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Original Article

Effects of PSCA rs2294008 (C/T) and c-MYC rs9642880 (G/T) polymorphisms on bladder cancer: evidence from a meta-analysis

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Abstract: Previous studies have investigated the associations between the two polymorphisms (prostate stem cell antigen (PSCA) rs2294008 C/T and c-MYC rs9642880 G/T) and bladder cancer (BC) risk. However, the results are inconsistent. We therefore carried out a meta-analysis to estimate the relationship between PSCA/c-MYC polymorphisms and BC risk. We searched PubMed up to November 2014 to identify potentially eligible literatures. Odds ratios (ORs) and 95% confidence intervals (CIs) were used to estimate the strength of the associations, the data were further stratified by ethnicity. Heterogeneity was evaluated by Q test and I^2 statistics. Begg's funnel plot and Egger's test were used to assess the publication bias. 11 studies from 9 articles were identified, including a total of 16,814 cancer cases and 52,868 case-free controls. We found a significant association between PSCA rs2294008 polymorphism and BC risk (the allele contrast model: OR = 1.14, 95% CI = 1.11-1.18; homozygote comparison: OR = 1.28, 95% CI = 1.20-1.37; heterozygote comparison: OR = 1.23, 95% CI = 1.17-1.30; dominant model: OR = 1.25, 95% CI = 1.19-1.31 and recessive model: OR = 1.13, 95% CI = 1.07-1.20). Moreover, a significant increased risk of BC was confirmed both in Caucasian and in Asians. For c-MYC rs9642880 polymorphism, significant increased BC risk was detected under the following genetic models (the allele contrast model: OR = 1.20, 95% CI = 1.13-1.27; homozygote comparison: OR = 1.37, 95% CI = 1.21-1.55; heterozygote comparison: OR = 1.20, 95% CI = 1.09-1.32; dominant model: OR = 1.25, 95% CI = 1.14-1.37 and recessive model: OR = 1.26, 95% CI = 1.13-1.40). Further stratified analysis by ethnicity also observed the same results. This meta-analysis suggested that PSCA rs2294008 and c-MYC rs9642880 polymorphisms may increase the BC risk. Further studies are needed to clarify the effects.

Keywords: PSCA, c-MYC, polymorphism, bladder cancer, meta-analysis

Introduction

Bladder cancer (BC) is one of the most common malignant cancer worldwide and the eighth cause of death in male cancer. As the second most frequent malignancy of the genitourinary tract, in 2014, the estimated number of new cases is 74,690 and result in 15,580 deaths in the US [1]. In china, BC is the 10th most common cancer, the incidence and mortality of BC is significantly increased from 1991 to 2005 [2]. The known risk factors are smoking and occupational exposures [3]. Furthermore, genetic factors also play an important role in BC susceptibility [4, 5].

Recently, genome-wide association studies (GWAS) show certain number of new BC-associated single-nucleotide polymorphisms (SNPs). Among them, rs2294008 (C/T) within the prostate stem cell antigen (PSCA) gene on 8q24.3 and rs9642880 (G/T) within c-MYC gene on 8q24.1 are most widely discussed in BC [6-9, 14-15].

PSCA gene is locate on chromosome 8q24.2, consists of 3 exons and 2 introns, encodes a 123-amino acid glycoprotein, which is belong to the LY-6/Thy-1 family of cell surface antigens [16]. PSCA was initially identified as a prostate-specific antigen, which is overexpressed in most of prostate cancer, and influence cell adhesion, proliferation, and survival [17]. However, it is also expressed in other solid tumors, such as pancreas cancer, bladder can-

