RESEARCH ARTICLE

Impact of Caspase-8 (CASP8) -652 6N Del and D302H Polymorphisms on Prostate Cancer in Different Ethnic Groups

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Abstract

Background: Despite evidence suggesting roles for caspase-8 (CASP8) -652 6N del and D302H polymorphisms in prostate cancer (PCa), the association of these polymorphisms with PCa risk remains inconclusive. Therefore, a meta-analysis was performed to more precisely estimate the association of CASP8 -652 6N del and D302H polymorphisms with PCa susceptibility. Materials and Methods: A comprehensive literature search was conducted to identify all case-control studies of CASP8 D302H and -652 6N del polymorphisms and PCa risk. Odds ratios (ORs) and 95% confidence intervals (CIs) were used to assess the strength of the association and the precision of the estimate, respectively. Results: Nine -625 6N del studies and 4 D302H studies were included. CASP8 -652 6N del and D302H polymorphisms were not significantly associated with PCa risk in the overall analyses. However, in the subgroup analysis stratified by ethnicity, -625 6N del was significantly associated with PCa risk in the East Asian and Indian populations under the recessive model. Furthermore, the subgroup analysis strongly suggested that D302H was associated with lower PCa risk in the Non-Indian population under the dominant model. Conclusions: In our meta-analysis, ethnic-specific differences were evident in the association of CASP8 -625 6N del and D302H polymorphisms with PCa risk.

Keywords: Prostate carcinoma - CASP8 - SNPs - meta-analysis - ethnic groups

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Introduction

Prostate cancer (PCa) is the second most common cause of cancer death among men in the United States. According to the cancer statistics report from the American Cancer Society, over 241,000 men were diagnosed with PCa and approximately 28,000 died from the disease in 2012 (Siegel et al., 2012). It is well known that multiple risk factors are associated with PCa, including advanced age, ethnicity, family history, and genetic variations. Currently, prostate-specific antigen (PSA)-based screening and its derivative measurements are the most common methods used to detect PCa. However, elevations in PSA can result from urinary tract manipulation (e.g., prostate biopsy, catheterization) and non-malignant conditions (e.g., benign prostatic hyperplasia or prostatitis) (Klein and Lowe, 1997). Therefore, traditional PSA-based screening lacks sufficient sensitivity and specificity to be considered ideal for PCa detection. Recent research has focused on identifying genetic polymorphisms associated with PCa risk, with the aim of improving early diagnosis, screening, and individualized chemotherapy. The number of single nucleotide polymorphisms (SNPs) associated with PCa susceptibility has been rapidly increasing (Zheng et al., 2008), and SNPs associated with tumor cell apoptosis have received the most attention. Caspases, a family of proteases, mediate the regulation of apoptosis. One of the initiator caspases, CASP8 (also known as FLICE), has been reported to play an important role in apoptosis (Ho and Hawkins, 2005). Given the role of CASP8 in apoptosis, genetic variants of CASP8 that can alter its function are likely to affect apoptosis in cancer cells.

Recently, many studies have reported that 2 common SNPs within the CASP8 promoter gene, -652 6N del and D302H, are associated with many cancer types. The -652 6N del polymorphism (rs3834129) is a 6-nucleotide insertion-deletion substitution at nucleotides 657_652. The D302H polymorphism (rs1045485) is a G-C substitution at 1207 bp, which results in an aspartic acid to histidine exchange at position 302 in the amino acid sequence. Sun et al. (2007) first reported that the -652 6N del variant reduced the risk of developing many types of cancer including lung, esophageal, gastric, colorectal, cervical, and breast cancers (Sun et al., 2007). However, in subsequent studies, demonstration of the protective effect of -652 6N del failed to be replicated in several cancer

