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Research Paper

Association between 8q24 Gene Polymorphisms and the Risk of Prostate Cancer: A Systematic Review and Meta-Analysis

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Abstract

Though numerous studies have been conducted to investigate the associations between five 8q24 polymorphisms (rs6983267 T>G, rs1447295 C>A, rs16901979 C>A, rs6983561 A>C and rs10090154 C>T) and prostate cancer (PCa) risk, the available results remained contradictory. Therefore, we performed a comprehensive meta-analysis to derive a precise estimation of such associations. We searched electronic databases PubMed, EMBASE, Web of Science and Wan Fang for the relevant available studies up to February 1st, 2017, and 39 articles were ultimately adopted in this meta-analysis. All data were extracted independently by two investigators and recorded in a unified form. The strength of association between 8q24 polymorphisms and PCa susceptibility was evaluated by the pooled odds ratios (ORs) with 95% confidence intervals (CIs). Subgroup analysis was conducted based on ethnicity, source of controls and genotypic method. Overall, a total of 39 articles containing 80 studies were adopted in this meta-analysis. The results of this meta-analysis indicated that five 8q24 polymorphisms above were all related to PCa susceptibility. Besides, in the subgroup analysis by ethnicity, all selected 8q24 polymorphisms were significantly associated with PCa risk in Asian population. In addition, stratification analysis by source of controls showed that significant results were mostly concentrated in the studies' controls from general population. Moreover, when stratified by genotypic method, significant increased PCa risks were found by TaqMan method. Therefore, this meta-analysis demonstrated that 8q24 polymorphisms (rs6983267 T>G, rs1447295 C>A, rs16901979 C>A, rs6983561 A>C and rs10090154 C>T) were associated with the susceptibility to PCa, which held the potential biomarkers for PCa risk.

Key words: 8q24, Polymorphisms, Prostate cancer, Meta-analysis.

Introduction

Prostate cancer (PCa) is one of the most common non-cutaneous malignancies among men in developed country, with an estimated 161,360 new cases and 26,730 deaths in the United States in 2017 [1]. Many influencing factors have been proved to be associated with the risk of PCa, including advancing age, ethnicity, smoking and alcohol consumption, endocrine system, and genetic factors. However, the underlying etiology of PCa is still confusing [2]. Recently, genetic predisposition of PCa have gradually attracted investigators' attention. Especially, it suggested that common genetic

polymorphisms such as single nucleotide polymorphic variants (SNPs) might be associated with sporadic cases of PCa [3]. In addition, several studies have identified the 8q24 polymorphisms increased the risk of PCa [4-6]. Therefore, we plan to study the etiology of PCa from the aspect of genetic predisposition.

Chromosomal region 8q24 has been proved to be associated with a wide spectrum of cancers, including cancers of the breast, prostate, bladder, colon, lung, ovaries and pancreas among different ethnicities [7-13]. A region on chromosome 8q24 was originally shown to confer PCa risk in a genome-wide linkage scan of 871 Icelandic men in 2006 [14]. In addition, 8q24 was considered as a gene-free region, flanked by the FAM84B and MYC genes on the centromeric and telomeric ends respectively [15]. Physical nearness might indicate the association between 8q24 and MYC proto-oncogene. As a highly conserved genomic region, three 8q24 regions (region 1: 128.54–128.62 Mb; region 2: 128.12–128.28 Mb; region 3: 128.47–128.54 Mb) have been identified to contain variants independently associated with PCa susceptibility [16]. Subsequently, multiple independent studies have been performed to extensively explore the roles of 8q24 SNPs in the risk of PCa. Thus, it was hypothesized that the genetic variations in the 8q24 region were likely to take effect in prostate carcinogenesis.

Genome-wide association studies (GWAS) have identified more than 100 common SNPs that were associated with the susceptibility of PCa. A large number of studies have explored the associations between these polymorphisms and the risk of PCa [17]. In previous studies, five 8q24 polymorphisms (rs6983267 T>G, rs1447295 C>A, rs16901979 C>A, rs6983561 A>C and rs10090154 C>T) among these SNPs might have strong associations with PCa susceptibility. Nevertheless, the results of these studies were inconsistent and inconclusive [4,18-20]. Hence, we conducted an updated meta-analysis including all eligible case-control studies to investigate the association between 8q24 gene polymorphisms and the risk of PCa.

Materials and Methods

We searched PubMed, EMBASE, Web of Science and Wan Fang databases comprehensively to obtain relevant studies published up to February 1st, 2017. The following searching keywords were utilized: “8q24”, “polymorphisms” or “mutations” or “variants”, and “prostate cancer” or “prostatic neoplasms”. Potential eligible articles were manually collected by searching from the reference lists of relevant literature and reviews. In addition, overlapping data from different articles were removed.

Then, all eligible articles were collected according the following inclusive criteria: (1) Independent case-control or cohort studies; (2) Possessing at least one of 8q24 polymorphisms (rs6983267 T>G, rs1447295 C>A, rs16901979 C>A, rs6983561 A>C and rs10090154 C>T); (3) Availability of genotype data of both cases and controls; (4) Enrolled patients with PCa confirmed by histopathological examination, and controls with no history of neoplasms. Meanwhile, the exclusive criteria were as follows: (1) No case-control study; (2) Duplicate or unavailable data; (3) Studies not related to 8q24 or prostate cancer.

Data extraction

All available data from the eligible studies identified were extracted independently by two investigators (Li R and Qin ZQ). If any disagreement appeared, a third investigator (Tang JY) would join in and make a better decision. All the extracted data were recorded in a unified form and the following items were collected: first author’ name, publication year, ethnicity, source of controls, genotypic method, the number of cases and controls, the number of 8q24 polymorphisms carriers and non-carriers respectively and the results of the Hardy-Weinberg equilibrium (HWE) test.

Statistical analysis

The Pearson’s goodness-of-fit chi-square test was adopted to access HWE in the control groups. Besides, *P* value was more than 0.05, which was regarded as significant equilibrium. The strength of associations between 8q24 polymorphisms and susceptibility to PCa were evaluated by the pooled odds ratios (ORs) with 95% confidence intervals (CIs) using five genetic comparison models: allele model, homozygous model, heterozygous model, dominant model and recessive model. Fixed effect model (a Mantel-Haenszel method) and random effect model (a DerSimonian-Laird method), as two common statistical models, were selected according to Cochrane Q test and Higgins I^2 statistic. If the heterogeneity is acceptable (I^2 < 50% suggested no obvious heterogeneity), the fixed effect model will be adopted; Otherwise, the random effect model will be performed to calculate the pooled ORs. Besides, the random effect model is a kind of method for disposing heterogeneous data, but it cannot replace the reason analysis of the source of heterogeneity. Normally, several reasons might induce the heterogeneity, including design scheme, measuring method, age, ethnicity and so on. In addition, subgroup analysis

according to ethnicity, source of controls and genotypic method was further used to explore the source of heterogeneity. To examine the stability and reliability of the results in this meta-analysis, sensitive analysis was adopted to recalculate the pooled ORs following the sequential exclusion of a single study at a time. Moreover, Begg's funnel plots and Egger's linear regression test were used to check out the publication bias between all included studies, and *P* values were considered as a significantly selective bias when less than 0.05. STATA 12.0 software (State Corporation, College Station, TX, USA) was utilized to dispose all above statistical analyses.

Results

Studies characteristics

Based on the retrieve strategy above, a total of related 182 articles were initially collected by a primary search of databases and reference lists. According to the inclusive criteria, 39 articles consisting of 80 studies were ultimately adopted in the present meta-analysis for a further evaluation, which had been accrued between March 2007 and January 2015 [4-6, 18-53]. The details of the literature search and screening process were shown in **Figure 1**. Among the eligible 80 studies, the distribution of genotypes in the controls was consistent with HWE, except three studies. In this meta-analysis, all of the baseline characteristics of the studies associated with the risk of PCa were listed in **Table 1**. These studies were conducted in Caucasians, Asians, Africans and Mixed. Furthermore, in order to distinguish between different sources of control group, investigators divided them into population-based group or hospital-based group in all studies. Besides, six genotypic methods were applied in these studies, such as Taqman, PCR-RFLP, iPLEX and so on.

Quantitative synthesis results

In general, the pooled ORs and 95% CIs were utilized to evaluate the strength of the association between 8q24 polymorphisms and PCa risk based on five genetic comparison models. Results of the association between 8q24 polymorphisms and PCa susceptibility were listed in **Table 2**. To explore the heterogeneity of these studies, stratification analysis by ethnicity, source of controls and genotypic method was conducted. Meanwhile, subgroups with less than three studies were excluded from further analysis to avoid the possible false associations.

