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Original Article

Variants on 8q24 and prostate cancer risk in Chinese population: a meta-analysis

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Abstract: Previous studies have identified 8q24 as an important region to prostate cancer (PCa) susceptibility. The aim of this study was to investigate the role of six genetic variants on 8q24 (rs1447295, A; rs6983267, G; rs6983561, C; rs7837688, T; rs10090154, T and rs16901979, A) on PCa risk in Chinese population. Online electronic databases were searched to retrieve related articles concerning the association between 8q24 variants and PCa risk in men of Chinese population published between 2000 and 2014. Odds ratio (ORs) with its 95% correspondence interval (CI) were employed to assess the strength of association. Total eleven case-control studies were screened out, including 2624 PCa patients and 2438 healthy controls. Our results showed that three risk alleles of rs1447295 A (OR=1.35, 95% CI=1.19-1.53, P<0.00001), rs6983561 C (C vs. A: OR=1.41, 95% CI=1.21-1.63, P<0.00001) and rs10090154 T (T vs. C: OR=1.48, 95% CI=1.22-1.80, P<0.00001) on8q24 were significantly associated with PCa risk in Chinese population. Furthermore, genotypes of rs1447295, AA+AC; rs6983561, CC+AC and CC; rs10090154, TT+TC; and rs16901979, AA were associated with PCa as well (P<0.01). No association was found between rs6983267, rs7837688 and PCa risk. In conclusions, variants including rs1447295, rs6983561, rs10090154 and rs16901979 on 8q24 might be associated with PCa risk in Chinese population, indicating these four variations may contribute risk to this disease. This meta-analysis was the first study to assess the role of 8q24 variants on PCa risk in Chinese population.

Keywords: Prostate cancer, 8q24, variant, meta-analysis

Introduction

Prostate cancer (PCa), a frequent noncutaneous cancer, is the third leading cancer for men in the world. The well-established risk factors for PCa are age, ethnicity, smoking, alcohol and family history [1]. Due to its high incidence and mortality, treatment costs, and lack of suitable therapy for any stage of this disease, PCa is becoming a significant public health issue. The incidence of PCa in Chinese population is much lower than that in Western men. In China, the incidence rate of PCa was $1.6/10^5$ person year. While in the United States, PCa is more common among men with an estimated 233000 new cases and 29480 death in 2014 [2]. Even so, the occurrence of this disease has rapidly increased among Chinese men in recent years, especially in developed areas [3]. Thus, there is pressing obligation to explore the mechanism under PCa and develop new therapeutic strategy.

Nowadays, hereditary factors are generally believed to contribute to PCa etiology [4]. Genome-wide association studies have identified common variants on human chromosome 8q24 which are associated with increased the risk of PCa. 8q24, a highly conserved genomic region, contains at least three independent risk regions for PCa (region 2: 128.14-128.28, region 3: 128.47-128.54, and region 1: 128.54-128.62) [5]. Numerous researches have discussed the role of variants on 8q24 in PCa risk. Cropp et al. demonstrated that rs2124036 on 8q24 was significantly associated with PCa risk in African-Barbadian men in a Black Population study [6]. Antczak et al. showed that the rs188140481 allele conferred a moderate increase in the risk of PCa in Polish men [7]. Zhang et al. suggested that A allele of rs10505474 and rs7387328 on 8q24 were associated with PCa and cumulatively confer risk in the Northern Chinese Han population [8]. Oskina et al. identified that the A allele of

rs1447295 and the T allele of rs10090154 were associated with PCa risk in the Russian population [9].

Although many studies proved that 8q24 variants were associated with PCa risk, the results still remain inconclusive. Furthermore, previous meta-analysis showed that the association between variants on 8q24 and PCa risk presented racial disparities [10]. Variants on 8q24 also have different effects on cancer development that depend on the tissue type [11]. Therefore, we conducted this meta-analysis to evaluate the role of 8q24 variants in PCa risk in Chinese population.

