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A meta-analysis of influence of MSMB promoter rs10993994 polymorphisms on prostate cancer risk

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Abstract. – OBJECTIVE: The aim of this meta-analysis was to assess the association between beta-microseminoprotein gene (MSMB) rs10993994 polymorphism and prostate cancer (PCa) risk.

MATERIALS AND METHODS: Relevant databases were searched to identify studies investigating the association between rs10993994 polymorphisms and the risk of PCa using allele contrast, recessive, dominant, and additive models. The assessment of the association was used by odds ratios (ORs) with 95% confidence intervals (CIs). Hardy-Weinberg equilibrium (HWE) was checked for each study. The sensitivity analysis and the assessment of publication bias were also performed.

RESULTS: Six reports involving 13 eligible studies (a total of 11,385 PCa patients and 9,115 controls) were included in the meta-analysis. Our data revealed that the T allele of MSMB rs10993994 polymorphism was significantly associated with PCa in all subjects (allele contrast: OR=1.24, 95% CI=1.19-1.29, $p<0.001$). Similarly, for recessive, dominant, and additive genetic models, significant associations were also found (recessive: OR=1.40, 95% CI=1.30-1.51; dominant: OR=1.28, 95% CI=1.21-1.36; and additive: OR=1.56, 95% CI=1.44-1.70). Significant associations were also found in Caucasians. The data for Asians showed significant association in allele contrast and recessive, additive genetic models, whereas no statistical significance was found in the dominant genetic model.

CONCLUSIONS: This study demonstrated a significant association between the MSMB rs10993994 polymorphisms and PCa risk. Further large-scale studies are warranted to confirm our findings.

Key Words:
Prostate cancer, Beta-microseminoprotein, MSMB, Meta-Analysis.

Introduction

Prostate cancer (PCa), a worldwide common malignant tumor, ranks second among the total cancer deaths in males[1]. The database of the International Agency for Research on Cancer (IARC, http://www.iarc.fr/) revealed the highest incidence rates of PCa in Australia/New Zealand and Northern America [ASR (age-standardized rate): 111.6 and 97.2 per 100,000, respectively]. It remains low in Asian populations with the estimated rates of 10.5 in Eastern Asia, 4.5 in South-Central Asia, and 2.6 in China[2,3]. The mortality rates are generally high in predominantly black populations (ASRs 29 per 100,000 in the Caribbean and 19-24 per 100,000 in sub-Saharan Africa), but very low in Asia (such as 2.9 per 100,000 in South-Central Asia), and intermediate in the Americas and Oceania. The incidence rates and mortality of prostate cancer showed an increasing trend[4]. It is generally accepted that the oncogenesis of PCa includes the combined actions of genetic and environmental factors[5-7]. Over 70 PCa associated genetic loci have been identified in genome-wide association and replication studies[8].

Recently, genome-wide association and several replication studies focused on the association between the rs10993994 polymorphisms of beta-microseminoprotein (MSMB) and PCa risk[9,10]. Stott-Miller et al[11] and Chang et al[12] showed that the T allele of rs10993994 in MSMB gene was associated with the increased risk of PCa, while Haiman et al[13]. demonstrated no significant association between T allele and PCa in American white men and black men Meanwhile, it has also been reported the significant association between rs10993994 and risk of PCa in China[14,15], which is different from the result of the previous one in Japanese. The contradictory results might partly come from the small sample size of those published studies. To more comprehensively evaluate the associations between MSMB rs10993994 polymorphisms and PCa risk, we performed a

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meta-analysis to enhance the statistical power for the estimation of genetic association based on the combining data from individual studies to increase the sample size.

Materials and Methods

Search Strategy and Inclusion Criteria

Relevant studies were searched from PubMed, Embase, and Chinese National Knowledge Infrastructure (CNKI) with the key words: "prostate cancer", "prostate carcinoma", "β-microsemino protein", "MSMB", "polymorphisms", "variant", and "haplotype". In addition, we carefully checked all the reference list of the relevant identified articles to retrieved studies that were not identified with the searched databases. The primary inclusion criteria included: (1) case-control studies published before December 2015; (2) studies evaluating the rs10993994 polymorphism and the risk of PCa; (3) having enough genotype frequency information for the OR calculation. We excluded the review articles and non-case-control studies.

