To avoid omitting related literature, "8q24" or "rs6983267" and "prostate cancer" were set as key words. The search coverage included those articles published in English from 2006 to 2014. Books and other literature not related to case-control studies or not aimed at prostate cancer research were excluded. Then, full texts of the

remaining articles were carefully examined and articles that did not contain quantified information on the genotypes of rs6983267 were removed. Finally, we checked for studies with overlapping study populations, and in those cases, we chose the more appropriate studies, which were restricted to studies with subjects of Asian and European descent.

All data were extracted independently by two reviewers (H.S. Zhu and J.F. Zhang). Preliminary evaluation was conducted based on the title and abstract, and full texts of potentially relevant studies were obtained and re-evaluated for inclusion. The following characteristics were collected from each study: year of publication, first author, race or ethnicity of samples, exact quantity of each genotype for cases and controls, Hardy-Weinberg equilibrium (HWE), P value, and genotyping method. In addition, clinical characteristic of cases such as Gleason score, tumor stage, and PSA level were collected, especially for studies with detailed genotype information. This article does not contain any studies with human participants performed by any of the authors

Statistical analysis

The statistical analyses were conducted with STATA 12 (Stata Corp LP, College Station, TX, United States). For all analyses, P values less than 0.05 were considered statistically significant. HWE in cases or controls was evaluated by the chi-square test, and P values over 0.05 were considered as significant equilibriums. HWE was also taken as a data-extraction factor and those studies with HWE P values over 0.05 were chosen for further analysis.

For more thorough analyses, three genetic models of inheritance were adopted: a dominant model (GG+GT *vs* TT), recessive model (GG *vs* GT+TT), and homozygote model (GG *vs* TT). In the dominant model, we investigated the distribution of genotypes GG and GT compared to genotype TT; as for the recessive model, the distribution of genotype GG compared to genotypes GT and TT was analyzed; in the homozygote model, we used TT as reference genotype and investigated the distribution of GG.

For each study, the quantities of the three genotypes in cases and controls were used as pooled data. As for the pooling analyses, a Mantel-Haenszel (M-H) fixed-effect model was applied to analyze datasets with insignificant heterogeneity and a DerSimonian and Laird (D-L) random-effects model was used for datasets with clear heterogeneity. In our analyses, the heterogeneity among studies was evaluated using the I^2 index. The higher the I^2 statistic, the more significant the heterogeneity was considered. Specifically, when I^2 was less than 50%, we considered there to be no significant heterogeneity among the pooled data, and then the M-H model was applied; for I^2 greater than 75%, heterogeneity was considered to exist and the D-L model was adopted; otherwise, both models were applied. For each analysis, the M-H model was used first to test for heterogeneity, and then an adequate model was chosen based on the test result of I^2 statistic. The pooled odds ratio (OR) and 95% confidence interval were calculated with the corresponding model, and the associated forest plots were generated to summarize the results.

As for the expanded evaluation, factors including the Gleason score, tumor stage, and PSA level were chosen, and their corresponding genotypes were collected, and risk allelic ORs comparing cases with controls were calculated to see whether there were differences between the groups with regards to the distinct clinical characteristics.

To evaluate publication bias, Begg funnel plots were generated on the basis of the analysis result and database size. The more asymmetric the funnel plot appeared, the more publication bias was potentially present. Meanwhile, Egger test was also performed for further bias investigation. For the Egger test, the significance level was set as P < 0.05.