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types, including breast and prostate tumors (Cybulski. et al., 2007; Haiman et al., 2008). Interestingly, the variant genotype (del/del) of -652 6N del exhibited a trend of increased PCa risk in a North Indian population (George et al., 2010; Kesarwani et al., 2011). In contrast, the same variant was highly associated with reduced PCa risk in a Chinese population (Fu et al., 2011). In contrast to -652 6N del, the D302H H variant has demonstrated a consistent protective effect for breast carcinoma risk (Sergentanis and Economopoulos, 2010). However, the association of D302H with PCa risk has been inconclusive. Lubahn et al. and Meyer et al. reported that the D302H polymorphism may play a protective role against PCa (Lubahn et al., 2010; Meyer et al., 2013); whereas, in a North Indian population, the H variant allele was associated with increased PCa risk (George et al., 2010).

Inconsistencies in the association of CASP8 polymorphisms with PCa risk may be attributable to different ethnicities. Therefore, we performed a meta-analysis to further evaluate the association of D302H and -652 6N del with PCa risk.

Materials and Methods

Literature search

We performed a literature search using the following keywords "CASP8 [MeSH]", "prostate cancer [MeSH]", and "polymorphism" or "variation" or "mutation" in PubMed, Cochrane Library, and Web of Science databases. All eligible studies were published before July 1st, 2014. The reference lists of review and retrieved articles were hand searched at the same time. Abstracts, unpublished reports, and articles written in non-English languages were not considered. When overlapping data of the same patient population were included in more than 1 publication (sending email to the communication author to confirm this), only the most recent or complete study was used in the meta-analysis.

Inclusion and exclusion criteria

The following inclusion criteria were used to select literature for the meta-analysis:

(1) information on the evaluation of CASP8 -652 6N del or CASP8 D302H polymorphisms and PCa susceptibility; (2) case-control studies; and (3) studies with sufficient genotype data to calculate odd ratios (ORs) with 95% confidence intervals (CIs). Major criteria for study exclusion were: (1) no controls; (2) reviews and duplication of the previous publication; and (3) no usable data reported.

Data extraction

Two of the authors independently extracted the study information from all eligible publications based on the inclusion criteria above. Any discrepancies regarding study inclusion were resolved by discussion, and a third party was involved when necessary. The following characteristics were recorded from each study: the name of the first author, publication year, ethnicity of the population, and genotype frequencies of -652 6N del and D302H polymorphisms in both PCa cases and controls. Ethnic descent was categorized into the following groups: Caucasian, Indian, East Asian, African, and other. For case-control studies, data were extracted separately for each group whenever possible.

Statistical analysis

Crude ORs with the corresponding 95% CIs were used to detect the strength of the association of -652 6N del and D302H polymorphisms with PCa risk. For both CASP8 polymorphisms, the relationship between genotypes and PCa susceptibility was evaluated using co-dominant, recessive, over-dominant, and dominant genetic models. The relationship between alleles and PCa susceptibility was also examined using an allelic model. A Z-test was used to determine the significance of the overall OR, and $P<0.05$ was considered statistically significant. Between-study heterogeneity and between-study inconsistency were evaluated using Cochran's Q statistic and estimating I^2, respectively (Higgins et al., 2003). $P<0.10$ was considered statistically significant heterogeneity, and I^2 was used to qualify variation in OR attributable to heterogeneity. In studies without substantial heterogeneity (Q-test $P\geq0.10$ or I^2 <50%), the fixed effects model (Mantel-Haenszel method) was used to estimate the overall OR (Mantel and Haenszel, 1959). The random effects model (DerSimonian and Laird method) was used in studies with substantial heterogeneity (DerSimonian and Laird, 1986). In addition to the comparison among all subjects, stratification analyses by ethnicity were performed to explore the reasons for heterogeneity. To adjust for multiple comparisons, we applied the Benjamini-Hochberg (BH) method (Benjamini and Hochberg, 1995) and stepdown Bonferroni method (Holm, 1979), which control for false discovery rate (FDR) and familywise error rate (FWE), respectively. One-way sensitivity analyses were performed to assess the stability of the results. To investigate the potential publication bias, both visual funnel plot and Egger's linear regression test were applied, and $P<0.05$ was considered statistically significant. All statistical analyses were performed mainly using STATA version 12.0 (Stata Corp, College Station, TX, USA) and R package version 3.1.0.