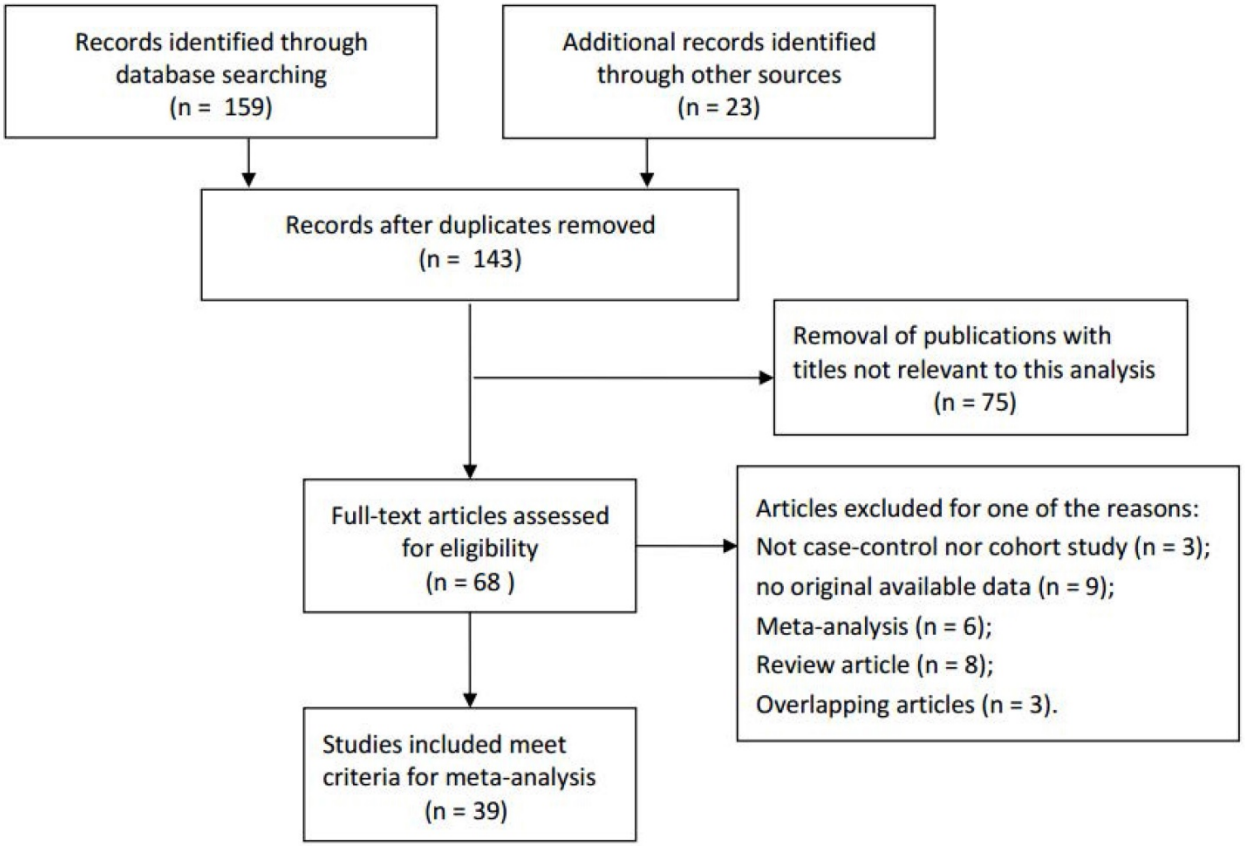

Figure 1. The flowchart of literature search and selection procedure.

Table 1. Characteristics of individual studies included in the meta-analysis.

rs6983267(T>G)							Case (n)			Control(n)			
Year	Surname	Ethnicity	SOC	Genotypic	Case	Control	TT	TG	GG	TT	TG	GG	HWE
2014	Oskina	Caucasian	PB	TaqMan	389	341	89	186	114	77	177	87	Y
2014	Zhang	Asian	PB	PCR-RFLP	124	138	42	54	28	45	67	26	Y
2014	Francisco	Caucasian	HB	TaqMan	82	21	19	33	30	5	13	3	Y
2013	Chan	Asian	HB	Illumina 1M chip	288	144	89	136	63	47	74	23	Y
2013	Brankovie	Caucasian	HB	PCR-RFLP	150	100	53	80	17	25	49	26	Y
2013	Zhao	Asian	PB	PCR-RFLP	282	282	77	149	56	94	137	51	Y
2012	Ho	Caucasian	PB	PCR-RFLP	216	248	70	104	42	66	136	46	Y
2012	Joung	Asian	HB	iPLEX	194	168	56	92	46	51	86	31	Y
2012	Liu	Asian	PB	PCR-RFLP	260	282	70	137	53	94	137	51	Y
2011	Okobia	African	HB	TaqMan	343	426	2	34	307	1	52	373	Y
2011	Papanikolopoulou	Caucasian	HB	TaqMan	86	99	16	46	24	39	47	13	Y
2011	Liu	Asian	PB	GWAS	792	1325	231	405	156	426	647	252	Y
2011	Liu	Asian	PB	PCR-RFLP	40	40	12	23	5	7	17	16	Y
2010	Zheng	Asian	PB	iPLEX	282	152	86	134	62	51	72	29	Y
2009	Liu	Asian	HB	TaqMan	391	323	151	181	59	147	151	25	Y
2009	Penney	Caucasian	PB	iPLEX	1305	1402	400	644	261	372	707	323	Y
2009	Penney	Caucasian	PB	iPLEX	3772	249	1184	1776	812	69	134	46	Y
2009	Beuten	Caucasian	PB	Illumina 1M chip	597	838	107	297	193	218	423	197	Y
2008	Terada	Asian	HB	PCR-RFLP	507	511	211	219	77	206	225	80	Y
2008	Salinas	Caucasian	PB	PCR-RFLP	1258	1238	242	652	364	308	617	313	Y
2008	Cheng	Caucasian	HB	TaqMan	417	417	76	215	126	106	206	105	Y
2008	Cheng	African	HB	TaqMan	89	89	1	14	74	4	11	74	N
2008	Wokolorczyk	Caucasian	PB	PCR-RFLP	1885	1910	385	942	558	513	977	420	Y
2007	Zheng	Caucasian	HB	iPLEX	1551	573	285	771	495	132	299	142	Y
2007	Yeager	Mixed	PB	GWAS	4296	4299	838	2104	1354	1072	2130	1097	Y
2007	Haiman	Caucasian	PB	TaqMan	1047	857	207	543	297	208	417	232	Y
2007	Haiman	Mixed	PB	TaqMan	708	718	290	310	108	335	300	83	Y
rs1447295C>A							Case (n)			Control(n)			
Year	Surname	Ethnicity	SOC	Genotypic	Case	Control	CC	AC	AA	CC	AC	AA	HWE
2014	Zhang	Asian	PB	PCR-RFLP	123	137	74	45	4	91	44	2	Y
2014	Oskina	Caucasian	PB	TaqMan	392	343	291	93	8	292	50	1	Y
2014	Cheryl	African	PB	iPLEX	515	507	223	224	68	226	215	66	Y
2014	Francisco	Caucasian	HB	TaqMan	83	21	56	23	4	16	4	1	Y
2013	Chan	Asian	HB	Illumina 1M chip	289	143	180	92	17	94	44	5	Y
2013	Brankovie	Caucasian	HB	PCR-RFLP	150	100	86	61	3	11	82	7	N
2013	Zhao	Asian	PB	PCR-RFLP	277	287	161	108	8	197	86	4	Y
2012	Joung	Asian	HB	iPLEX	193	168	114	67	12	127	38	3	Y
2012	Liu	Asian	PB	PCR-RFLP	260	287	150	102	8	197	86	4	Y
2011	Okobia	African	HB	TaqMan	354	438	156	162	36	173	207	58	Y
2011	Zeegers	Caucasian	PB	TaqMan	281	267	224	53	4	196	64	7	Y
2011	Liu	Asian	PB	PCR-RFLP	40	40	11	7	22	5	15	20	Y
2010	Benford	African	HB	TaqMan	189	523	86	77	26	237	221	65	Y
2010	Wokolorczyk	Caucasian	HB	PCR-RFLP	690	602	515	156	19	484	115	3	Y
2010	Zheng	Asian	PB	iPLEX	284	151	173	96	15	110	35	6	Y
2010	Xie	Asian	PB	PCR-RFLP	120	120	74	41	5	90	26	4	Y
2009	Liu	Asian	HB	TaqMan	391	323	217	149	25	218	89	16	Y
2009	Chen	Asian	PB	TaqMan	340	337	215	119	6	253	75	9	Y
2008	Terada	Asian	HB	PCR-RFLP	507	387	310	172	25	254	122	11	Y
2008	Salinas	Caucasian	PB	TaqMan	1252	1233	937	288	27	994	225	14	Y
2008	Cheng	Caucasian	HB	TaqMan	417	417	318	97	2	344	69	4	Y
2008	Cheng	African	HB	TaqMan	89	89	39	44	6	43	35	11	Y
2007	Schumacher	Caucasian	PB	TaqMan	11466	12988	8462	2736	268	10344	2472	172	Y
2007	Zheng	Caucasian	HB	iPLEX	1546	571	1169	346	31	485	82	4	Y
2007	Suurinirmi	Caucasian	PB	TaqMan	582	538	435	136	11	427	107	4	Y
2007	Severi	Caucasian	PB	TaqMan	821	732	595	212	14	586	135	11	Y
2007	Wang	Caucasian	PB	TaqMan	491	545	383	99	9	439	101	5	Y
rs16901979(C>A)							Case (n)			Control(n)			
Year	Surname	Ethnicity	SOC	Genotypic	Case	Control	CC	AC	AA	CC	AC	AA	HWE
2015	Geraldine	African	PB	TaqMan	489	534	143	239	107	192	253	89	Y
2014	Cheryl	African	PB	iPLEX	520	510	123	270	127	154	236	120	Y
2013	Chan	Asian	HB	Illumina 1Mchip	289	144	139	119	31	64	68	12	Y
2012	Joung	Asian	HB	iPLEX	194	169	99	81	14	100	57	12	Y
2011	Okobia	African	HB	TaqMan	338	426	81	158	99	131	193	102	Y
2010	Chen	Asian	HB	TaqMan	331	335	148	148	35	173	138	24	Y
2010	Benford	African	HB	TaqMan	192	512	45	97	50	188	237	87	Y
2010	Xie	Asian	PB	PCR-RFLP	120	120	54	56	10	58	54	8	Y
2010	Zheng	Asian	PB	iPLEX	283	145	110	139	34	85	52	8	Y