RESULTS

Characteristics of the studies included

In total, 187 papers were retrieved after the first search, among which 78 articles contained case-control studies targeting prostate cancer. After further evaluation, we found only 24 case-control studies from 19 articles that were suitable for our meta-analysis of rs6983267 (Haiman et al., 2007; Yeager et al., 2007; Zheng et al., 2007; Cheng et al., 2008; Salinas et al., 2008; Terada et al., 2008; Wokolorczyk et al., 2008; Beuten et al., 2009; Liu et al., 2009; Penney et al., 2009; Zheng et al., 2009; Liu et al., 2011; Papanikolopoulou et al., 2011; Joung et al., 2012; Brankovic et al., 2013; Ho et al., 2013; Chan et al., 2013; Zhao et al., 2013; Oskina et al., 2014). Among these, 16 studies included populations of European descent and 8 included populations of Asian descent. The flow chart of study inclusion and reasons for exclusion are presented in Figure 1. Characteristics of the studies included in the meta-analysis are presented in Table 1. All data in these studies were related to the association between 8q24 rs6983267 T/G polymorphism and human PCa susceptibility.
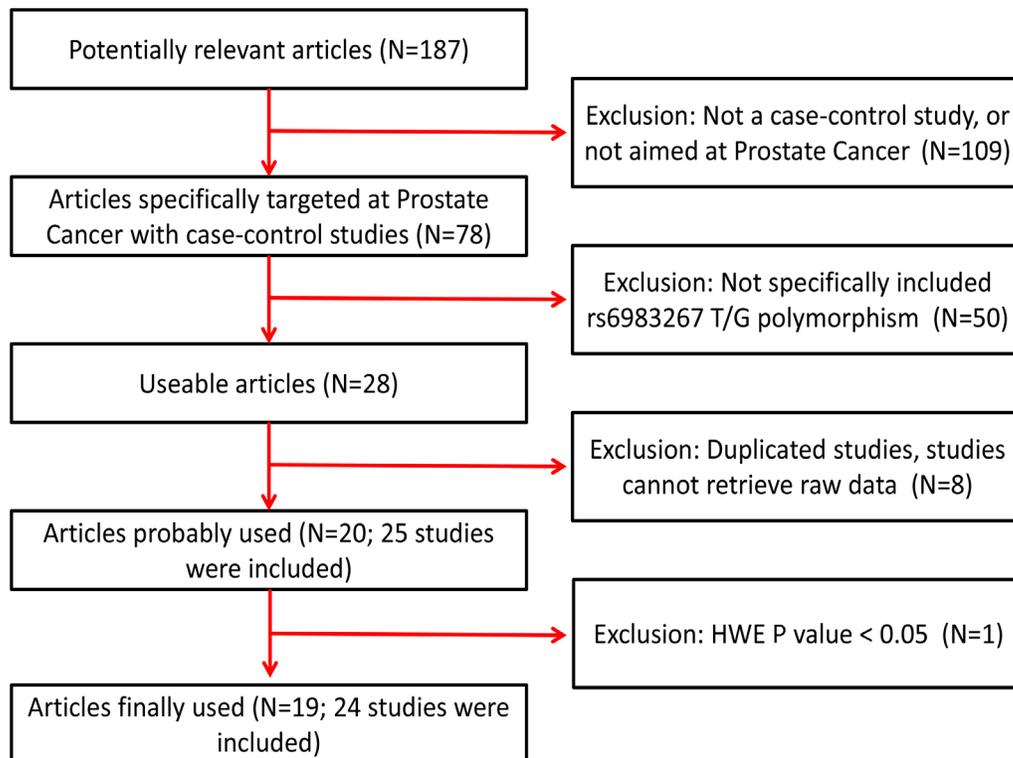
Figure 1. Flow chart of screened, excluded, and included studies with specific reasons for exclusion from the meta-analysis.

Table 1. Characteristics of the studies related to rs6983267 and prostate cancer included in the meta-analysis.