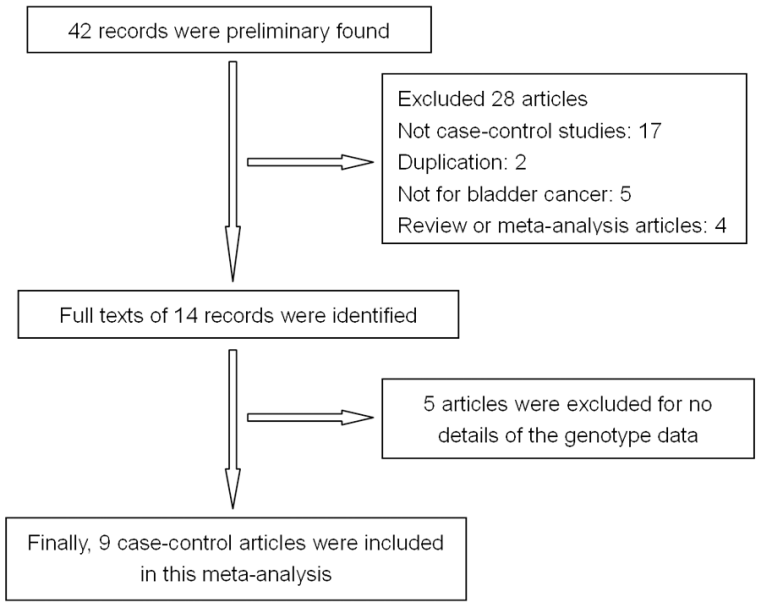

Figure 1. Flow chart showing the detailed steps for study selection.

cer, esophagus cancer and gastric cancer [14, 18-20]. c-MYC gene is a member of the MYC gene family, locate on band q24.1 of chromosome 8 and consists of 3 exons and 2 introns. c-MYC plays an essential role in the regulation of various physiological processes such as cell cycle, cell adhesion, apoptosis and protein synthesis [21]. Aberrant expression of c-MYC is very likely to attribute to direct gene alteration, which can lead to tumorigenesis and maintain tumor growth [22]. The inhibition of c-MYC is expected to become a therapeutic strategy of human cancer [23].

However, because of ethnic diversity and various backgrounds of the studies, there are controversial results regarding the association of PSCA/c-MYC polymorphisms with the risk of BC [6, 8, 9, 14, 15]. So we performed a meta-analysis to clarify the relationship between the PSCA rs2294008 (C/T) and c-MYC rs9642880 (G/T) polymorphisms and BC risk.

Materials and methods

Literature searching strategy

We searched for relevant literatures in PubMed up to November 2014 using the following terms: "PSCA rs2294008 (C/T)" "c-MYC rs9642880 (G/T)" "polymorphism" and "bladder cancer". Only studies published in English were included. To search for more potentially relevant studies, reference lists from studies included were reviewed to identify additional relevant publications.

Selection criteria

The inclusion criteria of this meta-analysis were as follows: (1) case-control studies; (2) the studies evaluated the relationship between the PSCA rs2294008 (C/T) or c-MYC rs9642880 (G/T) polymorphisms and BC risk; (3) the studies included detailed genotyping data.

The exclusion criteria were: (1) not case-control studies; (2) the source of cases and controls, and other essential information were not provided; (3) no available genotype frequency (4) reviews and duplicated publications.

Data extraction

For each study, the following data were collected: first author's surname, year of publication, country of origin, ethnicity, source of control, genotyping method, total numbers of cases and controls as well as numbers of cases and controls with CC (GG), CT (GT) and TT (TT) genotypes. Disagreement was resolved by discussion between all authors until a consensus was reached. The non-cancer controls had no history of any malignant disease. When studies included, subjects of ethnicity and genotype data were extracted separately according to ethnicities for subgroup analyses. We did not define any minimum number of patients for inclusion in our meta-analysis.

Statistical analysis

The association of PSCA rs2294008 (C/T) and c-MYC rs9642880 (G/T) polymorphisms with BC were measured by odds ratio (OR) with 95% confidence interval (CI). The statistical significance for each OR value was evaluated by the Z test. Statistical heterogeneity was measured by using the Q test and I^2 statistics. The Q test and I^2 were claimed to test the variation which was

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

First author	Year	Country	Ethnicity	Genotyping medthod	Source of control	Total sample size (case/control)	SNP No.	HWE (*P*)
Wang [8]	2014	China	Asian	TaqMan	Population	1210/1008	1,2	> 0.05
Ma [11]	2013	China	Asian	MassARRAY	Population	184/962	1,2	> 0.05
Fu [12]	2012	Europe	Caucasian	GWAS	Population	5416/7349	2	> 0.05
Yates DR [13]	2013	France	Caucasian	TaqMan	Hospital	231/261	1	> 0.05
Schwender H [7]	2012	Europe	Caucasian	TaqMan	Hospital	1595/1760	1	> 0.05
Golka K [9]	2009	Germany	Caucasian	TaqMan	Hospital	212/194	1	> 0.05
Golka K [9]	2009	Germany	Caucasian	TaqMan	Hospital	303/699	1	> 0.05
Wang [10]	2009	China	Asian	PCR-RFLP	Hospital	230/255	1	> 0.05
Wang [10]	2009	China	Asian	PCR-RFLP	Hospital	185/210	1	> 0.05
Wu [14]	2009	U.S.A	Caucasian	GWAS	Population	6667/39590	2	> 0.05
Wang [15]	2010	China	Asian	PCR-RFLP	Hospital	581/580	2	> 0.05