2008	Cheng	Caucasian	HB	TaqMan	417	416	375	41	1	393	22	1	Y
2008	Cheng	African	HB	TaqMan	89	88	23	43	23	27	50	11	Y
rs6983561A>C							Case (n)			Control(n)			
Year	Surname	Ethnicity	SOC	Genotypic	Case	Control	AA	AC	CC	AA	AC	CC	HWE
2014	Hui	Asian	HB	PCR-HRM	276	283	139	108	29	156	110	17	Y
2012	Zhang	Asian	PB	PCR-HRM	212	231	110	80	22	130	87	14	Y
2010	Benford	African	HB	TaqMan	186	508	48	88	50	171	232	105	Y
2010	Chen	Asian	PB	TaqMan	324	336	135	152	37	175	136	25	Y
2010	Xie	Asian	PB	PCR-RFLP	120	120	56	53	11	62	50	8	Y
2010	Zheng	Asian	PB	iPLEX	284	141	109	141	34	80	53	8	Y
2008	Salinas	Caucasian	PB	PCR-RFLP	1264	1236	1124	135	5	1156	78	2	Y
rs10090154C>T							Case (n)			Control(n)			
Year	Surname	Ethnicity	SOC	Genotypic	Case	Control	CC	CT	TT	CC	CT	TT	HWE
2014	Oskina	Caucasian	PB	TaqMan	368	314	289	73	6	280	33	1	Y
2014	Zhang	Asian	PB	PCR-RFLP	123	131	74	48	1	90	39	2	Y
2013	Zhao	Asian	PB	PCR-RFLP	279	280	168	106	5	203	73	4	Y
2011	Pu	Asian	PB	PCR-HRM	123	96	74	48	1	63	32	1	Y
2010	Benford	African	HB	TaqMan	189	505	124	59	6	357	131	17	Y
2010	Zheng	Asian	PB	iPLEX	282	148	170	98	14	112	30	6	N
2008	Cheng	Caucasian	PB	TaqMan	417	414	315	101	1	342	68	4	Y
2008	Cheng	African	PB	TaqMan	89	88	52	36	1	61	24	3	Y

SOC: Source of controls; PB: Population-based controls; HB: Hospital-based controls.

Rs6983267 T>G and PCa risk

Twenty-seven studies that met the inclusion criteria were retrieved, including 21,351 PCa cases and 17,190 controls. The pooled risk estimates indicated the significant association between rs6983267 T>G and PCa susceptibility under *allele model* (OR=1.14, 95% CI=1.06-1.22), *dominant model* (OR=1.18, 95% CI=1.06-1.30), *heterozygous model* (OR=1.13, 95% CI=1.03-1.23), *homozygous model* (OR=1.31, 95% CI=1.13-1.51) and *recessive model* (OR=1.21, 95% CI=1.10-1.34) (**Figure 2**). Furthermore, when stratified by ethnicity, the results were significant in both Caucasians and Asians. In the subgroup by source of control, the results were significant in both population-based controls and hospital-based controls. In addition, stratification analysis by genotypic method showed the significant association with PCa risk only in TaqMan under all genetic models, while no significant association was found using PCR-RFLP and iPLEX method.

Rs1447295 C>A and PCa risk

The current meta-analysis includes 22,142 PCa cases and 22,294 controls from a total of twenty-seven case-control studies on rs1447295 C>A polymorphism and PCa risk. The pooled ORs of these studies were 1.25 (95% CI: 1.13-1.39) for *allele model*, 1.29 (95% CI: 1.14-1.45) for *dominant model*, 1.27 (95% CI: 1.13-1.43) for *homozygote model*, 1.40 (95% CI: 1.07-1.82) for *heterozygote model* and 1.36 (95% CI: 1.09-1.69) for *recessive model*, which indicated a strong association between rs1447295 mutation and the susceptibility to PCa (**Figure 3**). Moreover, in the subgroup by ethnicity, significant associations were observed in Asian population and Caucasian population. For the subgroup by source of control, the result was significant only in population-based controls under all genetic models, while no significant result was found in hospital-based controls. The significant association was more prominent among these studies using iPLEX than TaqMan under most of genetic models (e.g. iPLEX with *allele model* (OR=1.52, 95% CI=1.08-2.14); *dominant model* (OR=1.59, 95% CI=1.13-2.24); and *heterogeneity model* (OR=1.54, 95% CI=1.13-2.10) vs. TaqMan with *allele model* (OR=1.25, 95% CI=1.11-1.40); *dominant model* (OR=1.31, 95% CI=1.16-1.48); and *heterogeneity model* (OR=1.31, 95% CI=1.17-1.48).

Rs16901979 C>A and PCa risk

Significant differences were found between rs16901979 C>A polymorphism and susceptibility of PCa under *allele model* (OR=1.30, 95% CI=1.20-1.40), *dominant model* (OR=1.42, 95% CI=1.27-1.58), *heterozygous model* (OR=1.36, 95% CI=1.21-1.52), *homozygous model* (OR=1.64, 95% CI=1.39-1.92), *recessive model* (OR=1.36, 95% CI=1.18-1.57) (**Figure 4**). In the stratification analysis by ethnicity, the significant PCa risk effects were observed in African, Asian, Caucasian population under all genetic models. Besides, when stratified by source of control, the positive results were detected in population-based controls and hospital-based controls. In addition, in the subgroup analysis by genotypic method, the results of studies were significant in TaqMan and iPLEX rather than Illumina 1M chip and PCR-RFLP.

Table 2. Meta-analysis results for the included studies of the association between 8q24 polymorphisms (rs6983267 T>G, rs1447295 C>A, rs16901979 C>A, rs6983561 A>C and rs10090154 C>T) and risk of prostate cancer.