Results

Eligible studies

Based on our inclusion criteria, 13 eligible independent studies in 7 reports were identified. Three of the reports contained data on different ethnic groups or variants (Haiman et al., 2008; George et al., 2010; Lubahn et al., 2010). Thirteen available studies with 5423 cases and 6994 controls were finally included in the meta-analysis. Among these 13 studies, 9 studies were eligible for the -652 6N del polymorphism (3955 PCa cases, 4241 controls) and 4 studies were eligible for the D302H polymorphism (1468 PCa cases, 2753 controls). The characteristics of the eligible studies are summarized in Table 1 and Table 2, respectively.

Meta-analyses

In the overall analysis, the -652 6N del polymorphism

Table 1. Characteristics of Eligible Studies For -652 6N Del

Author, published year Country	Ethnicity	Matching criteria	Source of control	Genotyping methods	No. of Cases/Controls	Cases			Controls			HWE
						ins/ins	ins/del	del/del	ins/ins	ins/del	del/del	
Cybulski[6], 2007 Poland	Caucasian	Region	PB	PCR-ASA	485/965	139	236	110	274	499	192	Yes
Haiman[7], 2008 USA	Other	Age,BMI,smoking	PB	TaqMan	852/616	175	437	240	127	308	181	Yes
Haiman[7], 2008 USA	East Asian	Age,BMI,smoking	PB	TaqMan	707/709	497	194	16	502	187	20	Yes
Haiman[7], 2008 USA	Other	Age,BMI,smoking	PB	TaqMan	110/111	35	59	16	27	58	26	Yes
Haiman[7], 2008 USA	Caucasian	Age,BMI,smoking	PB	TaqMan	617/607	246	275	96	257	269	81	yes
Haiman[7], 2008 USA	Caucasian	Age,BMI,smoking	PB	TaqMan	443/422	121	244	78	108	210	104	Yes
George[8], 2010 India	Indian	Age,smoking	PB	PCR-RFLP	165/208	84	69	12	116	83	6	Yes
Kesarwani[9], 2010 India	Indian	Age,smoking	HB	PCR-RFLP	170/198	86	72	12	109	83	6	Yes
Fu[10], 2011 China	East Asian	Age,smoking	HB	PCR-RFLP	406/408	257	132	17	211	159	38	Yes

PCR-ASA, Allele-Specific Amplification; **PCR-RFLP**, polymerase chain reaction-restriction fragment length polymorphism; **BMI**, body mass index; **HB**, hospital based; **PB**, population based; **HWE**, Hardy-Weinberg equilibrium; **Other**, Hawaii, African

Table 2. Characteristics of Eligible Studies For D302H

Author, published year	Country	Ethnicity	Matching criteria	Source of control	Genotyping methods	No. of Cases/Controls	Cases			Controls			HWE
							DD	DH	HH	DD	DH	HH	
George[8], 2010	India	Indian	Age,smoking	PB	PCR-PIRA	165/205	111	48	6	155	46	4	Yes
Lubahn[12], 2010	USA	Non-Indian	Age, PSA	PB	Direct Sequencing	150/359	137	11	2	305	52	2	Yes
Lubahn[12], 2010	USA	Non-Indian	Age, PSA	PB	Direct Sequencing	646/1701	524	117	5	1270	401	30	Yes
Meyer[13], 2010	Germany	Non-Indian	Age, PSA	HB	TaqMan	507/488	9	101	397	4	123	361	Yes

PCR-RFLP, primer-introduced restriction analysis; **PSA**, prostate antigen; **HB**, hospital based; **PB**, population based; **HWE**, Hardy-Weinberg equilibrium