Literature	Race/Ethnic group	Case			Control			HWE P value		Genotyping method
		TT	TG	GG	TT	TG	GG	Case	Control	
2014, Oskina (Oskina et al., 2014)	Russian	89	186	114	77	177	87	0.433	0.471	Real-time PCR
2013, Brankovic (Brankovic et al., 2013)	Caucasian	17	80	53	26	49	25	0.106	0.842	PCR-RFLP
2012, Papanikolopoulou (Papanikolopoulou et al., 2011)	Caucasian	16	46	24	39	47	13	0.463	0.844	Real-time PCR
2012, Ho (Ho et al., 2013)	Caucasian	70	104	42	66	136	46	0.762	0.102	Real-time PCR
2009, Penney (Penney et al., 2009)	Caucasian,PHS	261	644	400	323	707	372	0.951	0.714	Mass Spectrometry
2009, Beuten (Beuten et al., 2009)	Caucasian	107	297	193	218	423	197	0.695	0.768	The Gold Gate Assay
2008, Wokolorczyk (Wokolorczyk et al., 2008)	Caucasian	385	942	558	234	462	195	0.730	0.244	PCR-RFLP
2008, Salinas (Salinas et al., 2008)	Caucasian American	242	652	364	308	617	313	0.100	0.910	ABI 3730xl DNA Analyzer
2008, Cheng (Cheng et al., 2008)	European American	76	215	126	106	206	105	0.345	0.807	TaqMan Assay
2007, Zheng (Zheng et al., 2007)	European American	285	771	495	132	299	142	0.615	0.293	PCR
2007, Yeager(a) (Yeager et al., 2007)	European American, PLCO	223	598	351	301	579	277	0.262	0.965	NA
2007, Yeager(b) (Yeager et al., 2007)	European American, ACS	228	568	354	286	568	297	0.995	0.661	NA
2007, Yeager(c) (Yeager et al., 2007)	European, ATBC	173	428	293	222	436	238	0.456	0.428	NA
2007, Yeager(d) (Yeager et al., 2007)	European, FPCC	89	218	148	108	231	120	0.588	0.877	NA
2007, Yeager(e) (Yeager et al., 2007)	European American, HPFS	125	292	208	155	316	165	0.222	0.879	NA
2007, Haiman(a) (Haiman et al., 2007)	European American	207	543	297	208	417	232	0.146	0.445	Illumina BeadStudio, Sequenom MassArray, hME or ABI TaqMan
2013, Zhao (Zhao et al., 2013)	Chinese	77	149	56	94	137	51	0.293	0.930	PCR
2013, Chan (Chan et al., 2013)	Singaporean Chinese	89	136	63	47	74	23	0.417	0.493	Illumina human 1M BeadChip and Affymetrix Genome Wide Human SNP Array or PCR
2012, Joung (Joung et al., 2012)	Korean	56	92	46	51	86	31	0.495	0.618	MassArray
2011, Liu (Liu et al., 2011)	Han Chinese	231	405	156	426	647	252	0.368	0.820	MassArray
2010, Zheng (Zheng et al., 2009)	Han Chinese	86	134	62	51	72	29	0.473	0.690	MassArray
2009, Liu (Liu et al., 2009)	Native Japanese	199	234	70	147	151	25	0.927	0.104	TaqMan Assay
2008, Terada (Terada et al., 2008)	Native Japanese	211	219	77	165	169	53	0.109	0.357	PCR-RFLP
2007, Haiman(b) (Haiman et al., 2007)	Japanese American	290	310	108	335	300	83	0.097	0.208	Illumina BeadStudio, Sequenom MassArray, hME or ABI TaqMan

Evaluation of the association between the rs6983267 polymorphism and prostate cancer

There were 24 case-control studies included in our meta-analyses for the association between polymorphism rs6983267 and PCa. For the included studies, low heterogeneity was observed under all three models (for the dominant model, I^2 = 30.2%, P = 0.082; for the recessive model, I^2 = 2.7%, P = 0.424; and for the homozygote model, I^2 = 31.2%, P = 0.074). Based on these results, the M-H model was applied using the three different genetic models (recessive, dominant, and homozygote). Detailed results of the meta-analysis are shown in Table 2. Overall, when all eligible studies were pooled into the meta-analyses, we found that a significant PCa risk was associated with the rs6983267 polymorphism in the dominant model (GG *vs* GT+TT, pooled OR = 1.298, 95%CI = 1.232-1.368, P < 0.001); recessive model (GG+GT *vs* TT, pooled OR = 1.302, 95%CI = 1.236-1.372, P < 0.001); and homozygote model (GG *vs* TT, pooled OR = 1.494, 95%CI = 1.400-1.595, P < 0.001). The forest plots of the three models are shown in Figure 2.