Variables	No. of studies	Allele model			Dominant model			Heterozygous model			Homozygous model			Recessive model		
		OR (95% CI)	P values	I-squared (%)	OR (95% CI)	P values	I-squared (%)	OR (95% CI)	P values	I-squared (%)	OR (95% CI)	P values	I-squared (%)	OR (95% CI)	P values	I-squared (%)
rs6983267 T>G		G vs T			(TG+GG) vs TT			TG vs TT			GG vs TT			GG vs (TG+TT)		
All	27	**1.14 (1.06, 1.22)**	<0.001	73.7	**1.18 (1.06, 1.30)**	<0.001	66.4	**1.13 (1.03, 1.23)**	0.002	49.9	**1.31 (1.13, 1.51)**	<0.001	73.9	**1.21 (1.10, 1.34)**	<0.001	64.4
Ethnicity																
Caucasian	13	**1.14 (1.01, 1.28)**	<0.001	83.9	1.17 (0.98, 1.39)	<0.001	80.1	1.11 (0.96, 1.30)	<0.001	70.5	**1.31 (1.03, 1.65)**	<0.001	83.7	**1.21 (1.03, 1.42)**	<0.001	76.1
Asian	10	**1.11 (1.00, 1.22)**	0.091	39.9	**1.13 (1.02, 1.26)**	0.566	<0.1	1.10 (0.99, 1.23)	0.829	<0.1	**1.24 (1.00, 1.54)**	0.063	44.4	1.17 (0.96, 1.43)	0.041	48.7
African	2	1.17 (0.81, 1.68)	0.910	<0.1	1.35 (0.14, 13.32)	0.161	49.0	1.32 (0.09, 19.48)	0.111	60.7	1.35 (0.15, 12.50)	0.173	46.2	1.16 (0.78, 1.71)	0.677	<0.1
Mixed	2	**1.25 (1.19, 1.33)**	0.789	<0.1	**1.35 (1.23, 1.48)**	0.482	<0.1	**1.25 (1.13, 1.38)**	0.653	<0.1	**1.57 (1.40, 1.76)**	0.782	<0.1	**1.35 (1.23, 1.47)**	0.880	<0.1
Source of control																
PB	16	**1.12 (1.03, 1.21)**	<0.001	78.3	**1.16 (1.03, 1.31)**	<0.001	73.3	**1.13 (1.02, 1.25)**	0.001	60.2	**1.27 (1.08, 1.49)**	<0.001	77.2	**1.18 (1.06, 1.32)**	<0.001	66.8
HB	11	**1.18 (1.02, 1.37)**	0.001	66.1	1.20 (0.99, 1.47)	0.021	52.3	1.12 (0.95, 1.32)	0.179	27.9	**1.44 (1.02, 2.03)**	<0.001	70.1	**1.29 (1.02, 1.64)**	0.002	63.2
Method of genotype																
TaqMan	9	**1.24 (1.12, 1.36)**	0.193	28.3	**1.32 (1.13, 1.53)**	0.215	25.8	**1.23 (1.05, 1.45)**	0.209	26.4	**1.61 (1.26, 2.05)**	0.076	43.7	**1.34 (1.12, 1.59)**	0.099	40.2
PCR-RFLP	9	1.02 (0.88, 1.19)	<0.001	79.1	1.09 (0.90, 1.32)	0.001	68.7	1.11 (0.95, 1.30)	0.060	46.5	1.05 (0.78, 1.43)	<0.001	78.8	1.02 (0.81, 1.29)	<0.001	74.2
Illumina 1M chip	2	**1.34 (1.14, 1.57)**	0.262	20.7	1.37 (0.94, 2.01)	0.121	58.3	1.23 (0.85, 1.78)	0.151	51.5	**1.87 (1.42, 2.45)**	0.345	<0.1	**1.54 (1.24, 1.91)**	0.855	<0.1
iPLEX	5	1.06 (0.89, 1.27)	<0.001	80.1	1.01 (0.80, 1.27)	0.012	69.0	0.95 (0.79, 1.13)	0.130	43.8	1.14 (0.80, 1.63)	0.001	79.5	1.16 (0.89, 1.52)	0.004	73.5
GWAS	2	**1.18 (1.01, 1.37)**	0.028	79.2	**1.28 (1.08, 1.51)**	0.115	59.8	**1.24 (1.13, 1.36)**	0.441	<0.1	**1.37 (1.00, 1.88)**	0.025	80.2	1.21 (0.95, 1.54)	0.041	76.0
rs1447295 c>A		A vs C			(AC+AA) vs CC			AC vs CC			AA vs CC			AA vs (AC+CC)		
All	27	**1.25 (1.13, 1.39)**	<0.001	78.6	**1.29 (1.14, 1.45)**	<0.001	77.5	**1.27 (1.13, 1.43)**	<0.001	75.9	**1.40 (1.07, 1.82)**	<0.001	62.1	**1.36 (1.09, 1.69)**	0.005	46.5
Ethnicity																
Asian	11	**1.42 (1.29, 1.57)**	0.464	<0.1	**1.52 (1.32, 1.76)**	0.163	29.7	**1.49 (1.26, 1.76)**	0.058	43.9	**1.64 (1.21, 2.23)**	0.510	<0.1	**1.51 (1.12, 2.03)**	0.817	<0.1
Caucasian	12	**1.23 (1.03, 1.46)**	<0.001	86.0	**1.22 (1.01, 1.49)**	<0.001	85.9	1.20 (0.99, 1.46)	<0.001	84.8	1.52 (0.92, 2.50)	<0.001	69.3	**1.61 (1.10, 2.36)**	0.036	47.0
African	4	0.97 (0.86, 1.08)	0.508	<0.1	0.97 (0.83, 1.14)	0.549	<0.1	0.99 (0.84, 1.17)	0.545	<0.1	0.91 (0.71, 1.17)	0.401	<0.1	0.92 (0.72, 1.17)	0.383	1.9
Source of control																
PB	15	**1.32 (1.20, 1.45)**	0.005	55.3	**1.37 (1.23, 1.54)**	0.004	55.8	**1.36 (1.21, 1.52)**	0.004	56.1	**1.52 (1.16, 1.99)**	0.083	35.8	**1.46 (1.17, 1.83)**	0.211	21.8
HB	12	1.16 (0.91, 1.47)	<0.001	86.7	1.13 (0.85, 1.51)	<0.001	86.5	1.12 (0.84, 1.49)	<0.001	85.1	1.25 (0.74, 2.08)	<0.001	73.1	1.27 (0.85, 1.90)	0.006	57.8
Method of genotype																
PCR-RFLP	8	1.11 (0.79, 1.56)	<0.001	87.5	0.98 (0.63, 1.53)	<0.001	88.9	0.93 (0.59, 1.46)	<0.001	88.7	1.33 (0.55, 3.18)	<0.001	75.9	1.63 (0.97, 2.75)	0.112	40.1
TaqMan	14	**1.25 (1.11, 1.40)**	<0.001	70.7	**1.31 (1.16, 1.48)**	<0.001	64.4	**1.31 (1.17, 1.48)**	0.002	59.4	1.27 (0.92, 1.75)	0.003	58.4	1.20 (0.89, 1.62)	0.006	55.3
iPLEX	4	**1.52 (1.08, 2.14)**	<0.001	83.5	**1.59 (1.13, 2.24)**	0.005	76.6	**1.54 (1.13, 2.10)**	0.021	69.3	1.89 (0.94, 3.79)	0.052	61.2	1.64 (0.88, 3.06)	0.092	53.4
Illumina 1M chip	1	1.20 (0.84, 1.71)	-	-	1.16 (0.76, 1.77)	-	-	1.09 (0.71, 1.69)	-	-	1.78 (0.64, 4.96)	-	-	1.73 (0.62, 4.77)	-	-
rs16901979 C>A		A vs C			(AC+AA) vs CC			AC vs CC			AA vs CC			AA vs (AC+CC)		
All	11	**1.30 (1.20, 1.40)**	0.117	35.3	**1.42 (1.27, 1.58)**	0.125	34.2	**1.36 (1.21, 1.52)**	0.147	31.5	**1.64 (1.39, 1.92)**	0.519	<0.1	**1.36 (1.18, 1.57)**	0.514	<0.1
Ethnicity																
African	5	**1.29 (1.17, 1.42)**	0.351	9.7	**1.45 (1.25, 1.68)**	0.661	<0.1	**1.37 (1.17, 1.60)**	0.674	<0.1	**1.64 (1.36, 1.97)**	0.314	15.8	**1.33 (1.14, 1.56)**	0.158	39.4
Asian	5	**1.27 (1.11, 1.46)**	0.057	56.3	**1.33 (1.12, 1.58)**	0.027	63.6	**1.28 (1.06, 1.53)**	0.040	60.2	**1.65 (1.19, 2.29)**	0.367	7.0	**1.48 (1.07, 2.03)**	0.679	<0.1
Caucasian	1	**1.83 (1.10, 3.04)**	-	-	**1.91 (1.13, 3.24)**	-	-	**1.95 (1.14, 3.34)**	-	-	1.05 (0.07, 16.82)	-	-	1.00 (0.06, 16.00)	-	-
Source of control																
PB		**1.28 (1.14, 1.42)**	0.066	58.3	**1.46 (1.24, 1.72)**	0.144	44.5	**1.41 (1.19, 1.68)**	0.220	32.1	**1.57 (1.25, 1.97)**	0.245	27.8	**1.26 (1.03, 1.54)**	0.230	30.3
HB		**1.31 (1.18, 1.46)**	0.232	25.8	**1.39 (1.20, 1.61)**	0.144	37.3	**1.31 (1.12, 1.53)**	0.136	38.4	**1.71 (1.36, 2.15)**	0.595	<0.1	**1.47 (1.20, 1.80)**	0.726	<0.1
Method of genotype																
TaqMan	6	**1.35 (1.22, 1.49)**	0.551	<0.1	**1.46 (1.27, 1.69)**	0.585	<0.1	**1.37 (1.17, 1.59)**	0.518	<0.1	**1.77 (1.44, 2.18)**	0.724	<0.1	**1.49 (1.24, 1.78)**	0.729	<0.1
iPLEX	3	**1.29 (1.12, 1.48)**	0.033	70.6	**1.56 (1.28, 1.91)**	0.146	48.0	**1.57 (1.27, 1.94)**	0.346	5.9	**1.50 (1.12, 2.01)**	0.114	53.9	1.15 (0.90, 1.48)	0.172	43.2
Illumina 1M chip	1	0.97 (0.72, 1.32)	-	-	0.86 (0.58, 1.29)	-	-	0.81 (0.53, 1.23)	-	-	1.19 (0.57, 2.47)	-	-	1.32 (0.66, 2.66)	-	-
PCR-RFLP	1	1.13 (0.76,	-	-	1.14 (0.69,	-	-	1.11 (0.66,	-	-	1.34 (0.49,	-	-	1.27 (0.48,	-	-