Data Extraction and Quality Assessment

In this study, relevant studies were extracted respectively with the same criteria by two independent authors (Fu Shi and Huang Yinglong). For each study, the following information was included: the first author, publication year, study population (country and ethnicity), number of patients and control, and method of genotyping. Any disagreement was resolved by further discussion until consensus was reached.

Statistical Analysis

To examine whether the distribution of the genotype frequency in control groups deviated from the Hardy-Weinberg Equilibrium (HWE), the exact test was performed[16]. Then, the association between MSMB rs10993994 polymorphisms and PCa risk was examined based on allele contrast and three genetic models: T *vs.* C (allelic contrast), TT+CT *vs.* CC (dominant), TT *vs.* CT+CC (recessive), and TT *vs.* CC (additive model). Stratified analysis was conducted by ethnicity and all the subjects were assigned to three groups (Caucasians, Asians, and other populations). The ORs and 95% confidence intervals (CI) were used to estimate the association between MSMB rs10993994 polymorphisms and PCa risk for each study. The significance of the pooled OR was determined by *Z* test. The fixed-effect method was adopted for homologous effect; otherwise, the random-effect model was used. In this study, heterogeneity among studies was estimated using a Chi-square-based Cochran's *Q* statistic[17] and the I^2 statistic ($I^2 = 100\% \times (Q\text{-}df)/Q$)[18], which lied between 0% and 100% and was typically considered low for $I^2 < 25\%$, moderate for 25-50% and large for >50%. When I^2 was greater than 50%, heterogeneity among studies was considered to be significant and based on such occasion, a random-effects model was carried out for the meta-analysis. In contrast, a fixed-effects model was used. Additionally, sensitivity analysis was also performed by removing one study at a time[19]. Publication bias was investigated by visually inspecting the asymmetry of the funnel plot and Egger's linear regression test[20]. At last, the "Venice criteria" was applied to assess the credibility for the meta-analysis. Each meta-analysis was assigned of grades (A, B or C) based on the amount of evidence, extent of replication, and protection from bias[19,21]. All above *p*-values less than 0.05 were considered statistically significant. All statistical tests for meta-analysis were conducted using the STATA version 12.0 (Stata Corp LP, College Station, TX, USA) and R software (http://www.r-project.org/).

Results

Characteristics of Eligible Studies

A total of 43 unique studies were identified. After full text review, a total of six reports involving 13 eligible studies were included in the final meta-analysis (Figure 1). The detailed characteristics of the selected studies are presented in Table I. All these 13 studies had passed HWE test. The studies included populations of different racial descent, with seven studies involving Caucasian, three Asians, one Africans, one Latinos, and one Native Hawaiian. The total sample size was 20,500, including 11,385 PCa patients and 9,115 matched controls.

Meta-Analysis Results

As shown in Table II, allele contrast showed moderate heterogeneity in all populations (I^2=42.9%), Caucasian (I^2=41.5%), and Asian populations (I^2=38.5%) except for other populations (I^2=71.0%) which contained American Africans, Latinos, and Native Hawaiian. Therefore, we used fixed-effects model to perform me-

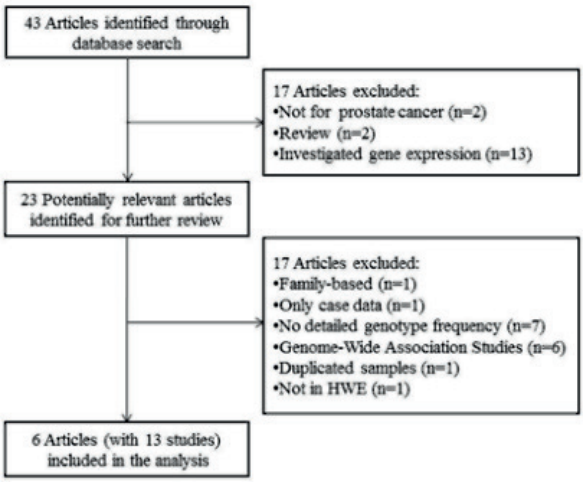

Figure 1. Flow diagram of the study selection process.