CC: case-control; PCR: polymerase chain reaction; RFLP: restriction fragment length polymorphism; GWAS: Genome-wide association studies; HWE: Hardy-Weinberg equilibrium; SNP: single-nucleotide polymorphisms; SNP No. 1: c-MYC rs9642880 (G/T); 2: PSCA rs2294008 (C/T).

Table 2. PSCA rs2294008 and c-MYC rs9642880 polymorphisms genotype distribution and allele frequency in cases and controls

First author	Genotype (N)								Allele frequency (N)				MAF
	Case				Control				Case		Control		
	total	AA	AB	BB	total	AA	AB	BB	A	B	A	B	
rs9642880													
Wang 2014	1210	550	536	124	1008	514	389	105	1636	784	1417	599	0.32
Ma 2013	171	74	74	23	962	489	371	102	222	120	1349	575	0.35
Yates DR 2013	231	64	114	53	261	81	130	50	242	220	292	230	0.48
Schwender H 2012	1584	391	767	426	1738	486	876	376	1549	1619	1848	1628	0.51
Golka K 2009	212	47	93	72	194	52	97	45	187	237	201	187	0.56
Golka K 2009	303	74	151	78	699	178	364	157	299	307	720	678	0.51
Wang 2009	230	81	114	35	255	120	109	26	276	184	349	161	0.4
Wang 2009	185	68	89	28	210	103	83	24	225	145	289	131	0.39
rs2294008													
Wang 2014	1210	604	509	97	1008	566	376	66	1717	703	1508	508	0.29
Ma 2013	175	84	80	11	962	543	355	64	248	102	1441	483	0.29
Fu 2012	5393	1363	2804	1226	7324	2107	3645	1572	5530	5256	7859	6789	0.49
Wu 2009	5038	1288	2613	1137	9363	2842	4668	1853	5189	4887	10352	8374	0.49
Wang 2010	581	272	259	50	580	316	220	44	803	359	852	308	0.31

A represents the major allele, B represents the minor allele. MAF: minor allele frequencies.

due to heterogeneity or by random error, when *P* value of heterogeneity tests was no more than 0.1 ($P \leq 0.1$), we used random effects model. On the contrary ($P > 0.1$), the fixed effects model was performed. Additionally, subgroup analysis was conducted on the basis of ethnicity. Funnel plots were used to assess publication bias. All of the calculations were performed using the review manager version 5.3 (Revman; The Cochrane Collaboration, Oxford, UK), and all statistical tests were two-sided, *P* value less than 0.05 was considered significant.

Results

Characteristics of studies

As shown in **Figure 1**, we preliminarily identified 42 studies about the relationship between the PSCA rs2294008 and c-MYC rs9642880 polymorphisms and BC risk. Following the above inclusion and exclusion criteria, we excluded 33 studies (17 were not case-control studies, 2 were duplicate literature, 5 were not for bladder cancer, 4 were review or meta-analysis articles, 5 did not report detailed allele frequency data).