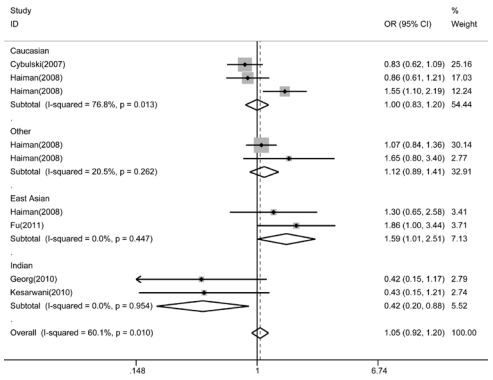

Figure 1. Forest Plot of Odd Ratios (ORs) of -652 6N Del Polymorphism Heterogeneous Co-Dominant Model (ins/del versus del/del) Associated with PCa Stratified by Ethnicity Using a Fixed-Effect Mode

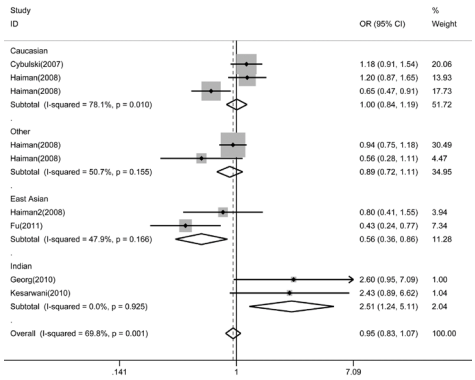

Figure 2. Forest Plot of Odd Ratios (ORs) of -652 6N Del Polymorphism Recessive Model (del/del *vs.* ins/ins+ins/del) Associated with PCa Stratified by Ethnicity Using a Fixed-Effect Mode

was not significantly associated with PCa risk in the dominant (ins/del+del/del *vs*. ins/ins), recessive (del/del *vs*. ins/ins+ins/del), heterogeneous co-dominant (ins/del *vs*. del/del), or over-dominant (ins/ins+del/del *vs*. ins/del) genetic models. Interestingly, in the stratified analysis by ethnicity, the ins/del versus del/del showed different effects among the Indian (OR=0.42; 95% CI=0.20-0.88; p=0.021; P_{bon}=0.063; P_{fdr}=0.042), East Asian (OR=1.59; 95% CI=1.01-2.51; P=0.047; P_{bon}=0.144; P_{fdr}=0.094) and Caucasian (OR=1.03; 95% CI=0.70-1.51; P=0.899; P_{bon}=1; P_{fdr}=0.919; Figure 1) populations in the heterogeneous co-dominant model. Further investigation using the recessive model showed a significant positive association of the -652 6N del polymorphism with PCa risk in the Indian population (OR=2.51; 95% CI=1.24-5.11; P=0.001; P_{bon}=0.044; P_{fdr}=0.042), whereas the -652 6N del polymorphism was negatively associated with PCa risk in the East Asian population (OR=0.56; 95% CI=0.36-0.86; P=0.008; P_{bon}=0.032; P_{fdr}=0.032; Figure 2 and Table 3).

The pooled meta-analysis results for the D302H polymorphism were similar to those for the -652 6N del polymorphism; the D302H polymorphism was not significantly associated with PCa risk in the dominant (DH+HH *vs*. DD), recessive (DD *vs*. HH+DH), heterogeneous co-dominant (DH *vs*. DD), or