Materials and methods

Identification and eligibility of relevant studies

We systematically searched the online electronic databases of PubMed, Medline, CNKI (Chinese National Knowledge Infrastructure) and Wanfang to retrieve related articles published between 2000 and 2014. The following terms: "prostate cancer or prostate carcinoma", "8q24", "polymorphism or variant or mutation" and "Chinese population" as well as their combinations were used. The corresponding Chinese terms were used in the Chinese library. When the same authors or laboratory reported one gene polymorphism twice, only the most recent article was included.

Inclusion criteria

The studies must meet the following criteria: 1) case-control studies; 2) evaluating gene variants on 8q24 and PCa risk; 3) the participants should be Chinese population; 4) cases should be diagnosed with histologically confirmed PCa, the controls were age-matched healthy local residents; 5) the results were presented as odds ratio (OR) with a corresponding 95% confidence interval (CI); and 6) genotype distribution information in cases and controls were available to extract, and must be in Hardy-Weinberg equilibrium for a certain polymorphism in controls.

Exclusion criteria

The exclusion criteria were as follows: 1) articles concerned the non-Chinese population; 2) articles without control group or participants in control group were not health population; 3) controls were not age, race-matched; 4) studies were review articles or conference papers; and 5) information of genotype distribution was not available to extract.

Data extraction and quality assessment

Two investigators assessed the data collecting from eligible studies independently. Any disagreement was subsequently resolved by discussion with the third expert and then reached consensus on each item. The following information was sought from each article: first-author, year of publication, total numbers of cases and controls, and genotype distribution, respectively.

Statistical analysis

The strength of the association between polymorphisms on 8q24 and PCa risk was measured by pooled OR with its 95% CI. The significance of the pooled OR was determined by the Z test, and a *P* value less than 0.05 was considered significant. The allelic model (A vs. B: A represents the risk allele; B represents the non-risk allele) and genotype genetic models (dominant effect: AA+AB vs. BB; and recessive effect: AA vs. AB+BB;) were examined to evaluate the 8q24 polymorphisms and PCa risk. The heterogeneity among studies was estimated with the I^2 test which used to evaluate the proportion of statistical heterogeneity and the Q-statistic test which used to define the degree of heterogeneity. The fixed-effect model was employed when the effects are assumed to be homogenous (the *P*-value more than 0.10 for the Q-test and I^2 less than 50%), while the random-effect model is used when they are heterogeneous. Analyses were performed using the software Review Manager 5.2 (Oxford, England, UK). All the comparisons of genetic models were conducted according the description by Collaboration et al. [12]. All *p*-values were two-sided.

Results

Study inclusion

The literature search initially identified 106 studies that concerning the relationship between 8q24 polymorphisms and PCa risk. After applying the inclusion criteria, only 11