Table 3. Meta-analysis results

Comparisons	OR	95% CI	*P* value	Heterogeneity		Effects model
				I^2	*P* value	
B vs A						
rs9642880	1.20	1.13–1.27	< 0.00001	0%	0.53	F
Caucasian	1.18	1.09-1.28	< 0.0001	0%	0.63	F
Asian	1.22	1.11-1.35	< 0.0001	25%	0.26	F
rs2294008	1.14	1.11-1.18	< 0.00001	14%	0.32	F
Caucasian	1.13	1.09-1.17	< 0.00001	69%	0.07	F
Asian	1.22	1.11-1.35	< 0.0001	0%	0.99	F
BB vs AA						
rs9642880	1.37	1.21–1.55	< 0.00001	0%	0.54	F
Caucasian	1.39	1.19-1.62	< 0.0001	0%	0.71	F
Asian	1.33	1.07-1.65	0.009	33%	0.21	F
rs2294008	1.28	1.20-1.37	< 0.00001	0%	0.57	F
Caucasian	1.28	1.19-1.37	< 0.00001	61%	0.11	F
Asian	1.32	1.03-1.69	0.03	0%	0.86	F
AB vs AA						
rs9642880	1.20	1.09–1.32	0.0002	6%	0.39	F
Caucasian	1.07	0.94-1.23	0.30	0%	0.97	F
Asian	1.36	1.18-1.54	< 0.0001	0%	0.68	F
rs2294008	1.23	1.17-1.30	< 0.00001	0%	0.65	F
Caucasian	1.21	1.14-1.29	< 0.00001	0%	0.53	F
Asian	1.32	1.16-1.51	< 0.0001	0%	0.74	F
AB + BB vs AA						
rs9642880	1.25	1.14–1.37	< 0.00001	0%	0.56	F
Caucasian	1.17	1.03-1.33	0.01	0%	0.90	F
Asian	1.35	1.18-1.54	< 0.00001	0%	0.41	F
rs2294008	1.25	1.19-1.31	< 0.00001	0%	0.64	F
Caucasian	1.23	1.17-1.30	< 0.00001	13%	0.28	F
Asian	1.32	1.17-1.50	< 0.0001	0%	0.86	F
BB vs AA + AB						
rs9642880	1.26	1.13-1.40	< 0.0001	0%	0.54	F
Caucasian	1.33	1.17-1.51	< 0.0001	0%	0.63	F
Asian	1.09	0.89-1.34	0.40	0%	0.63	F
rs2294008	1.13	1.07-1.20	< 0.0001	0%	0.56	F
Caucasian	1.13	1.06-1.20	< 0.0001	57%	0.13	F
Asian	1.17	0.92-1.48	0.20	0%	0.76	F

A represents the major allele, B represents the minor allele, F: fixed effects model, R: random effects model.

Finally, 11 studies from 9 articles were included in this meta-analysis [7-15], including a total of 15,138 BC cases and 22,594 case-free controls. The characteristics of the included studies are listed in **Table 1**. Detailed genotypes data for PSCA rs2294008 (C/T) and c-MYC rs9642880 (G/T) polymorphism are list in **Table 2**.

Meta-analysis results

The main results of this meta-analysis were listed in **Table 3**. There were 8 studies including 4,126 cases and 5,327 controls used to evaluate the relationship between PSCA rs2294008 (C/T) polymorphism and BC susceptibility, and 5 studies including 12,397 cases and 19,237 controls were performed to assess the effect of c-MYC rs9642880 (G/T) polymorphism and BC susceptibility.

As shown in **Table 3** and **Figure 2**, the individuals carrying variant genotypes of PSCA rs2294008 had an increased risk of BC in all genetic models (the allele contrast model: OR = 1.14, 95% CI = 1.11-1.18; homozygote comparison: OR = 1.28, 95% CI = 1.20-1.37; heterozygote comparison: OR = 1.23, 95% CI = 1.17-1.30; dominant model: OR = 1.25, 95% CI = 1.19-1.31 and recessive model: OR = 1.13, 95% CI = 1.07-1.20). In the stratified analysis by ethnicity, significant increased BC risk were detected both in Caucasians and in Asians in the following genetic models (the allele contrast model: OR =1.13, 95% CI = 1.09-1.17; homozygote comparison: OR = 1.28, 95% CI = 1.19-1.37; heterozygote comparison: OR = 1.21, 95% CI = 1.14-1.29; dominant model: OR = 1.23, 95% CI = 1.17-1.30 and recessive model: OR = 1.13, 95% CI = 1.06-1.20 for Caucasians. the allele contrast model: OR = 1.22, 95% CI = 1.11-1.35; homozygote comparison: OR = 1.32, 95% CI = 1.03-1.69; heterozygote comparison: OR = 1.32, 95% CI = 1.16-1.51 and dominant model: OR = 1.32, 95% CI = 1.17-1.50 for Asians).