Table 2. Meta-analysis of rs6983267 with the dominant model (GG+GT *vs* TT), recessive model (GG *vs* GT+TT), and homozygote model (GG *vs* TT) for the entire database, populations with European descent, and populations with Asian descent.

Analysis model	Pooling model	Heterogeneity		OR (95%CI)				Publication bias	
		I^2 (%)	P value	Overall	Lower	Upper	P value	Begg test (P value)	Egger test (P value)
For entire database									
Dominant	M-H	30.2	0.082	1.298	1.232	1.368	<0.001	0.47	0.854
Recessive	M-H	2.7	0.424	1.302	1.236	1.372	<0.001	1.17	0.255
Homozygote	M-H	31.2	0.074	1.494	1.400	1.595	<0.001	0.37	0.498
For populations with European descent									
Dominant	M-H	41.8	0.040	1.346	1.266	1.432	<0.001	0.05	0.469
Recessive	M-H	4.0	0.407	1.317	1.244	1.395	<0.001	1.13	0.229
Homozygote	M-H	38.8	0.057	1.541	1.432	1.658	<0.001	0.86	0.289
For populations with Asian descent									
Dominant	M-H	0	0.940	1.179	1.067	1.303	0.001	0.87	0.680
Recessive	M-H	0	0.431	1.228	1.080	1.397	0.002	1.36	0.094
Homozygote	M-H	0	0.594	1.328	1.149	1.533	<0.001	1.11	0.267

Similarly, we performed subgroup analyses as shown in Table 2. For the subgroup analyses, the M-H fixed-effect model was first applied on each subgroup dataset using the three genetic models (recessive, dominant, and homozygote) to test the heterogeneity. For the 16 studies with populations of European descent, the M-H model was applied for all three genetic models, which revealed low heterogeneity (for the dominant model, I^2 = 41.8%, P = 0.040; for the recessive model, I^2 = 4.0%, P = 0.407; and for the homozygote model, I^2 = 38.8%, P = 0.057). As shown in Table 2, significant PCa risks associated with the rs6983267 polymorphism were found using the recessive model (GG+GT *vs* TT, pooled OR = 1.317, 95%CI = 1.244-1.395, P < 0.001); the dominant model (GG *vs* GT+TT, pooled OR = 1.346, 95%CI = 1.266-1.432, P < 0.001); and the homozygote model (GG *vs* TT, pooled OR = 1.541, 95%CI = 1.432-1.658, P < 0.001). The corresponding forest plots for the three genetic models are shown in Figure 3. For the 8 studies with populations of Asian descent, the M-H model was also applied for all three genetic models and low heterogeneity was found (for the dominant model, I^2 = 0, P = 0.940; for the recessive model, I^2 = 0, P = 0.431; and for the homozygote model, I^2 = 0, P = 0.594). Additionally, significant PCa risks associated with the rs6983267 polymorphism were observed in the Asian group using the dominant model (GG *vs*

GT+TT, pooled OR = 1.179, 95%CI = 1.067-1.303; P = 0.001), recessive model (GG+GT *vs* TT, pooled OR = 1.228, 95%CI = 1.080-1.397, P = 0.002), and homozygote model (GG *vs* TT, pooled OR = 1.328, 95%CI = 1.149-1.533, P < 0.001). The corresponding forest plots for the three genetic models are shown in Figure 4.
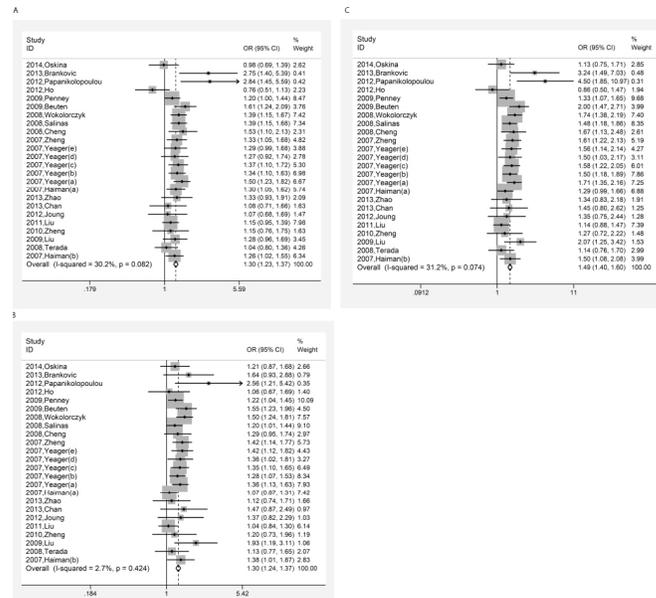