Variables	No. of studies	Allele model			Dominant model			Heterozygous model			Homozygous model			Recessive model		
		OR (95% CI)	P values	I-squared (%)	OR (95% CI)	P values	I-squared (%)	OR (95% CI)	P values	I-squared (%)	OR (95% CI)	P values	I-squared (%)	OR (95% CI)	P values	I-squared (%)
		1.66)			1.90)			1.89)			3.65)			3.34)		
rs6983561 A>C		C vs A			(AC+CC) vs AA			AC vs AA			CC vs AA			CC vs (AC+AA)		
All	7	**1.41 (1.27, 1.57)**	0.311	15.6	**1.50 (1.31, 1.71)**	0.248	23.7	**1.42 (1.23, 1.63)**	0.186	31.7	**1.93 (1.50, 2.49)**	0.923	<0.1	**1.64 (1.30, 2.08)**	0.943	<0.1
Ethnicity																
Asian	5	**1.37 (1.21, 1.56)**	0.406	<0.1	**1.41 (1.20, 1.67)**	0.216	30.9	**1.32 (1.11, 1.57)**	0.225	29.5	**2.02 (1.48, 2.76)**	0.826	<0.1	**1.77 (1.30, 2.39)**	0.948	<0.1
African	1	**1.33 (1.05, 1.68)**	-	-	**1.46 (1.00, 2.13)**	-	-	1.35 (0.90, 2.02)	-	-	**1.70 (1.07, 2.70)**	-	-	1.41 (0.96, 2.08)	-	-
Caucasian	1	**1.77 (1.34, 2.34)**	-	-	**1.80 (1.35, 2.40)**	-	-	**1.78 (1.33, 2.38)**	-	-	2.57 (0.50, 13.28)	-	-	2.45 (0.47, 12.65)	-	-
Source of control																
PB	5	**1.48 (1.30, 1.69)**	0.227	29.3	**1.58 (1.35, 1.85)**	0.208	32.0	**1.51 (1.28, 1.78)**	0.184	35.6	**2.07 (1.46, 2.94)**	0.816	<0.1	**1.77 (1.26, 2.49)**	0.930	<0.1
HB	2	**1.30 (1.09, 1.55)**	0.776	<0.1	**1.32 (1.03, 1.69)**	0.467	<0.1	1.20 (0.92, 2.57)	0.454	<0.1	**1.77 (1.22, 2.58)**	0.765	<0.1	**1.53 (1.10, 2.12)**	0.481	<0.1
Method of genotype																
PCR-HRM	2	**1.25 (1.03, 1.53)**	0.959	<0.1	1.20 (0.94, 1.54)	0.955	<0.1	1.10 (0.84, 1.42)	0.959	<0.1	**1.89 (1.17, 3.05)**	0.951	<0.1	**1.82 (1.14, 2.89)**	0.961	<0.1
TaqMan	2	**1.36 (1.15, 1.61)**	0.755	<0.1	**1.50 (1.18, 1.90)**	0.865	<0.1	**1.41 (1.10, 1.81)**	0.791	<0.1	**1.79 (1.25, 2.55)**	0.739	<0.1	**1.48 (1.08, 2.02)**	0.703	<0.1
PCR-RFLP	2	**1.56 (1.25, 1.96)**	0.110	60.8	**1.64 (1.28, 2.11)**	0.192	41.2	**1.62 (1.26, 2.09)**	0.176	45.4	1.76 (0.77, 4.07)	0.591	<0.1	1.64 (0.73, 3.70)	0.569	<0.1
iPLEX	1	**1.80 (1.30, 2.48)**	-	-	**2.11 (1.40, 3.17)**	-	-	**1.95 (1.27, 2.99)**	-	-	**3.12 (1.37, 7.10)**	-	-	**2.26 (1.02, 5.02)**	-	-
rs10090154 C>T		T vs C			(CT+TT) vs CC			CT vs CC			TT vs CC			TT vs (CT+CC)		
All	8	**1.46 (1.28, 1.67)**	0.342	11.4	**1.62 (1.40, 1.88)**	0.502	<0.1	**1.66 (1.42, 1.93)**	0.624	<0.1	1.18 (0.72, 1.93)	0.585	<0.1	1.02 (0.62, 1.66)	0.607	<0.1
Ethnicity																
Caucasian	2	**1.67 (1.30, 2.13)**	0.079	67.6	**1.78 (1.37, 2.33)**	0.175	45.7	**1.80 (1.37, 2.36)**	0.320	<0.1	1.43 (0.45, 4.57)	0.049	74.2	1.28 (0.40, 4.11)	0.050	73.9
Asian	4	**1.48 (1.22, 1.80)**	0.592	<0.1	**1.67 (1.34, 2.09)**	0.549	<0.1	**1.70 (1.35, 2.13)**	0.529	<0.1	1.35 (0.66, 2.76)	0.893	<0.1	1.11 (0.55, 2.27)	0.917	<0.1
African	2	1.22 (0.93, 1.59)	0.728	<0.1	1.34 (0.99, 1.83)	0.510	<0.1	**1.40 (1.02, 1.93)**	0.415	<0.1	0.87 (0.36, 2.08)	0.450	<0.1	0.79 (0.33, 1.88)	0.394	<0.1
Source of control																
PB	7	**1.53 (1.32, 1.78)**	0.449	<0.1	**1.71 (1.45, 2.01)**	0.660	<0.1	**1.74 (1.47, 2.06)**	0.769	<0.1	1.24 (0.70, 2.22)	0.480	<0.1	1.05 (0.59, 1.87)	0.492	<0.1
HB	1	1.18 (0.87, 1.61)	-	-	1.26 (0.89, 1.81)	-	-	1.30 (0.90, 1.88)	-	-	1.02 (0.39, 2.63)	-	-	0.94 (0.37, 2.42)	-	-
Method of genotype																
TaqMan	4	**1.45 (1.21, 1.73)**	0.115	49.4	**1.59 (1.30, 1.94)**	0.252	26.6	**1.63 (1.32, 2.00)**	0.391	<0.1	1.04 (0.52, 2.06)	0.199	35.6	0.93 (0.47, 1.86)	0.190	37.0
PCR-RFLP	2	**1.47 (1.13, 1.89)**	0.525	<0.1	**1.64 (1.23, 2.20)**	0.572	<0.1	**1.67 (1.24, 2.24)**	0.624	<0.1	1.21 (0.38, 3.80)	0.518	<0.1	1.02 (0.33, 3.19)	0.537	<0.1
PCR-HRM	1	1.19 (0.73, 1.92)	-	-	1.26 (0.73, 2.20)	-	-	1.28 (0.73, 2.23)	-	-	0.85 (0.05, 13.89)	-	-	0.78 (0.05, 12.61)	-	-
iPLEX	1	**1.74 (1.19, 2.55)**	-	-	**2.05 (1.31, 3.20)**	-	-	**2.15 (1.34, 3.46)**	-	-	1.54 (0.57, 4.12)	-	-	1.24 (0.47, 3.29)	-	-

Rs6983561 A>C and PCa risk

Seven studies that met the inclusion criteria were retrieved, including 2,666 PCa cases and 2,855 controls. Significant association between rs6983561 A>C and PCa risk was observed by the pooled risk estimates under *allele model* (OR=1.41, 95% CI=1.27-1.57), *dominant model* (OR=1.50, 95% CI=1.31-1.71), *heterozygous model* (OR=1.42, 95% CI=1.23-1.63), *homozygous model* (OR=1.93, 95% CI=1.50-2.49) and *recessive model* (OR=1.64, 95% CI=1.30-2.08) (**Figure 5**). For subgroups by ethnicity, the results of these studies in Asians indicated the significant association with PCa risk under all genetic models. Similarly, stratified analysis by source of control detected a significant association in both population-based controls and hospital-based controls. Moreover, since all of the study number less than three for genotypic method, further analysis is not necessary.

Rs10090154 C>T and PCa risk

The pooled risk estimates indicated the significant association between rs10090154 C>T and the risk of PCa under *allele model* (OR=1.46, 95% CI=1.28-1.67), *dominant model* (OR=1.62, 95% CI=1.40-1.88), *heterozygous model* (OR=1.66, 95% CI=1.42-1.93). However, no significant association was found under *homozygous model* (OR=1.18, 95% CI=0.72-1.93), *recessive model* (OR=1.02, 95% CI=0.62-1.66) (**Figure 6**). Stratification analyses by ethnicity also detected that rs10090154 polymorphism increased PCa risk in Asians and Caucasians. Besides, increased PCa susceptibility associated with rs10090154 was observed only in population-based studies. Stratification analyses by genotypic method

found that the meta-analysis results were significant in TaqMan, PCR-RFLP and iPLEX method, instead of PCR-HRM.

Sensitivity analysis

Individual studies were consecutively omitted in the sensitivity analysis to detect the influence of each study on the pooled OR. The sensitivity analysis for the results of 8q24 genetic polymorphisms and PCa risk demonstrated that the obtained results were statistically robust and no individual study affected the pooled OR significantly (**Figure 7**).

Publication bias

The Begg's funnel plot and Egger's test were adopted to evaluate the publication bias of articles in this meta-analysis. As illustrated in **Figure 8**, the shapes of funnel plot were symmetric, suggesting that there was no evidence of publication bias under dominant model in this meta-analysis. Therefore, our results were reliable according to the included articles.

Discussion

Chromosomal region 8q24 is a risk locus for a wide spectrum of cancers, and it is a risk region for PCa which has been investigated extensively. On the basis of racial differences and the fine-mapping study, 8q24 region contains at least three independent risk regions for PCa. Region 1 (126.54–128.62 Mb) was initially identified through a study of Icelandic families, which indicated that this region might confer risk of PCa and contribute to a higher incidence of PCa in Africa-American men than men of European ancestry [14]. Region 2 (128.14–128.28 Mb) contains a 14-SNP haplotype that efficiently tags a relatively uncommon (2–4%) susceptibility variant in individuals of European descent, which happens to be very common (42%) in Africa-American [54]. And region 3 (128.47–128.54 Mb) is defined as a recombination hot-spot among European Americans [47, 55]. Moreover, 8q24 is considered as a gene-free region, flanked by the FAM84B and MYC genes on the centromeric and telomeric ends respectively [55]. Though its biological significance in PCa is still unclear, some evidence in vitro and vivo experiments indicated that risk loci at 8q24 might be tissue-specific enhancers of MYC [15]. Especially, rs6983267 represents Region 1/Block 4 at 8q24 could be associated with MYC expression and CARLo-5, one of the long noncoding RNAs (CARLos) in the 8q24 region, is significantly related to the rs6983267 allele associated with increased cancer susceptibility [56]. However, their association with MYC expression in PCa is not conclusive and others failed to find clear association between rs6983267 genotype and MYC expression. Hence, more significant studies should be conducted to explore the function of these risk loci in the development of PCa.