For c-MYC rs9642880 (G/T), from **Table 3** and **Figure 3**, we also observed an increased risk of bladder cancer in all genetic models (the allele

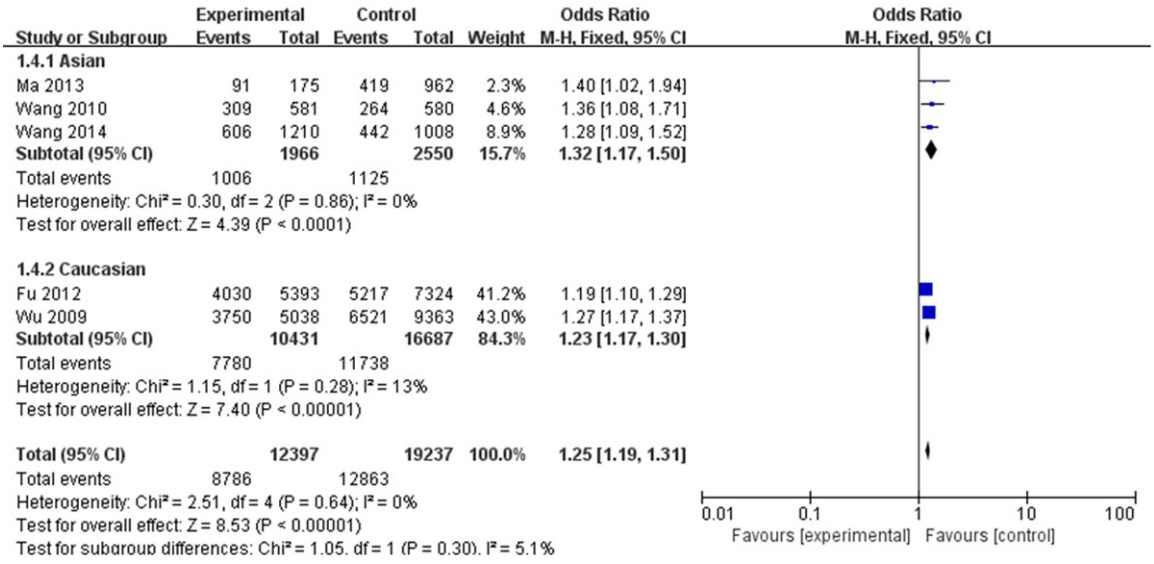

Figure 2. Forest Plot for the association between PSCA rs2294008 polymorphism and BC risk (AB + BB vs AA; subgroup analysis base on ethnicity). CI: confidence interval; OR: odds ratio; M-H: Mantel-Haenszel.