ta-analysis for all four genetic models except for the allele contrast in the other populations with a random-effects model. The summary results revealed that the T allele of MSMB rs10993994 polymorphism was significantly associated with PCa in all populations (allele contrast: OR = 1.24, 95% CI=1.19-1.29, $p<0.001$). Similarly, for recessive, dominant, and additive genetic models, significant associations were also found (recessive: OR = 1.40, 95% CI = 1.30-1.51; dominant: OR = 1.28, 95% CI=1.21-1.36; and additive: OR=1.56, 95% CI=1.44-1.70). We also found the same results in Caucasian population. In Asians, significant associations were found in allele contrast and recessive, additive genetic models. However, the dominant genetic model did not show the same results (OR = 1.19, 95% CI=0.95-1.49). Moreover, no significant association was noted in other populations for allele contrast and recessive, additive genetic models. The summary of meta-analysis was provided in Table II and Figure 2.

Publication Bias and Sensitivity Analysis

There was no evidence of publication bias, both quantitatively (Egger's linear regression test, $p=0.671$ for T *vs.* C; $p=0.523$ for TT *vs.* TC+CC; $p=0.840$ for TT+TC *vs.* CC; $p=0.613$ for TT *vs.* CC), and qualitatively, on visual inspection of the funnel plot (Table III and Figure 3). Next, we conducted sensitivity analysis by excluding each of the studies in turn and the result did not alter the significance of the summary statistics, indicating the robustness of the summary effects for each of the investigated genetic model.

According to the Venice criteria to assess the credibility of meta-analysis[21], results under all four genetic models were all graded as "A" or "B" for "amount of evidence", "replication consistency", and "protection from bias". These results indicated that there was moderate evidence of the association between MSMBrs10993994 polymorphism and PCa risk.

Discussion

In recent decades, the morbidity of PCa has exceeded lung cancer and the mortality of PCa ranks only behind that of lung cancer. Currently,

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

Authors	Year	Population	Ethnic group	Numbers		*p* for HWE	Genotype methods
				PCa	Controls		
Stott-Miller et al[11]	2013	Americans	Caucasian	1,239	1,232	0.276	TaqMan
Haiman et al[13]	2013	Americans	Caucasian	213	217	0.094	TaqMan
Haiman et al[13]	2013	African Americans	African	337	331	0.817	TaqMan
Haiman et al[13]	2013	Latinos	Latinos	227	225	0.237	TaqMan
Haiman et al[13]	2013	Japanese	Asian	384	418	0.766	TaqMan
Haiman et al[13]	2013	Native Hawaiian	Hawaiian	60	39	0.498	TaqMan
FitzGerald et al[22]	2012	Americans	Caucasian	1,257	1,253	0.338	TaqMan
Wang et al[14]	2011	Chinese	Asian	110	91	0.528	PCR
Xu et al[15]	2010	Chinese	Asian	251	258	0.167	TaqMan
Chang et al[12]	2009	Swedish	Caucasian	2,863	1,701	0.919	MassARRAY
Chang et al[12]	2009	Americans	Caucasian	1,511	476	0.351	MassARRAY
Chang et al[12]	2009	Americans	Caucasian	1,176	1,101	0.329	MassARRAY
Chang et al[12]	2009	Americans	Caucasian	1,757	1,773	0.725	MassARRAY

Abbreviations: PCa, Prostate cancer; HWE, Hardy-Weinberg equilibrium.

Table II. Meta-analysis of associations between MSMB rs10993994 polymorphisms and PCa.