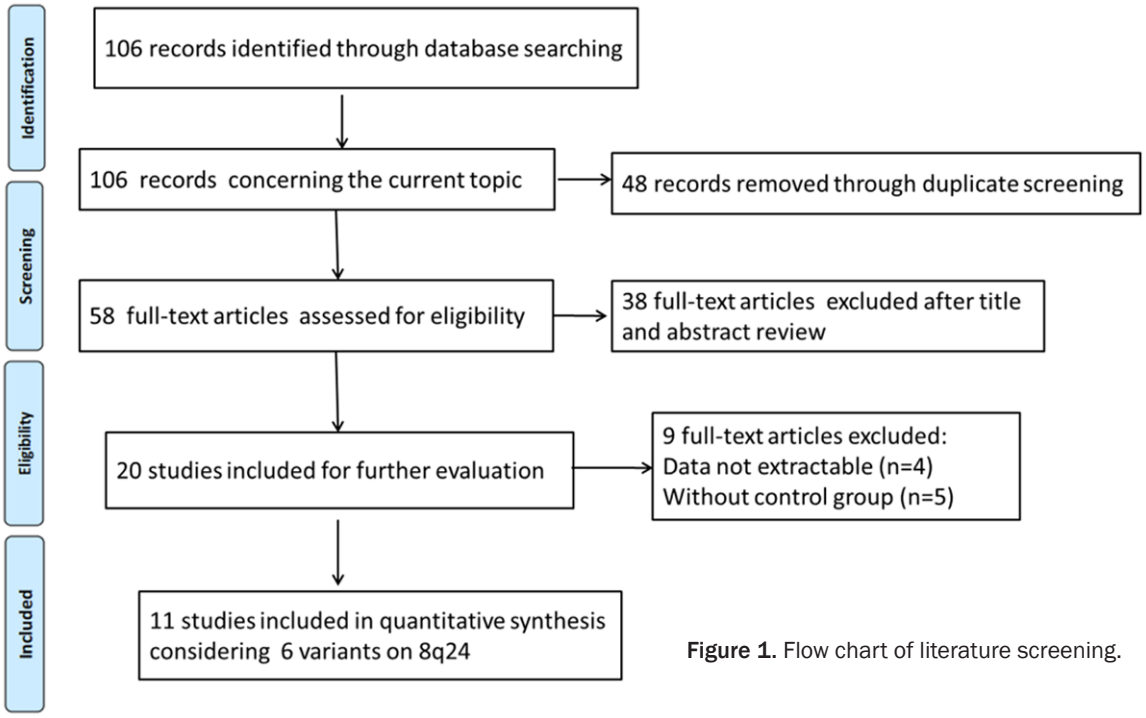

Figure 1. Flow chart of literature screening.

studies (6 in English [13-18] and 5 in Chinese [19-23]) were finally included. The study selection process was shown in **Figure 1**. Six SNPs was discussed, including rs1447295, rs6983267, rs6983561, rs7837688, rs10090154 and rs16901979. All of the included studies wereconducted in Chinese population. The sample size ranged from 80 to 1036. **Table 1** presented the main characteristics and genotype information of included studies.

Meta-analysis of 8q24 variants on PCa risk in Chinese population

Table 2 listed the results of allelic effect, dominant effect and recessive effect of all the six 8q24 polymorphisms on PCa risk.

rs1447295

Eight studies that met the inclusion criteria were retrieved, including 1964 PCa cases and 1760 controls. No significant heterogeneity was found among studies and the fixed-effect model was used. Overall, our result discovered that the frequency of A risk allele was higher in cases than that in controls (19.8% vs. 15.2%), showing a significant association between the A allele and PCa risk (OR=1.35, 95% CI=1.19-1.53, P<0.00001) as shown in **Figure 2**. This significant relationship was also seen in dominant effect (AA+AC vs. CC: OR=1.42, 95% CI=1.23-1.64, P<0.00001), while was not found in receive effect (AA vs. AC+CC: OR=1.40, 95% CI=0.96-2.05, P=0.08).

rs6983267

We identified five studies that reported genotype frequencies of rs6983267, containing 1016 cases and 756 controls. No significant association was found between rs6983267 risk allele and PCa risk under any genetic models (G vs. T: OR=1.05, 95% CI=0.85-1.29, P=0.67; GG+GT vs. TT: OR=1.12, 95% CI=0.91-1.37, P=0.30; GG vs. GT+TT: OR=1.06, 95% CI=0.72-1.58, P=0.76).

rs6983561

Four articles were screened out concerning the relationship between rs6983561 and PCa risk, and including 940 cases and 828 controls. The C allele rate was higher in patients than that in controls (33.7% vs. 26.3%), and genotyping studies indicated that the C allele was associated with a higher risk for PCa (C vs. A: OR=1.41, 95% CI=1.21-1.63, P<0.00001). The CC+AC genotype in dominant effect and CC genotype in receive effect were significant increased the