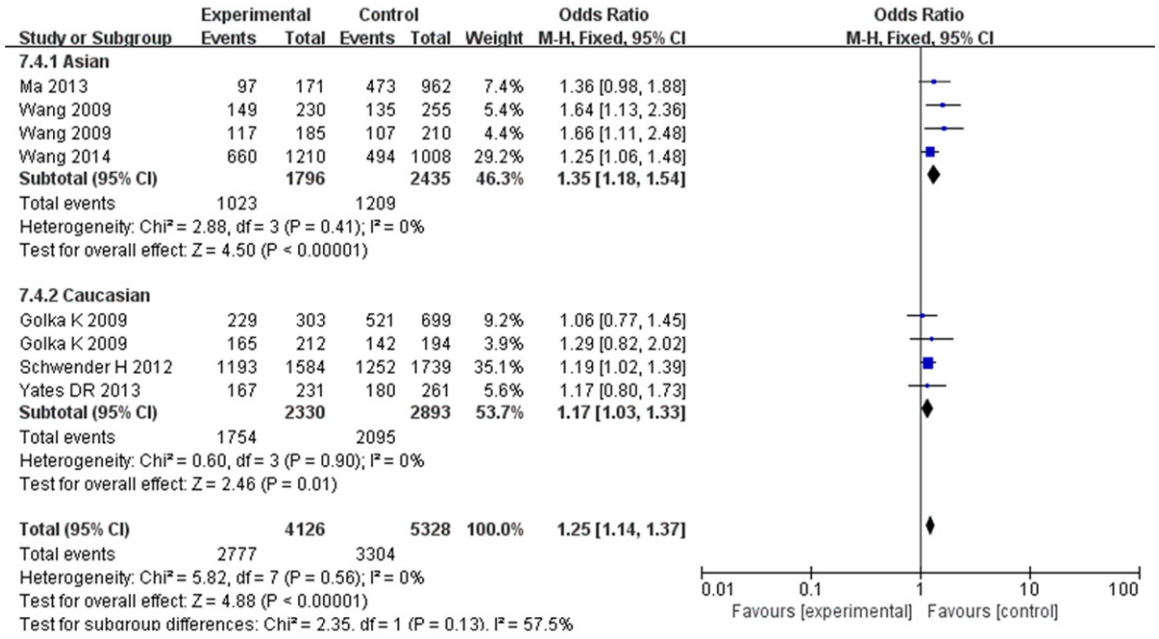

Figure 3. Forest Plot for the association between c-MYC rs9642880 polymorphism and BC risk (AB + BB vs AA; subgroup analysis base on ethnicity). CI: confidence interval; OR: odds ratio; M-H: Mantel-Haenszel.

contrast model: OR = 1.20, 95% CI = 1.13-1.27; homozygote comparison: OR = 1.37, 95% CI = 1.21-1.55; heterozygote comparison: OR = 1.20, 95% CI = 1.09-1.32; dominant model: OR = 1.25, 95% CI = 1.14-1.37 and recessive model: OR = 1.26, 95% CI = 1.13-1.40). When stratified by ethnicity, an increased BC risk was found in Caucasians under the allele contrast model (OR = 1.18, 95% CI = 1.09-1.28), homozygote comparison (OR = 1.39, 95% CI = 1.19-1.62), dominant model (OR = 1.17, 95% CI = 1.03-1.33) and recessive model (OR = 1.13, 95% CI = 1.17-1.51), but not the heterozygote comparison (OR = 1.07, 95% CI = 0.94-1.23). For Asian, the same effects were observed in the allele contrast model (OR = 1.22, 95% CI =

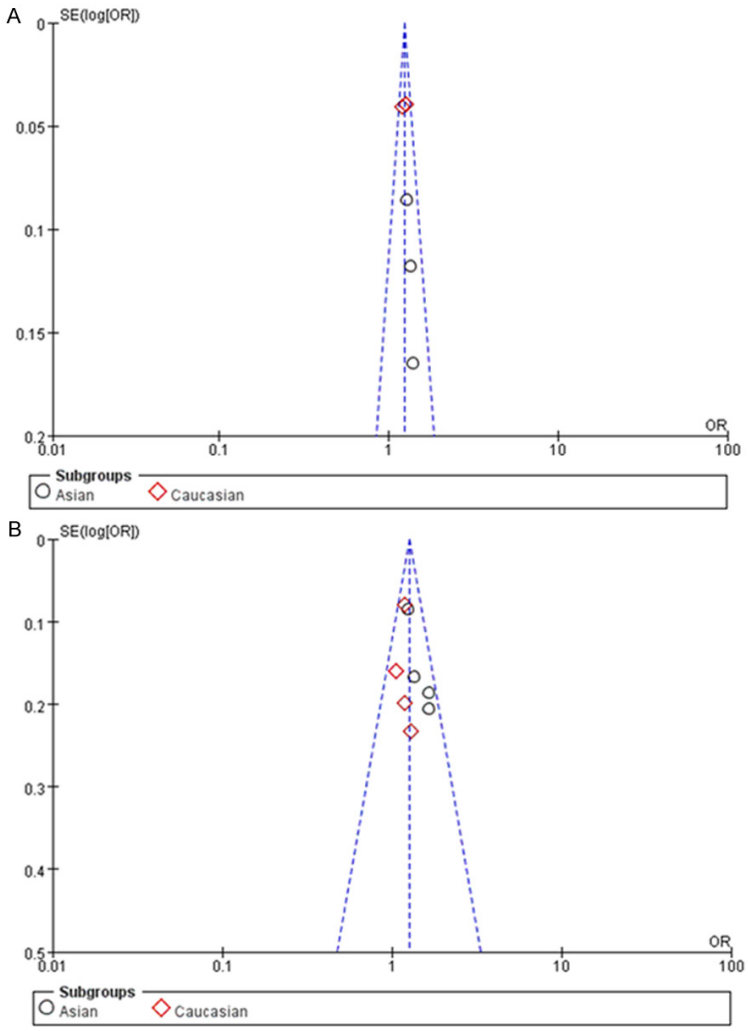

Figure 4. Funnel plot assessing evidence of publication bias (A: PSCA rs2294008; B: c-MYC rs9642880).