Comparison	Study populations	Studies	Test of association			Test of heterogeneity			Venice criteria grade	Test of publication bias Egger's test
			OR	95% CI	*p*-value	Model	p_Q-value	I^2 (%)		
T *vs.* C	Overall	13	1.24	(1.19,1.29)	< 0.001	F	0.050	42.9	ABB	0.671
(allele contrast)	Caucasian	7	1.25	(1.20,1.30)	< 0.001	F	0.114	41.5	ABB	0.524
	Asian	3	1.22	(1.06,1.41)	0.006	F	0.197	38.5	ABB	0.345
	Other population	3	1.17	(0.83,1.65)	0.379	R	0.032	71	ACB	0.961
TT *vs.* TC+CC	Overall	13	1.40	(1.30,1.51)	< 0.001	F	0.221	22	AAB	0.523
(recessive)	Caucasian	7	1.43	(1.32,1.55)	< 0.001	F	0.425	0	AAB	0.469
	Asian	3	1.44	(1.13,1.84)	0.003	F	0.344	6.2	AAB	0.651
	Other population	3	1.13	(0.88,1.45)	0.354	F	0.134	50.2	ACB	0.813
TT+TC *vs.* CC	Overall	13	1.28	(1.21,1.36)	< 0.001	F	0.181	26.1	ABB	0.84
(dominant)	Caucasian	7	1.29	(1.21,1.37)	< 0.001	F	0.175	33.1	ABB	0.654
	Asian	3	1.19	(0.95,1.49)	0.134	F	0.224	33.2	ABB	0.075
	Other population	3	1.35	(1.03,1.78)	0.031	F	0.161	45.3	ABB	0.678
TT *vs.* CC	Overall	13	1.56	(1.44,1.70)	< 0.001	F	0.092	36.3	ABB	0.613
(additive)	Caucasian	7	1.58	(1.45,1.73)	< 0.001	F	0.14	37.9	ABB	0.565
	Asian	3	1.51	(1.13,2.00)	0.005	F	0.201	37.6	ABB	0.336
	Other population	3	1.36	(0.98,1.91)	0.069	F	0.075	61.4	ACB	0.919

Abbreviations: OR, odds ratio; PCa, prostate cancer; R, random effects model; F, fixed effects model.