Figure 2. Forest plots of the studies included for the total populations using **A.** dominant model, **B.** recessive model, and **C.** homozygote comparison.
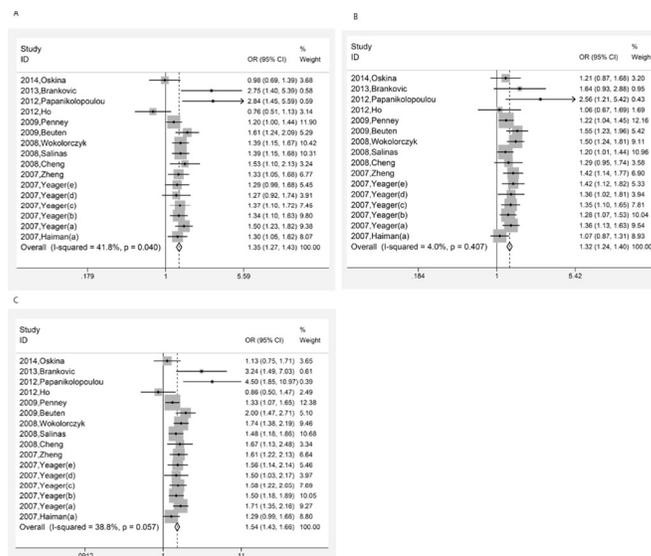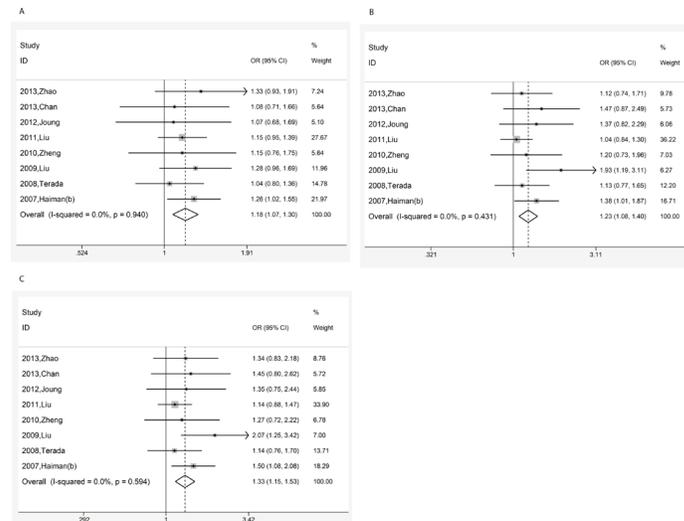

Figure 3. Forest plots of studies with populations of European descent for **A.** dominant model, **B.** recessive model, and **C.** homozygote comparison.

Figure 4. Forest plots of studies with populations of Asian descent for **A.** dominant model, **B.** recessive model, and **C.** homozygote comparison.

Expanded evaluation with different clinical characteristics

In addition to the overall and subgroup analyses, we evaluated the risk of rs6983267 with different clinical characteristics including the Gleason score, tumor stage, and PSA level, and the detailed results are shown in Table 3. As for cases with Gleason scores less than or equal to 7, the risk allelic OR was 1.195 (95%CI = 1.082-1.318, P < 0.001), and for cases with Gleason scores greater than 7, the risk allelic OR was 1.164 (95%CI = 1.023-1.323, P = 0.021). As for cases with tumor stages between 1 and 2, the risk allelic OR was 1.261 (95%CI = 1.082-1.471, P = 0.003), and for cases with tumor stages between 3 and 4, the risk allelic OR was 1.275 (95%CI = 1.031-1.577, P = 0.025). As for cases with PSA levels less than or equal to 10 ng/mL, the risk allelic OR was 1.236 (95%CI = 1.041-1.468; P = 0.015), and for cases with PSA levels greater than 10 ng/mL, the risk allelic OR was 1.214 (95%CI = 1.031-1.430, P = 0.020). The corresponding forest plots are shown as Figure 5.