Table 1. Main characteristics and genotype information of included studies

First author	Year	Cases	Controls	Cases					Controls				
				AA	AB	BB	A	B	AA	AB	BB	A	B
rs1447295 (C/A)				AA	AC	CC	A	C	AA	AC	CC	A	C
Wang L	2007	491	545	9	99	383	117	865	5	101	439	111	979
Chen M	2009	340	337	6	119	215	131	549	9	75	253	93	581
Xie HJ	2010	120	120	5	41	74	51	189	4	26	90	34	206
Zheng SL	2010	288	155	15	96	173	126	442	6	35	110	47	255
Liu Y	2011	40	40	22	7	11	51	29	20	15	5	55	25
Chan J	2013	289	144	17	92	180	126	452	5	44	94	54	232
Zhao CX	2013	289	288	8	108	161	124	430	4	86	197	94	480
Zhang Z	2014	123	137	4	45	74	53	193	2	44	91	48	226
rs6983267 (T/G)				GG	GT	TT	G	T	GG	GT	TT	G	T
Zheng SL	2010	288	155	62	134	86	258	306	29	72	51	130	174
Liu Y	2011	40	40	5	23	12	33	47	16	17	7	49	31
Chan J	2013	289	144	63	136	89	262	314	23	74	47	120	168
Zhao CX	2013	289	288	56	149	77	261	303	51	137	94	239	325
Zhang Z	2014	124	138	28	54	42	110	138	26	67	45	119	157
rs6983561 (A/C)				CC	AC	AA	C	A	CC	AC	AA	C	A
Chen M	2010	324	336	37	152	135	226	422	25	136	175	186	486
Xie HJ	2010	120	120	11	53	56	75	165	8	50	62	66	174
Zheng SL	2010	288	155	34	141	109	209	359	8	53	80	69	213
Zhang YR	2012	212	231	22	80	110	124	300	14	87	130	115	347
rs7837688 (G/T)				TT	GT	GG	T	G	TT	GT	GG	T	G
Zhao CX	2013	289	288	5	103	171	113	445	4	84	194	92	472
Zhang Z	2014	122	135	1	46	75	48	196	2	48	85	52	218
rs10090154 (C/T)				TT	CT	CC	T	C	TT	CT	CC	T	C
Zheng SL	2010	288	155	14	98	170	126	438	6	30	112	42	254
Pu LM	2011	124	111	1	48	74	50	196	1	32	63	34	158
Zhao CX	2013	289	288	5	106	168	116	442	4	73	203	81	479
Zhang Z	2014	123	131	1	48	74	50	196	2	39	90	43	219
rs16901979 (C/A)				AA	AC	CC	A	C	AA	AC	CC	A	C
Chen M	2010	331	335	35	148	148	218	444	24	138	173	186	484
Xie HJ	2010	120	120	10	56	54	76	164	8	54	58	70	170
Zheng SL	2010	288	155	34	139	110	207	359	8	52	85	68	222
Chan J	2013	289	144	31	119	139	181	397	12	68	64	92	196

A = risk allele; B = non-risk allele; AA = homozygous risk alleles; AB = heterozygous; BB = homozygous non-risk alleles.

PCa risk as well (CC+AC vs. AA: OR=1.49, 95% CI=1.23-1.80, P<0.0001; CC vs. AC+AA: OR=1.74, 95% CI=1.23-2.47, P=0.002). **Figure 3** showed the results of 8q24 rs6983561 on PCa risk.

rs7837688

For rs7837688 variant, two studies were assessed, including 401 cases and 417 controls. Overall, our study did not find a significant association between this SNP and PCa risk in any genetic models in a fixed-effect model (T vs. G: OR=1.21, 95% CI=0.94-1.55, P=0.14; TT+GT vs. GG: OR=1.28, 95% CI=0.96-1.70, P=0.09; TT vs. GT+GG: OR=1.03, 95% CI=0.33-3.24, P=0.95).

rs10090154

This SNP was genotyped in men with PCa in 4 studies, including 807 cases and 655 controls.

Table 2. Meta-analysis of 8q24 variants on prostate cancer risk in Chinese population