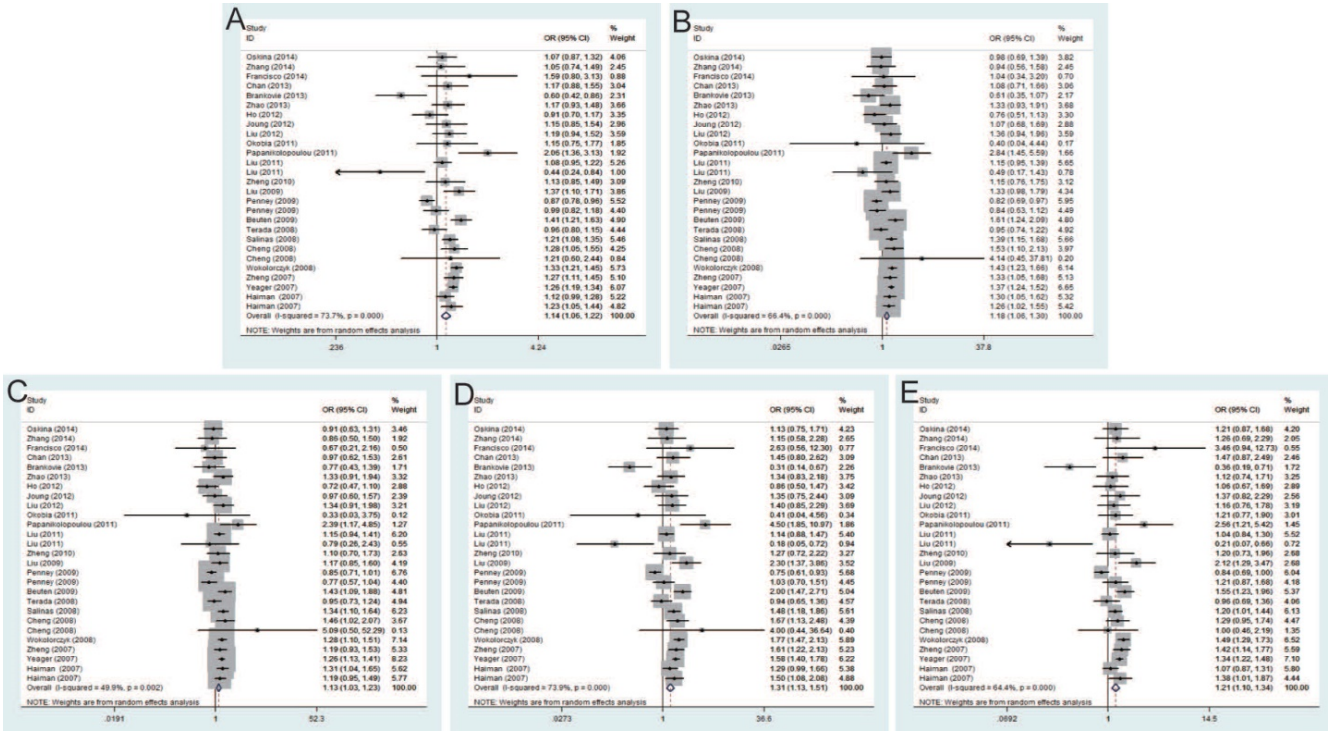

Figure 2. Forest plot of the association between the rs6983267 T>G and prostate cancer risk. A: allele model; B: dominant model; C: heterozygote model; D: homozygote model; E: recessive model.

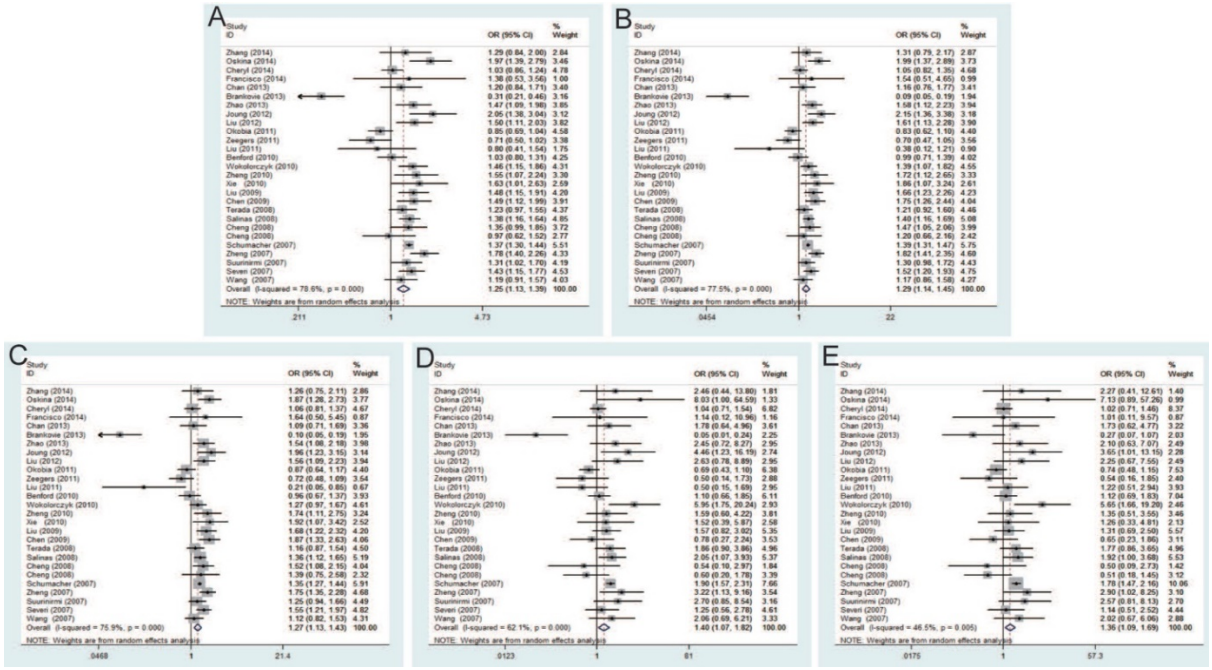

Figure 3. Forest plot of the association between the rs1447295 C>A and prostate cancer risk. A: allele model; B: dominant model; C: heterozygote model; D: homozygote model; E: recessive model.

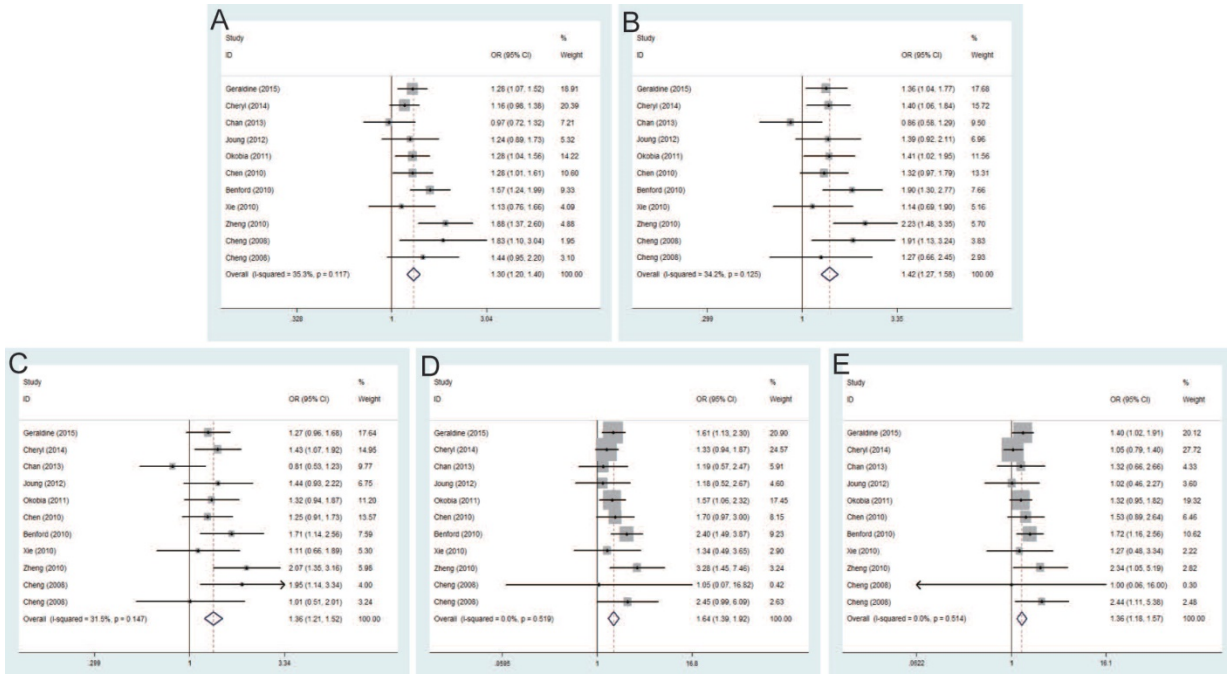

Figure 4. Forest plot of the association between the rs16901979 C>A and prostate cancer risk. A: allele model; B: dominant model; C: heterozygote model; D: homozygote model; E: recessive model.