Publication bias

To test for publication bias, both Begg and Egger tests were performed for the entire database. Results of the publication bias analysis are shown in Table 2, and no publication bias was observed under any of the three genetic models (all P values for the Begg test and Egger test were greater than 0.05). Additionally, after samples were stratified by ethnicity, no publication bias was observed under any model (all P values of Begg test and Egger test were greater than 0.05). Funnel plots for entire database and two subgroups are separately summarized in Figure 6 and 7. Similar evaluations were also conducted in analyses of the clinical characteristics, and no publication bias was observed except for the group of Gleason score ≤7 (Egger test P = 0.005). The corresponding funnel plots are shown as Figure 8.

**Table 3.** Meta-analysis for rs6983267 with different clinical characteristics.

| Study	Control				Publication Bias		Case				Publication Bias	
	T	G	I² P value	Allelic OR* (95%CI) P value	Begg test (P value)	Egger test (P value)	T	G	I² P value	Allelic OR* (95%CI) P value	Begg test (P value)	Egger test (P value)
				Gleason score ≤7						Gleason score >7		
2008, Terada (Terada et al., 2008)	499	275	65.3%	1.195	1.71	0.005	246	122	35.4%	1.164	0.24	0.890
2012, Papanikolopoulou (Papanikolopoulou et al., 2011)	125	73	0.021	(1.082-1.318)			9	9	0.186	(1.023-1.323)		
2013, Brankovic (Brankovic et al., 2013)	101	99		<0.001			22	22		0.021		
2007, Haiman(a) (Haiman et al., 2007)	833	881					265	369				
2007, Haiman(b) (Haiman et al., 2007)	970	466					159	89				
				Tumor stage 1-2						Tumor stage 3-4		
2008, Terada (Terada et al., 2008)	499	275	63.7%	1.261	1.70	0.075	108	56	52.8%	1.275	1.70	0.127
2012, Papanikolopoulou (Papanikolopoulou et al., 2011)	125	73	0.041	(1.082-1.471)			20	24	0.096	(1.031-1.577)		
2013, Brankovic (Brankovic et al., 2013)	77	123		0.003			37	63		0.025		
2013, Chan (Chan et al., 2013)	201	163					98	90				
				PSA level ≤10 ng/mL						PSA level >10 ng/mL		
2008, Terada (Terada et al., 2008)	499	275	48.9%	1.236	0.34	0.327	363	197	72.1%	1.214	1.02	0.068
2012, Papanikolopoulou (Papanikolopoulou et al., 2011)	125	73	0.118	(1.041-1.468)			24	30	0.013	(1.031-1.430)		
2013, Brankovic (Brankovic et al., 2013)	101	99		0.015			72	130		0.020		
2013, Chan (Chan et al., 2013)	168	120					141	121				