SNPs	N	Risk allele	Comparison	Z test of studies		*P*-value for homogeneity		Model
				OR (95% CI)	P	Ph	I^2	
rs1447295	8	A	A vs. C	1.35 (1.19, 1.53)	<0.00001	0.59	0%	F
			AA+AC vs. CC	1.42 (1.23, 1.64)	<0.00001	0.13	37%	F
			AA vs. AC+CC	1.40 (0.96, 2.05)	0.08	0.84	0%	F
rs6983267	5	G	G vs. T	1.05 (0.85, 1.29)	0.67	0.08	52%	R
			GG+GT vs. TT	1.12 (0.91, 1.37)	0.30	0.46	0%	F
			GG vs. GT+TT	1.06 (0.72, 1.58)	0.76	0.05	58%	R
rs6983561	4	C	C vs. A	1.41 (1.21, 1.63)	<0.00001	0.32	15%	F
			CC+AC vs. AA	1.49 (1.23, 1.80)	<0.0001	0.20	36%	F
			CC vs. AC+AA	1.74 (1.23, 2.47)	0.002	0.87	0%	F
rs7837688	2	T	T vs. G	1.21 (0.94, 1.55)	0.14	0.38	0%	F
			TT+GT vs. GG	1.28 (0.96, 1.70)	0.09	0.39	0%	F
			TT vs. GT+GG	1.03 (0.33, 3.24)	0.95	0.55	0%	F
rs10090154	4	T	T vs. C	1.48 (1.22, 1.80)	<0.00001	0.59	0%	F
			TT+TC vs. CC	1.67 (1.34, 2.09)	<0.00001	0.55	0%	F
			TT vs. TC+CC	1.11 (0.55, 2.27)	0.77	0.92	0%	F
rs16901979	4	A	A vs. C	1.28 (0.98, 1.67)	0.07	0.03	67%	R
			AA+AC vs. CC	1.31 (0.90, 1.92)	0.16	0.01	73%	R
			AA vs. AC+CC	1.58 (1.11, 2.24)	0.01	0.71	0%	F

SNP, single nucleotide polymorphism; N, number of included studies for a certain variant; Ph, *p*-value of heterogeneity; F, fixed-effect model; R, random-effect model.

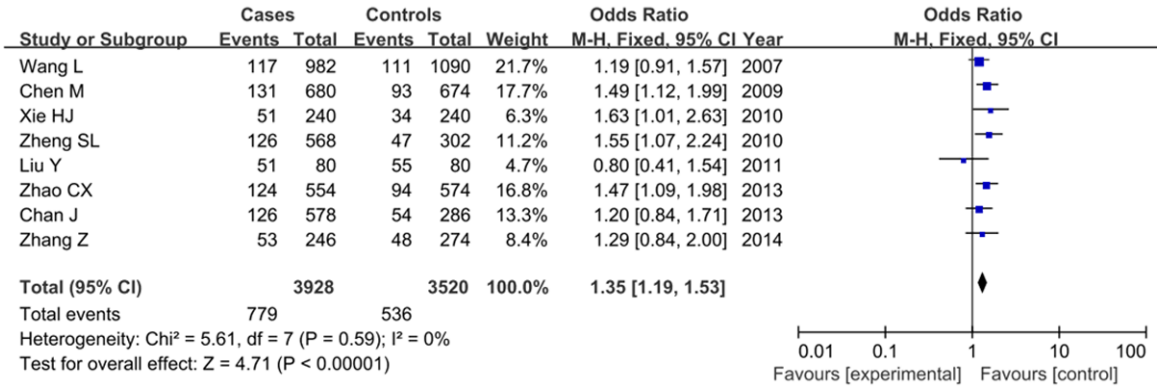

Figure 2. Forest plot on the association for allelic model (A vs. C) of rs1447295 on 8q24 and risk of PCa in a fixed-effects model.

We found a significantly higher frequency of the C risk allele in cases than in controls (21.2% vs. 15.3%). The results indicated a significant association between the rs10090154 risk allele and PCa risk in allele effect and dominant effect (T vs. C: OR=1.48, 95% CI=1.22-1.80, P<0.00001; TT+TC vs. CC: OR=1.67, 95% CI= 1.34-2.09, P<0.00001) as shown in **Figure 4**. However, no significant relationship was found between TT genotype in receive effect and PCa risk (OR=1.11, 95% CI=0.55-2.27, P=0.77).

rs16901979

Four studies assessed rs16901979 in Chinese population, containing 1023 patients and 744 controls. Our meta-analysis found that rs16901979 AA genotype significantly increased the risk of PCa in receive model (AA vs. AC+CC: OR=1.58, 95% CI=1.11-2.24, P=0.01) in fixed-effect model as shown in **Figure 5**. However, this relationship was not found in other genetic models in random-effect model (A vs. C:

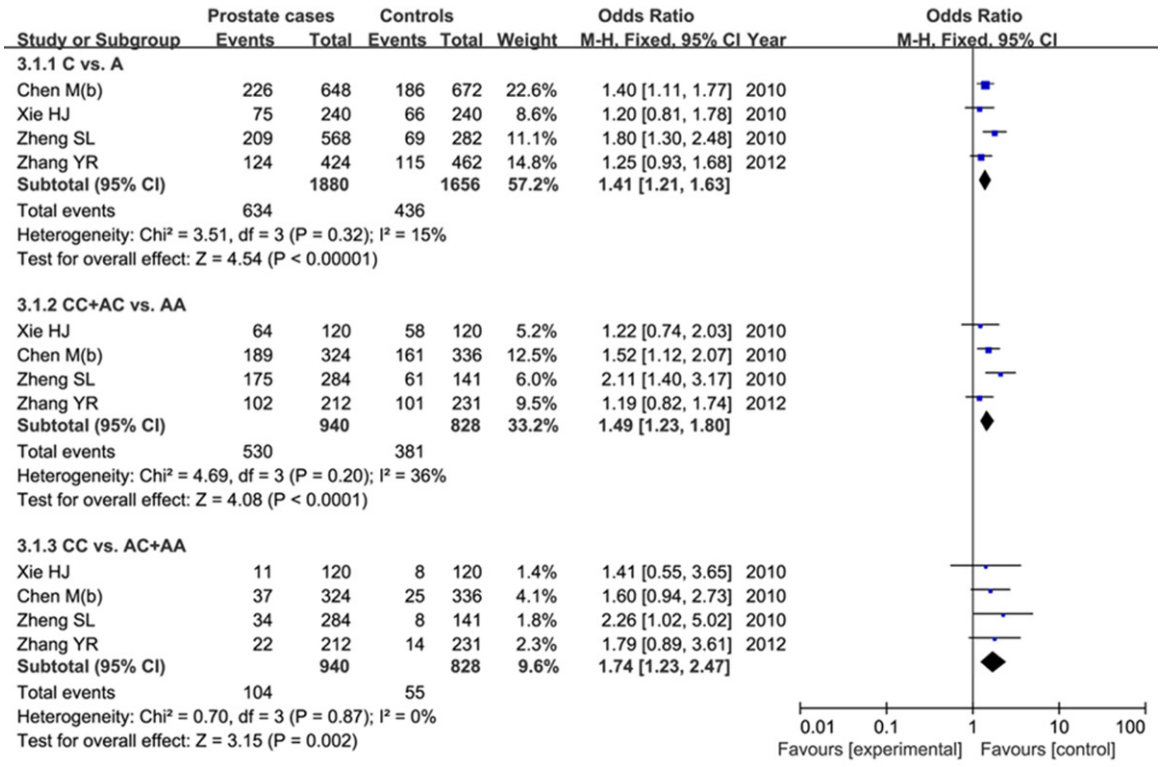

Figure 3. Forest plot of the results of 8q24 rs6983561 on PCa risk.