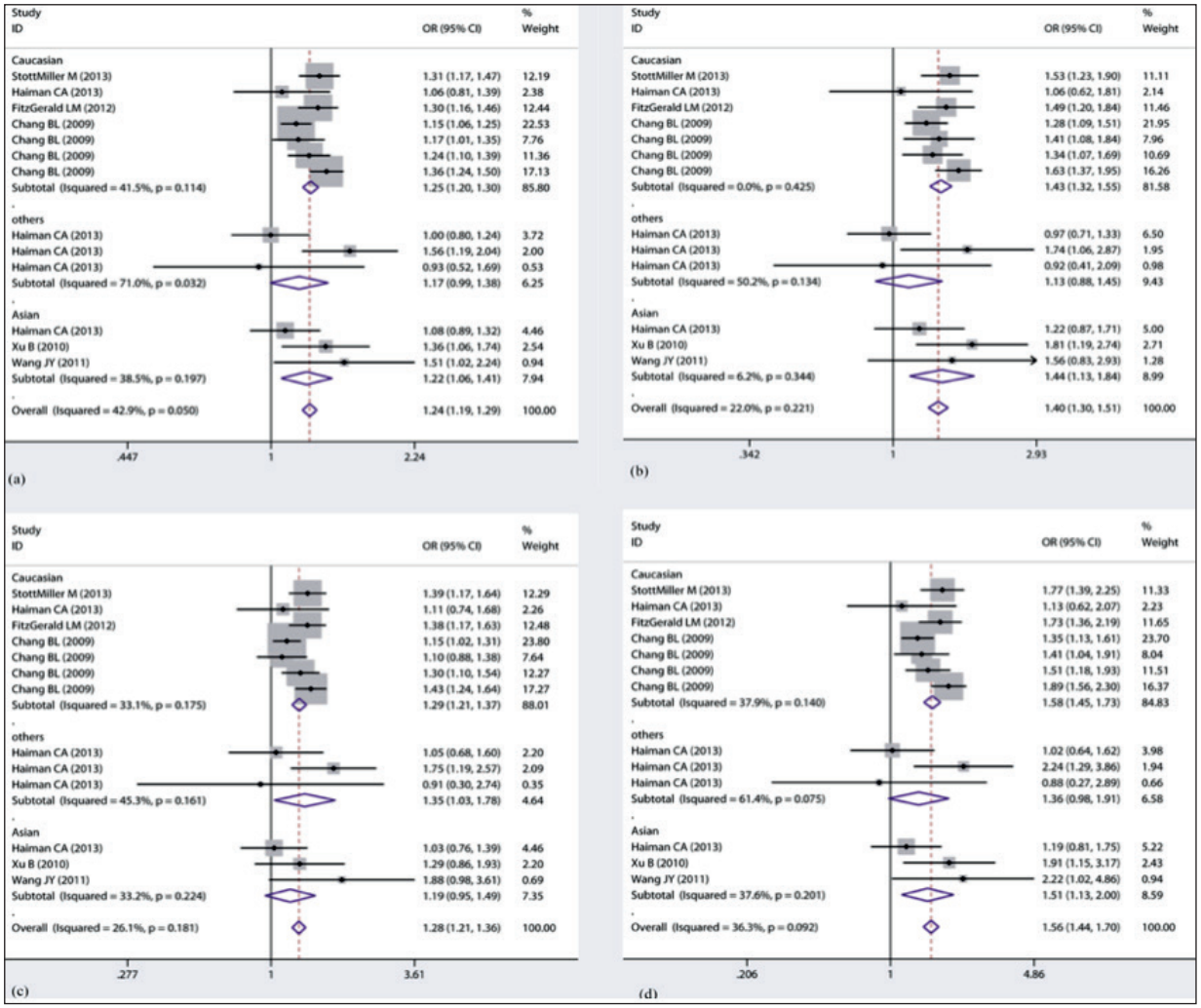

Figure 2. Forest plots for all major meta-analysis outcomes under fixed models with allele contrast and three genetic models: **(a)** T allele; **(b)** TT+TC *vs.* CC model; **(c)** TT *vs.* TC+CC model; **(d)** TT *vs.* CC model.

PCa has become one of the most common malignancies[4]. Recent advances in high-throughput sequencing technologies provide the opportunity of the identification of the potential PCa genetic risk factors, prediction of potential risk and insight into the etiology of PCa[23,24]. Two genome-wide association studies have discovered the association between rs10993994 polymorphism and PCa risk[9,10]. Rs10993994 is located upstream from the gene MSMB on chromosome 10 and the gene product, MSMB, is an immunoglobulin superfamily protein synthesized by prostate epithelial cells and then secreted into seminal plasma[25]. The risk allele of rs10993994 has been reported to be associated with higher PSA levels and transcriptional level of the MSMB and NCOA4, which may mediate the prostate carcinogenesis[24,26]. However, in the previous studies on PCa, the results of genetic association were still conflicting. Hereby, we reviewed the current published reports and performed a comprehensive meta-analysis to evaluate whether the combined evidence demonstrates an association between the MSMB rs10993994 polymorphism and PCa.

To the best of our knowledge, this is the first meta-analysis examining the association between MSMBrs10993994 polymorphism and PCa risk in different ethnic group of populations. Our findings indicated that MSMBrs10993994 polymorphism was significantly associated with the increased risk of PCa and almost consistent results were found among subgroups of Caucasians and Asians, as well as across the four investigated

Table III. Sensitivity analysis for MSMB rs10993994 polymorphisms with meta-analysis.