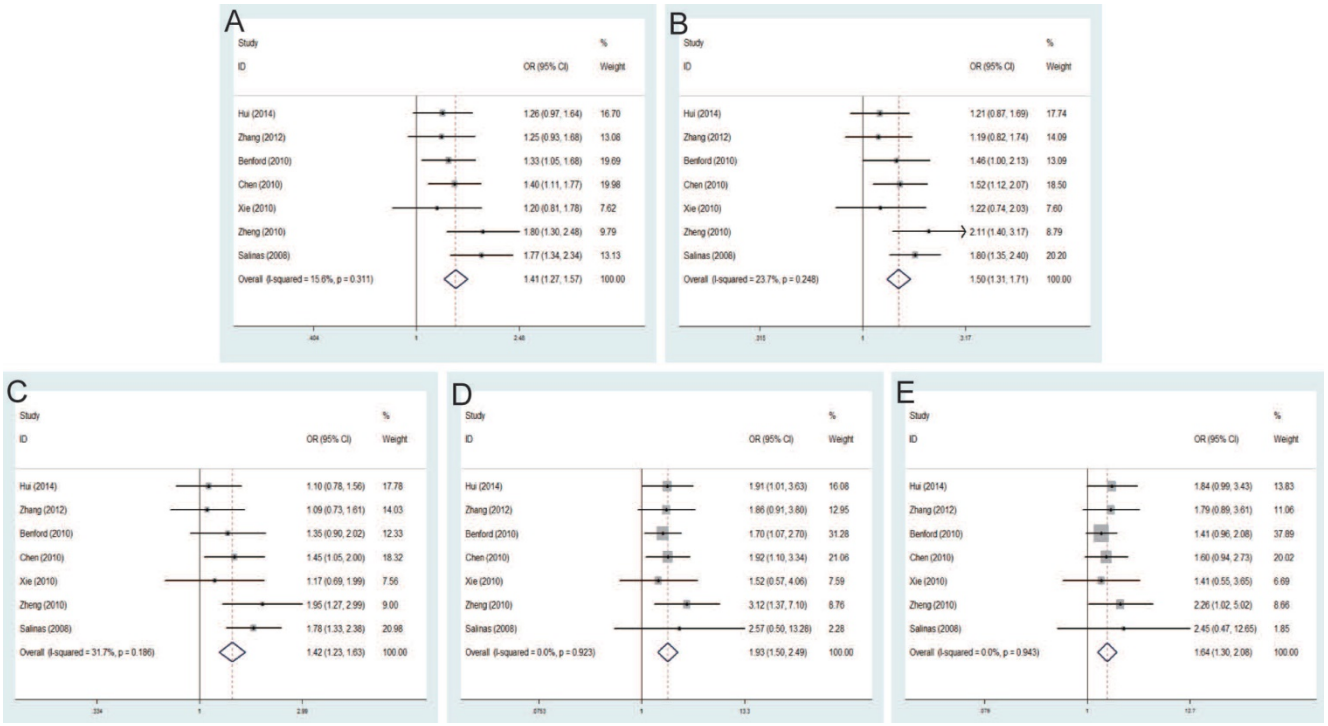

Figure 5. Forest plot of the association between the rs6983561 A>C and prostate cancer risk. A: allele model; B: dominant model; C: heterozygote model; D: homozygote model; E: recessive model.

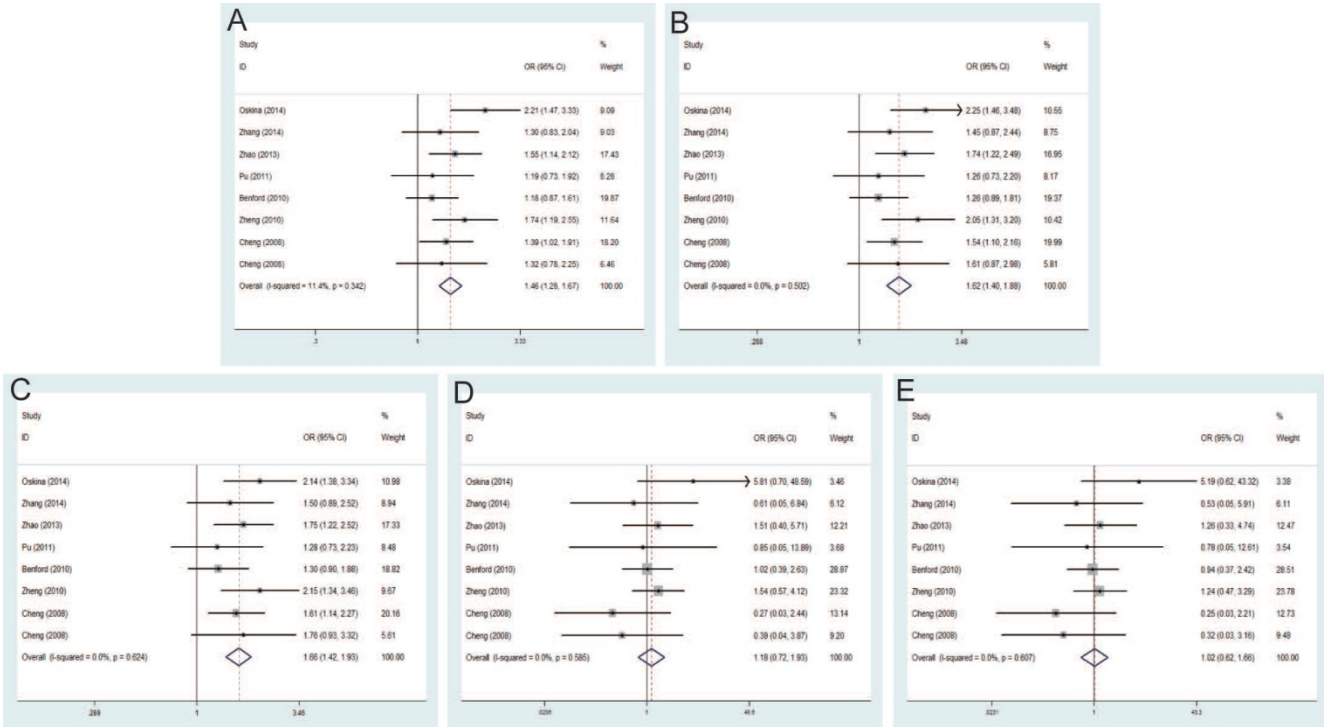

Figure 6. Forest plot of the association between the rs10090154 C>T and prostate cancer risk. A: allele model; B: dominant model; C: heterozygote model; D: homozygote model; E: recessive model.

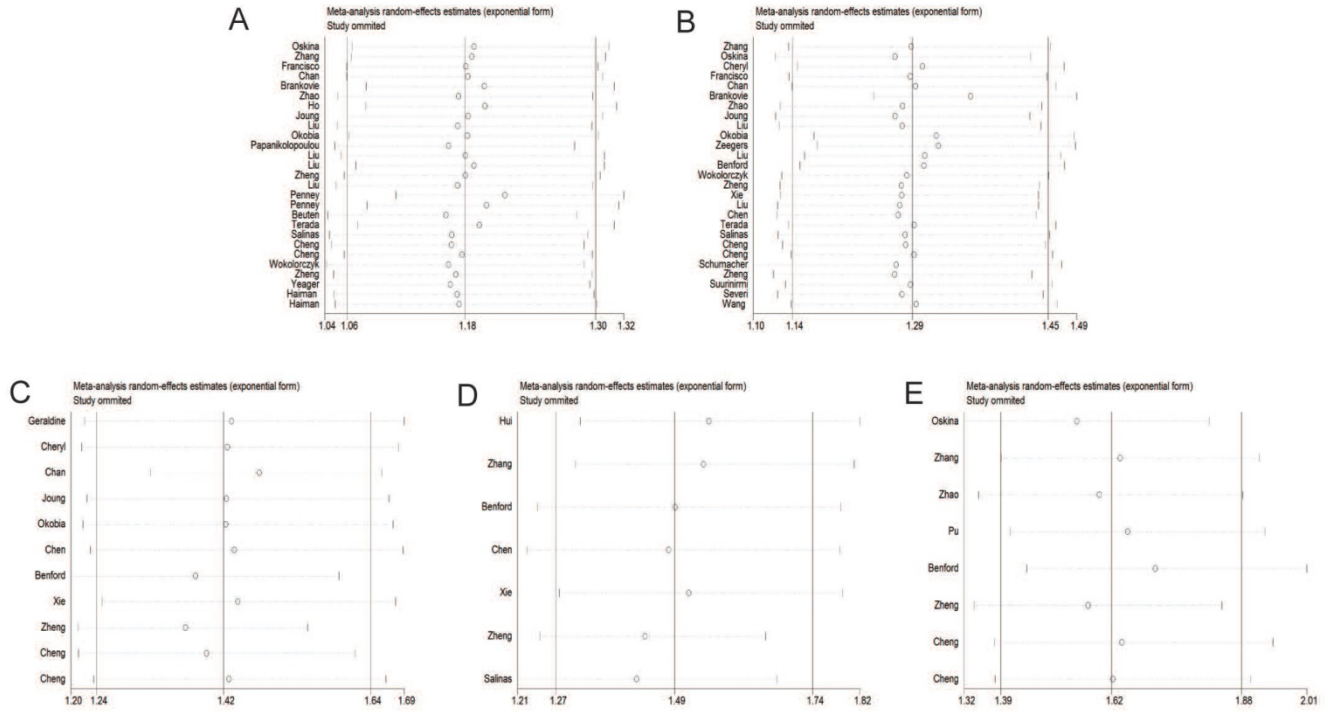

Figure 7. Sensitivity analysis under the dominant model. A: rs6983267 T>G; B: rs1447295 C>A; C: rs16901979 C>A; D: rs6983561 A>C; E: rs10090154 C>T.