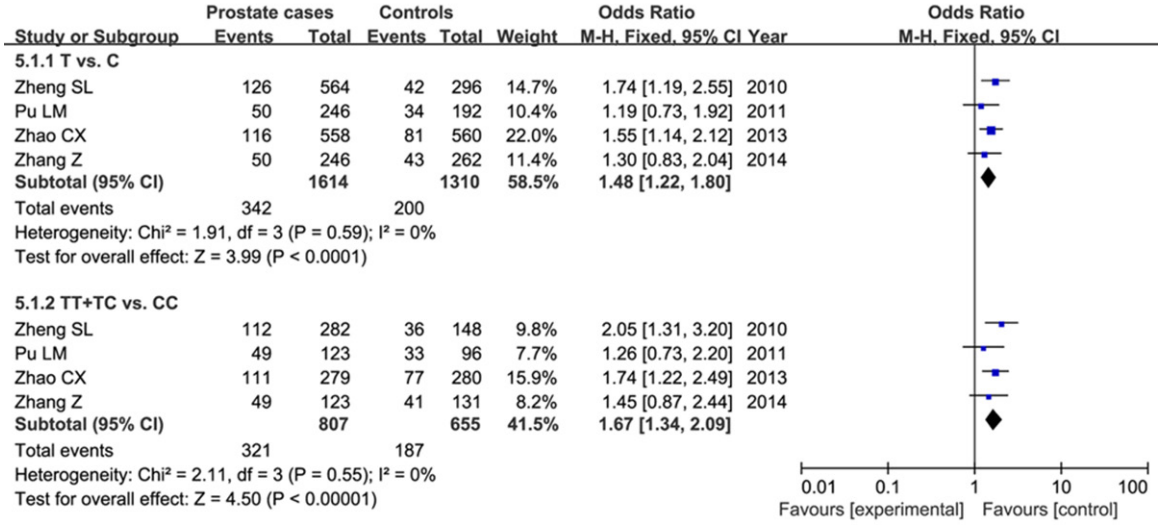

Figure 4. Forest plot of the role of T allele in allelic model and TT+TC in dominant model on PCa risk.

OR=1.28, 95% CI=0.98-1.67, P=0.07; AA+AC vs. CC: OR=1.31, 95% CI=0.90-2.24, P=0.16).

Publication bias

Each study in any comparisons was deleted once a time, and the ORs were not significantly changed, indicating no publication bias was presented. Furthermore, the funnel plot did not show an asymmetry as shown in **Figure 6**.

Discussion

Human chromosome 8q24 is a risk locus for many cancers, and is currently considered as the most important susceptibility region for

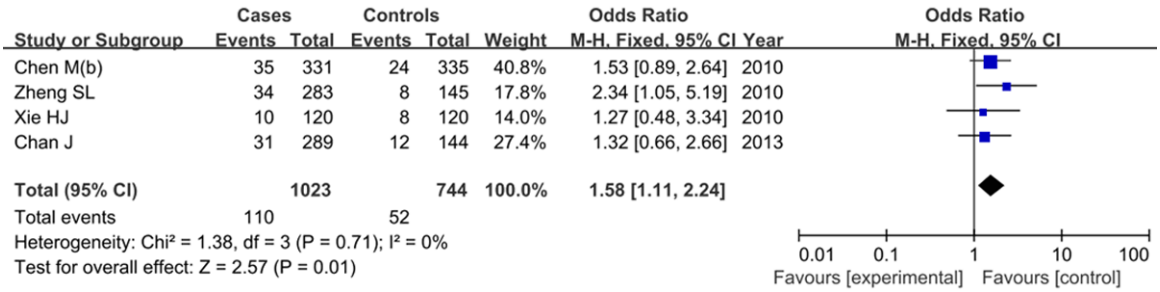

Figure 5. Forest plot of AA genotype in recessive model of rs16901979 on PCa risk.

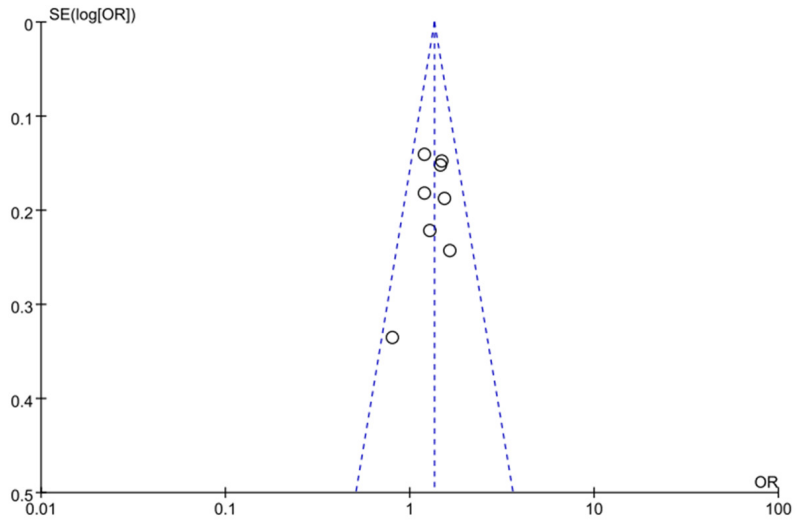

Figure 6. Funnel plot on the association for allelic model (A vs. C) of rs1447295 on 8q24 and PCa risk in a fixed-effects model.