1.11-1.35), homozygote comparison (OR = 1.33, 95% CI = 1.07-1.65), heterozygote comparison (OR = 1.36, 95% CI = 1.18-1.54) and dominant model (OR = 1.35, 95% CI = 1.18-1.54), except the recessive model (OR = 1.09, 95% CI = 0.89-1.34).

Tests of heterogeneity

Statistically significant heterogeneity was observed between trials of the following analyses by using Q statistic. As shown in **Table 3**, there was no significant heterogeneity in any genetic models, so the fixed-effects model was performed in all analysis.

Publication bias

Begg's funnel plot and Egger's test were performed to assess the publication bias. As show in **Figure 4**, the shape of the funnel plots was symmetrical in all comparison models. The statistical results did not suggest any evidence of publication bias in this meta-analysis ($P > 0.05$).

Discussion

Although there had great progress in the treatment of BC, the prognosis of BC patients was still poor. To the best of our knowledge, the most important risk factors are smoking and occupational exposures, but there also have significant differences within the same Lifestyle. Therefore, we need to explore other new biomarkers, which have a great relationship of BC risk. By genome-wide association studies (GWAS), we observed that PSCA rs2294008 (C/T) and c-MYC rs9642880 (G/T) polymorphisms were closely associated with the risk and survival of BC [6-9, 14, 15].

PSCA was initially identified as a prostate-specific cell-surface antigen, and not only expressed in normal prostate and prostate cancer but also in other non-prostatic malignancies [24]. Cheng et al. reported immunocytochemical analysis of PSCA on archived voided urine samples may provided a complementary marker for cytological diagnosis of urothelial carcinoma [25]. The PSCA expression level could be a valuable prognostic marker of recurrence in superficial transitional cell carcinoma (TCC) of the bladder [26]. c-MYC also expressed in a wide range of malignancies, which was involved in cell apoptosis, senescence, and DNA damage responses [27]. C-MYC plays an important role in tumor progression and maintenance [28]. Thus, c-MYC become feasible target for novel therapies of human malignancies, recently, some low-molecular weight compounds were found have a potential to be developed into therapeutic drugs in cancer therapy, which target the transcription of c-MYC gene directly or the c-MYC downstream pathway [29].

The relationships between the PSCA/c-MYC polymorphisms and BC are inconsistent [6, 8, 9, 14, 15]. In this meta-analysis, we pooled 11 eligible case-control studies to estimate the effects of PSCA rs2294008 and c-MYC rs9642880 on BC risk. We found that the two polymorphisms had significant increased risk of BC in the overall population. Kiemeney et al. observed c-MYC rs9642880 polymorphism was susceptibility to urinary bladder cancer in hospital-based case-control groups, if there was scarce specific occupational exposure [6]. Ma et al. obtained the same result [11]. In addition, by stratified analysis in non-muscle invasive cases, PSCA rs2294008 had potential effect on non-muscle invasive bladder cancer, but not on muscle invasive BC [11]. The results suggested the pathological stage and environment factors may influence the relationship between PSCA or c-MYC polymorphism and BC. Therefore, association studies with detailed pathological stage and individual data need to be performed in large samples in the future to validate the relationship between PSCA/c-MYC and BC.

In the subgroup analysis based on ethnicity, we also found this result, except the recessive model in Asians for PSCA, heterozygote comparison in Caucasian for c-MYC and recessive mode in Asian for c-MYC. However, there were no studies to evaluate the ethnic differences between the susceptibility gene and BC, especially on differences between Caucasians and Asians. Further investigations with large scale on Caucasian and Asian populations were needed to verify this result.

Some limitations of this meta-analysis should be noted. Firstly, this meta-analysis was based on pooled data and no individual data was available, thus, we could not assess the risk of cancer according to stratification of age, gender, pathological stage, environment factors or other risk factors of bladder cancer. Secondly, small study effect, in which effects reported in small studies were larger, could not be avoided in that some studies were of a relative small size. Moreover, further large scale multicenter studies with more detailed individual data, and different environmental background are needed to further validate gene-gene and gene-environment interactions on PSCA/c-MYC polymorphism and BC risk.

Conclusion

In summary, this meta-analysis provides evidence of the association between PSCA/c-MYC polymorphisms and BC risk. PSCA rs2294008 and c-MYC rs9642880 are both significantly associated with the increased BC risk. Further studies based on different ethnicity are warranted to verify our findings.

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Disclosure of conflict of interest

None.

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