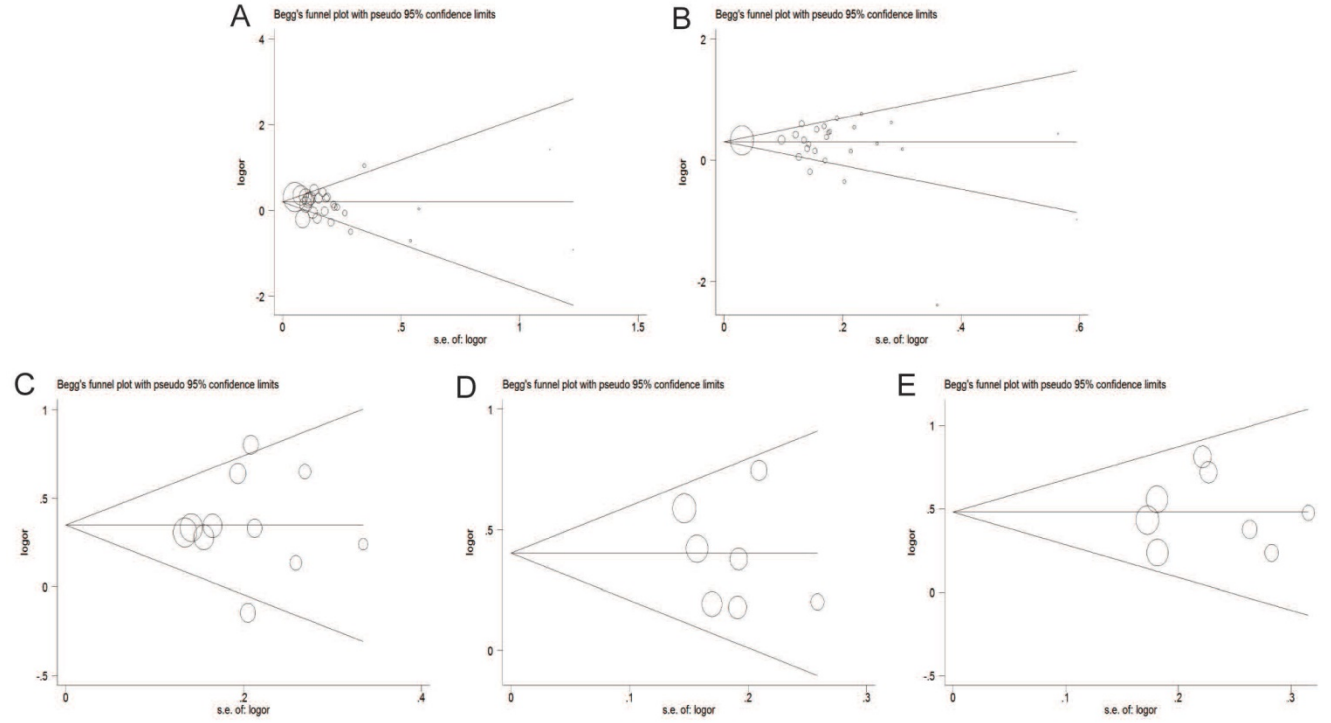

Figure 8. Begg's funnel plot of publication bias test under the dominant model. A: rs6983267 T>G; B: rs1447295 C>A; C: rs16901979 C>A; D: rs6983561 A>C; E: rs10090154 C>T.

Although previous meta-analysis has explored the associations between these 8q24 polymorphisms and PCa risk, we conducted a more detailed analysis with a larger sample size that included the most up-to-date research. To the best of our knowledge, this is the largest meta-analysis containing 80 studies to investigate associations between the selected 8q24 polymorphisms and PCa risk. During the past few years, many case-control studies have demonstrated the strong associations of 8q24 polymorphisms with

the susceptibility to PCa. Nevertheless, the findings were controversial [2,4-6]. For example, no significant association between rs6983267 polymorphism at 8q24 and PCa risk was found reported by Ren et al. [57]. However, Li *et al.* suggested that there is a significant PCa risk associated with the rs6983267 polymorphism at 8q24 [16]. As a powerful tool, meta-analysis was performed to provide a more comprehensive understanding of such associations compared to a single study, especially in analyzing unexplained studies. We took advantages of meta-analysis to prove the associations between 8q24 polymorphisms with PCa. According to quantitative synthesis results, all selected 8q24 polymorphisms (rs6983267 T>G, rs1447295 C>A, rs16901979 C>A, rs6983561 A>C and rs10090154 C>T) were found significant associations with PCa risk under the most assumed genetic models in this meta-analysis.

When stratified by ethnicity, significant association was found between all selected risk loci and PCa risk in Asians. Studies in Caucasians found significant association between rs6983267 T>G and rs1447295 C>A polymorphisms and PCa risk. Meanwhile, significant association between the rs16901979 C>A polymorphism and PCa risk was found in Africans, but as for rs1447295 C>A, the result is contrary, which is consistent with the results as reported by Okobia *et al.* [58]. The ethnic-specific findings indicated that racial differences might have a relationship with the association between 8q24 polymorphisms and the susceptibility of PCa [59]. Though the exact mechanism was unclear, it was likely that different ethnic groups with various genetic backgrounds might have different gene polymorphisms risk in the development of PCa. The observation of highly variable PCa rates by ethnicities provided benefits to disease gene detection [60]. However, the related articles to explain these genetic differences were still scarce. More studies should be undertaken to investigate evolutionary and population genetics relationships across ethnicities.

In the subgroup analysis by source of controls, rs1447295 C>A polymorphism showed significant association with PCa risk in the population-based control studies under all genetic models. While, no significant results were found in the hospital-based control studies under all genetic models. The possible reason might be that hospital-based controls might not have the similar representativeness of general populations. Meanwhile, when we selected the controls from hospitals, inherent selection biases might happen inevitably. Especially, the risk factors of PCa susceptibility were complex. Some ignored risk factors might interfere the results of this meta-analysis.

After stratified analysis by method of genotype, the significant results were observed in these studies using TaqMan method for all selected risk loci, while no significant results were found in these studies by PCR-RFLP method for rs6983267 T>G, rs1447295 C>A and rs16901979 C>A polymorphisms. One possible reason for these discrepancies was that different genotypic methods had their own benefits in diverse aspects, which might lead to different statistical results. PCR-RFLP, as a traditional detecting technology of genetic polymorphisms, can only detect part of the SNP, which makes sequencing time-consuming and laborious. Besides, the two-level structure of DNA chain is also likely to cause artificial false and sequencing result deviation [61, 62]. However, the advantages of TaqMan are that since the reaction is carried out in the PCR process, the separation and elution process is not needed, thus reducing the possibility of PCR pollution [62]. Accordingly, only applying the same appropriate genotypic method would make the results more significant and reliable in the detection of the selected genetic polymorphisms.

To a certain extent, several limitations of this meta-analysis should be considered. (1) Some published studies involved in the 8q24 polymorphisms are not accord with the HWE, resulting in potential bias during control selection or genotypic errors; (2) The number of included studies in the stratified analyses was relatively small. Though we did not make further discussion in the subgroups with less than three studies to avoid the false associations, it might potentially also limit the enough statistical power to explore the real relationship; (3) Adjusted estimates could not be conducted in this meta-analysis. Due to inadequate information, we failed to adjust estimates by other covariates, such as age, obesity, smoking, lifestyle and so on; (4) PCa is a multifactorial disease and complex interactions between genetic and environment factors, which may affect the occurrence and development of PCa. The investigation of single gene region cannot interpret the association of PCa risk comprehensively. Therefore, more attention should be paid to interactions of SNP-SNP, gene-gene, and gene-environment in future large multicentric studies.

Conclusion

In summary, the results of this meta-analysis suggested that five 8q24 polymorphisms (rs6983267 T>G, rs1447295 C>A, rs16901979 C>A, rs6983561 A>C and rs10090154 C>T) had strong associations with the susceptibility to PCa. Therefore, the 8q24 polymorphisms might be considered the ideal markers in PCa diagnosis and therapy, which is

worthy to exploring extensively in the subsequent studies. In addition, more high-quality and multicentric studies with larger sample sizes are needed to confirm these real associations.

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Competing Interests

The authors have declared that no competing interest exists.

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