PCa risk. But the results from previous studies still remained objectionable between different populations. In this meta-analysis, we evaluated the association between six single nucleotide polymorphism (SNPs) on 8q24 and PCa risk in men of Chinese population. The result showed that the A allele in rs1447295, C allele in rs6983561 and T allele in rs10090154 significantly increased the risk of PCa. Furthermore, genotypes of AA+AC in rs1447295, CC+AC and CC in rs6983561, TT+TC in rs10090154 and AA in rs16901979 were associated with PCa risk as well. No significant association was found between rs6983267, rs7837688 and PCa risk. This is the first study to systematically evaluate the role of 8q24 variants on PCa risk in Chinese population.

The mechanism of 8q24 affect the process of PCa is still poorly understood. Evidences have shown that this risk region may function as a regulatory hub by physical interactions with multiple genes important for prostate carcinogenesis such as PVT1 (a host gene for several miRNAs), FAM84B and GSDMC [24]. 8q24 cancer-associated variants increase prostate enhancer activity whose expression mimics that of the nearby MYC (a transcriptional activator controlling cell growth, apoptosis, differentiation and other cellular responses) proto-oncogene in vivo [25, 26]. The 8q24 risk locus is proposed to operate through a common mechanism-as tissue-specific enhancers of MYC [26]. The region surrounding rs378854 on 8q24 is proved to be interacted with the MYC and PVT1 promoters [27]. 8q24 amplification is associated with MYC expression and PCa progression and is an independent predictor of recurrence after radical prostatectomy [28]. Furthermore, a rare variant rs188140481, which destroys a FoxA1 site at 8q24, is associated with PCa risk [29].

Many SNPs are proved to be associated with PCa risk. The rs6983267 in region 3 of the chromosome 8q24 appears to be a prominent risk factor for PCa [30]. A new low-frequency variant, rs188140481 [A] at 8q24 has been identified to be associated with PCa in European populations [31]. This variant also conferred greater risk and its carriers were 6.73-fold more likely to develop PCa than non-carriers [32]. Zhao et al. discovered that the rs4242382-A variation might be associated with increased

PCa susceptibility and might be a useful risk biomarker for PCa in multi-ethnic populations [33]. Chung et al. suggested that SNPs between rs1456315 and rs7463708 to be most significantly associated with PC susceptibility [34]. Okobia et al. found that SNP rs16901979 in region 2 was associated with significantly increased risk of PCa with the risk stronger in men with early-onset PCa [35]. Hui et al. showed that the loci including rs10086908, rs1016343, and rs6983561 at 8q24 could be associated with PCa in Jing-jin residents in northern China [36].

Previous studies have also shown that 8q24 variants increased the risk of other cancers. rs35252396 [CG] located at 8q24.21, was proved to be significantly associated with renal cell carcinoma and had an average risk allele frequency in controls of 46% [37]. Bladder cancer risk was associated specifically with variation in the discrete 8q24 region containing rs9642880 [38]. Three polymorphic sites at chromosome 8q24 (rs7837328, rs10808555, rs6983267) had been associated with risk for colorectal adenomas and colorectal epithelial cell proliferation [39]. The SNP rs10505477 might contribute to the survival of gastric cancer and be a potential prognostic biomarker of gastric cancer [40]. Rs13281615, rs6983267 polymorphisms in 8q24 may contribute to susceptibility to breast cancer risk [41].

Several limitations were presented in the meta-analysis. Firstly, the number of included studies was small, for example, only two articles were retrieved for rs7837688. Secondly, SNP-SNP interaction should be considered. Zheng et al. have discussed the cumulative association of SNPs on 8q24, and the results showed that when the most significant SNPs from different regions were included in a multivariate analysis, each SNP remained significant after adjustment for other SNPs and family history [42]. Thirdly, we only assessed the Chinese population, while other population should be considered as well. Lastly, other risk factors such as smoking, age should be included in the future research.

In conclusion, our results showed that rs1447295 A allele, rs6983561 C allele and rs10090154 T allele are significantly associated with increased the risk of PCa. No significant association was found between rs6983267, rs7837688 and PCa risk. Further studies are needed to systematically evaluate 8q24 variants on PCa risk among all populations.

Disclosure of conflict of interest

None.

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