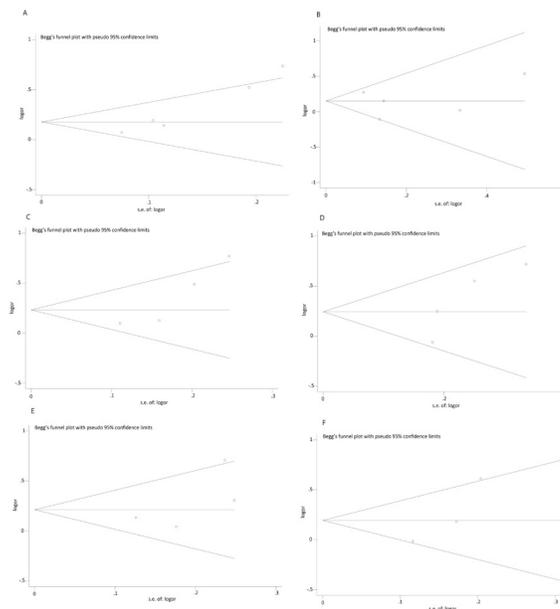*Represents allelic OR comparing cases to controls.
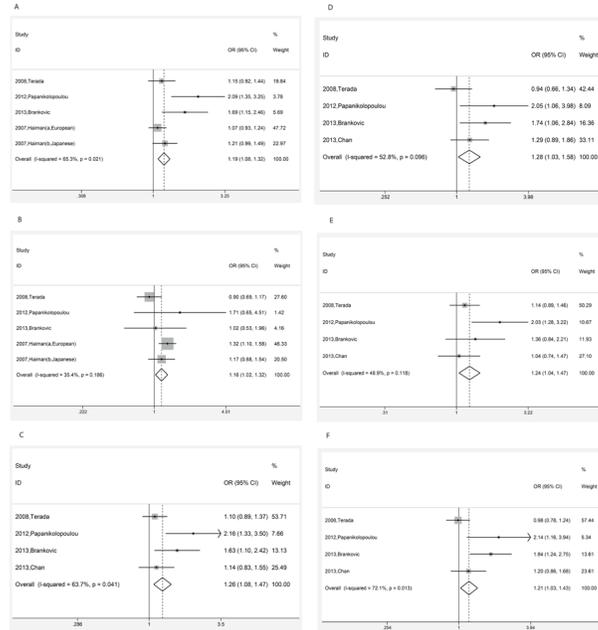
Figure 5. Forest plots of studies with different clinical characteristics for **A.** cases with Gleason scores ≤7, **B.** cases with Gleason scores >7, **C.** cases with tumor stage 1 to 2, **D.** cases with tumor stage 3 to 4, **E.** cases with PSA levels ≤10 ng/mL, and **F.** cases with PSA levels >10 ng/mL.
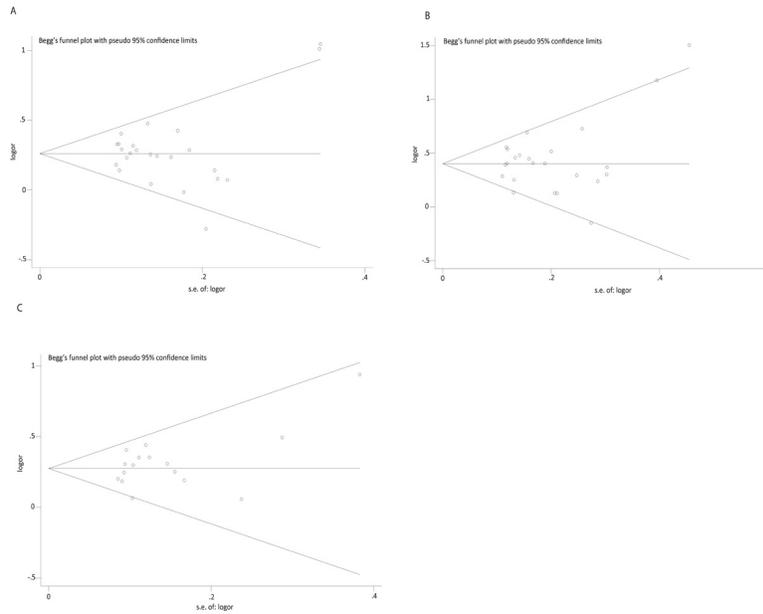
Figure 6. Funnel plots of studies with overall populations for **A.** dominant model, **B.** recessive model, and **C.** homozygote comparison.
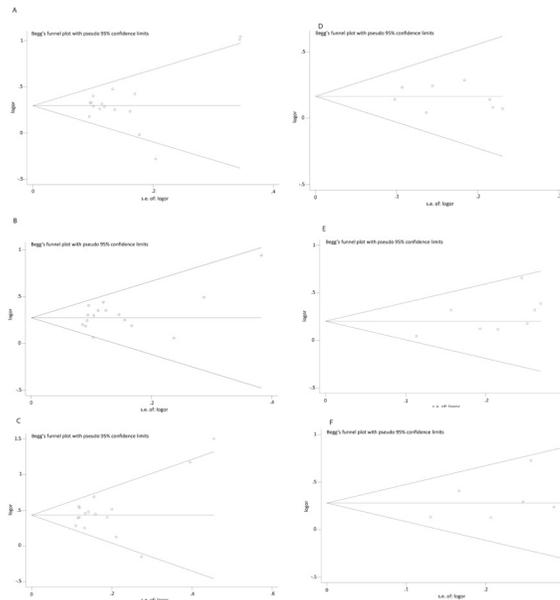
Figure 7. Funnel plots of studies with populations of European and Asian descent for **A.** dominant model for European populations, **B.** recessive model for European populations, **C.** homozygote comparison for European populations, **D.** dominant model for Asian populations, **E.** recessive model for Asian populations, and **F.** homozygote comparison for Asian populations.