Study omitted	Allele contrast		Dominant model		Recessive model		Additive model	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Stott-Miller et al[11]	1.23	1.18-1.29	1.27	1.19-1.35	1.39	1.28-1.50	1.54	1.41-1.68
Haiman et al[13]	1.25	1.20-1.30	1.29	1.21-1.37	1.41	1.31-1.52	1.57	1.45-1.71
Haiman et al[13]	1.25	1.20-1.30	1.29	1.21-1.37	1.43	1.33-1.55	1.59	1.46-1.73
Haiman et al[13]	1.23	1.19-1.29	1.27	1.20-1.35	1.40	1.30-1.50	1.55	1.42-1.69
Haiman et al[13]	1.25	1.20-1.30	1.29	1.22-1.38	1.41	1.31-1.52	1.58	1.45-1.72
Haiman et al[13]	1.24	1.19-1.29	1.28	1.21-1.36	1.41	1.31-1.52	1.57	1.44-1.70
FitzGerald et al[22]	1.23	1.18-1.29	1.27	1.19-1.35	1.39	1.29-1.50	1.54	1.41-1.68
Xu et al[15]	1.24	1.19-1.29	1.28	1.21-1.36	1.39	1.29-1.50	1.55	1.43-1.69
Chang et al[12]	1.27	1.21-1.33	1.32	1.24-1.42	1.44	1.32-1.56	1.63	1.48-1.79
Chang et al[12]	1.25	1.20-1.30	1.30	1.22-1.38	1.40	1.30-1.51	1.58	1.45-1.72
Chang et al[12]	1.24	1.19-1.30	1.28	1.20-1.36	1.41	1.30-1.52	1.57	1.44-1.71
Chang et al[12]	1.22	1.16-1.27	1.25	1.17-1.34	1.36	1.25-1.47	1.50	1.37-1.64
Wang et al[14]	1.24	1.19-1.29	1.28	1.20-1.36	1.40	1.30-1.51	1.56	1.43-1.69
Combined	1.24	1.19-1.29	1.28	1.21-1.36	1.40	1.30-1.51	1.56	1.44-1.70

Abbreviations: OR, Odds ratio; 95% CI, 95% confidence interval.

genetic models. Publication bias and sensitivity analysis further confirmed the robustness of our findings.

This meta-analysis revealed that T allele (allele contrast) and three genetic models (TT+CT *vs.* CC, TT *vs.* CT+CC, and TT *vs.* CC) were all sig-