Figure 8. Funnel plots of studies with different clinical characteristics samples for **A.** cases with Gleason scores ≤7, **B.** cases with Gleason scores >7, **C.** cases with tumor stage 1 to 2, **D.** cases with tumor stage 3 to 4, **E.** cases with PSA levels ≤10 ng/mL, and **F.** cases with PSA levels >10 ng/mL.

DISCUSSION

In the current study, we analyzed the association between polymorphism rs6983267 and the risk of PCa for individuals of European and Asian descent. Although previous meta-analyses have investigated the association between rs6983267 and PCa, we performed a more detailed analysis with a larger data pool that included the most up-to-date research. Our results revealed that polymorphism rs6983267 was associated with the risk of PCa development for individuals of both European and Asian descent.

Although a prior meta-analysis investigated rs6983267 in PCa, the study only included case and control numbers as the dataset without the specific rs6983267 genotypes. Moreover, the previous meta-analysis for rs6983267 was completed in 2012, and the data herein includes those from European and Asian populations collected from 2006 to 2014. Therefore, compared to the previous meta-analysis, two new studies for the European group and three new studies for the Asian group have been included in addition to the specific genotype data. Furthermore, the previous meta-analysis only showed that there was a higher frequency of the rs6983267 polymorphism in PCa cases than in controls in European populations, whereas no significant differences were detected in Asian populations. However, in the current study, PCa cases in both the European and Asian groups had a significant increase in the frequency of genotype GG+GT, genotype GG, and allele G.

In the present study, the I^2 statistics were calculated to test for heterogeneity. For all included studies, low heterogeneity existed under the dominant, recessive, and homozygote models. However, the heterogeneity decreased when the samples were stratified according to ethnicity. For the European studies, low heterogeneity was observed under the dominant, recessive, and homozygote models, while no statistically significant heterogeneity was observed under any model in the Asian studies. Our analysis indicated that ethnicity may play an important role in genetic heterogeneity of rs6983267. Publication bias is another important factor that can affect the quality of meta-analyses. We found no significant publication bias for any model as determined by funnel plot analysis and Egger test (all P-values of Egger test were <0.05) (Table 2 and Figure 6 and 7).

There were several limitations of this study. First, of the 24 studies included for analysis, 8 included populations of Asian descent, but accounted for only 6.52% of the total study population. Second, because the study populations were from 10 countries and the controls were not uniform, the results should be interpreted cautiously. Third, the genetic heterogeneity among different populations emphasizes the need to interpret the results with caution.

The current meta-analysis suggests that rs6983267 T/G is associated with susceptibility to PCa in individuals of both European and Asian descent, and more specifically, the genotype GG+GT, genotype GG, and allele G may significantly increase the risk of PCa in those two groups. Because of the small size of the database, larger and well-designed studies based on different subgroups are needed to confirm our results, especially for Asian populations.

Conflicts of interest

The authors declare no conflict of interest.

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