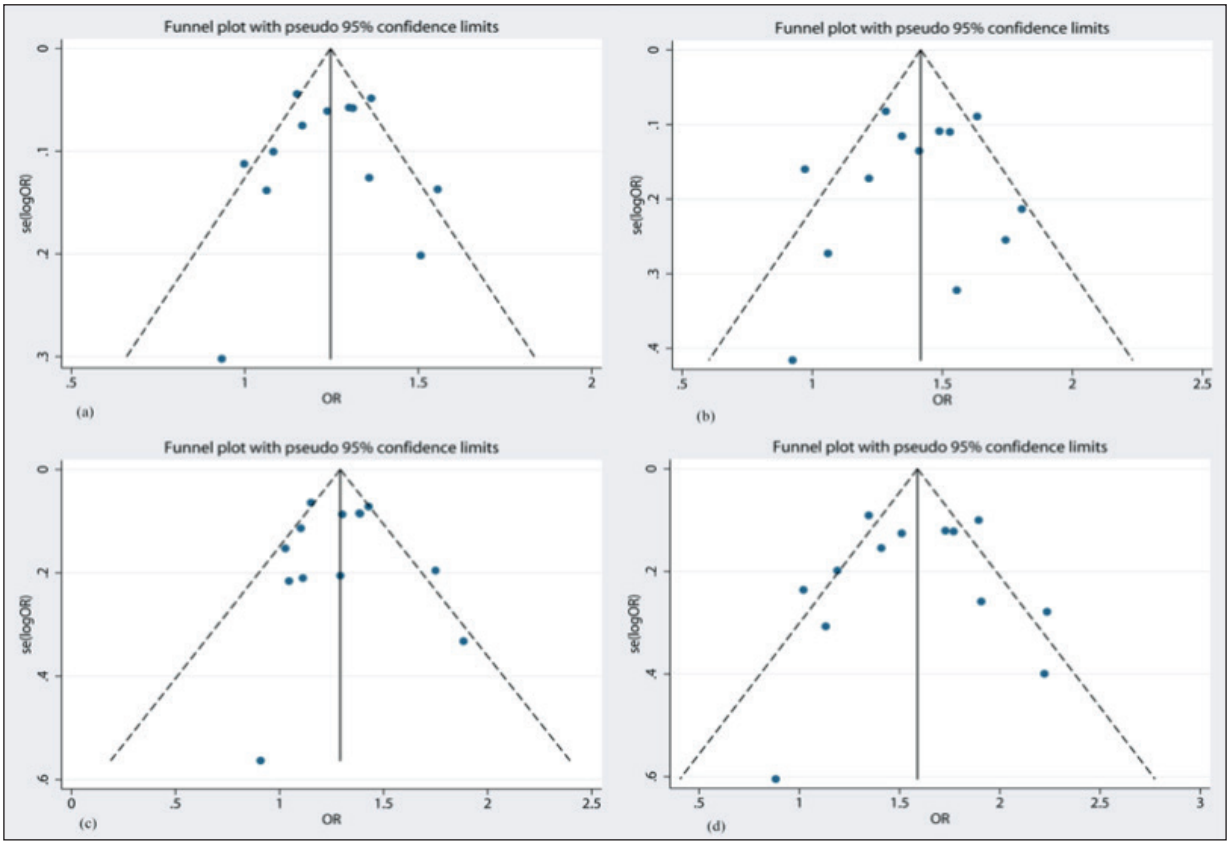

Figure 3. Funnel plots of the meta-analysis of the MSMB rs10993994 polymorphism and PCa: **(a)** T allele; **(b)** TT+TC *vs.* CC model; **(c)** TT *vs.* TC+CC model; **(d)** TT *vs.* CC model.

nificantly associated with risk of PCa in all subjects and Caucasians. Meanwhile, we also found the significant association between the allele contrast and recessive, additive models and PCa risk in Asians. However, no significant association with dominant model was found in Asians. The difference may attribute to the limited sample size of Asians and the ethnic difference. Therefore, further large cohort studies should be conducted to confirm the associations.

This study had several strengths. First, more than 20,000 samples were involved in our study, which significantly improved the statistical power for the meta-analysis. Second, we developed an exhaustive search strategy for major databases to minimize missing relevant studies to our question. Third, two reviewers independently extracted data and judged the eligibility of each selected study with discrepancies resolved by consensus. Fourth, we used the adjusted OR with 95%CI from individual study to generate the pooled ORs, which increased the accuracy of summary estimates.

However, several limitations should also be addressed for this meta-analysis. First, studies from some geographical regions were sparse or absent, for example, Europeans. Further studies are required to replicate the association in Europeans. Moderate heterogeneity was also indicated when data were pooled from all studies in four genetic models. However, subgroup analyses showed, in several cases, the heterogeneity reduced or even disappeared when stratified by geographical location. Second, some unmeasured risk factors contributing to PCa could influence the combined estimates. Third, due to the unavailability of individual patient level data, we could not fully investigate the source of other potential heterogeneity. Moreover, the effects of MSMBrs10993994 polymorphisms on PCa related characteristics (e.g., age, BMI, diet, family history) were not assessed in our meta-analysis.

Conclusions

Our meta-analysis suggests a significant association between MSMB rs10993994 polymorphisms and PCa risk. Almost consistent results are indicated among subgroups of Caucasians and Asians, as well as across the four investigated genetic models. Publication bias and sensitivity analysis further confirm the robustness of our findings. However, this conclusion should be confirmed by further large-scale studies.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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