Table 3. Meta-Analysis of the CASP8 -652 6N del Gene Polymorphisms On PCa Risk

Comparison	Population	Test of association					Mode	Egger's test	Heterogeneity
		OR	95%CI	*P*	*P* (BON)	*P* (FDR)		*P*	I^2
(ins/del+del/del) vs. ins/ins	Overall	0.97	0.88-1.07	0.514	1	0.824	F	0.785	47.70%
	Indian	1.23	0.92-1.64	0.169	0.338	0.225	F	-	0.00%
	East Asian	0.8	0.49-1.31	0.381	0.762	0.508	R	-	86.40%
	Caucasian	1.02	0.88-1.18	0.825	1	0.919	F	-	0.00%
del/del vs. (ins/del+ins/ins)	Overall	0.93	0.71-1.21	0.572	1	0.824	R	0.976	69.80%
	Indian	**2.51**	**1.24-5.11**	**0.011**	**0.044**	**0.042**	**F**	**-**	**0.00%**
	East Asian	**0.56**	**0.36-0.86**	**0.008**	**0.032**	**0.032**	**F**	**-**	**47.90%**
	Caucasian	0.98	0.67-1.43	0.919	1	0.919	R	-	78.10%
(del/del+ins/ins) vs. ins/del	Overall	1	0.91-1.09	0.998	1	0.998	F	0.899	0.00%
	Indian	0.96	0.72-1.29	0.809	0.809	0.809	F	-	0.00%
	East Asian	1.11	0.80-1.54	0.538	0.762	0.538	R	-	68.20%
	Caucasian	0.99	0.86-1.13	0.867	1	0.919	F	-	44.90%
ins/del vs. del/del	Overall	1.06	0.83-1.36	0.618	1	0.063	R	0.931	60.10%
	Indian	**0.42**	**0.20-0.88**	**0.021**	**0.063**	**0.042**	**F**	**-**	**0.00%**
	East Asian	**1.59**	**1.01-2.51**	**0.047**	**0.141**	**0.094**	**F**	**-**	**0.00%**
	Caucasian	1.03	0.70-1.51	0.899	1	0.919	R	-	76.80%

OR, odds ratio; **CI,** confidence intervals; **R**, random effects model; **F**, fixed effects model; **P (FDR)** *p* value from Benjamini-Hochberg method; **P (BON)** *p* value in stepdown Bonferroni testing; The values given in **bold** represent statistically significant results

Table 4. Meta-analysis of The Casp8 D302H Polymorphism On PCa Risk

Comparison	Population	Test of association					Mode	Egger's test	Heterogeneity
		OR	95%CI	*P*	*P* (BON)	*P* (FDR)		*P*	I^2
(DH+HH) vs. DD	Overall	0.77	0.47-1.28	0.317	0.705	0.317	R	0.97	73.60%
	Overall	0.76*	0.63-0.91	0.003	-	-	F	-	73.60%
	Indian	1.51	0.96-2.38	0.077	0.308	0.193	-	-	-
	Non-Indian	**0.66**	**0.53-0.81**	**<0.001**	**0.002**	**0.001**	**F**	**-**	**0%**
HH vs. (DD+DH)	Overall	1.17	0.90-1.52	0.249	0.705	0.317	F	0.892	45.80%
	Indian	1.9	0.53-1.83	0.335	0.354	0.335	-	-	-
	Non-Indian	0.97	0.42-2.25	0.952	0.952	0.952	R	-	60.20%
(DD+HH) vs. DH	Overall	1.27	0.92-1.75	0.152	0.608	0.317	R	0.861	66.70%
	Overall	1.31*	1.11-1.54	0.001	-	-	F	0.861	66.70%
	Indian	0.71	0.44-1.113	0.145	0.354	0.193	-	-	-
	Non-Indian	**1.43**	**1.20-1.70**	**<0.001**	**<0.001**	**<0.001**	**F**	**-**	**0%**
DH vs. DD	Overall	0.73	0.44-1.22	0.235	0.705	0.317	R	0.856	72.70%
	Indian	1.46	0.91-2.34	0.118	0.354	0.193	-	-	-
	Non-Indian	**0.66**	**0.53-0.82**	**<0.001**	**<0.001**	**<0.001**	**F**	**-**	**9.60%**

OR, odds ratio; CI, confidence intervals; **R**, random effects model; **F**, fixed effects model; **P (FDR)** *p* value from Benjamini-Hochberg method; **P (BON)** *p* value in stepdown Bonferroni testing; The values given in **bold** represent statistically significant results; the values marked with a * represent the results of the alternative approach (fixed effects despite heterogeneity)

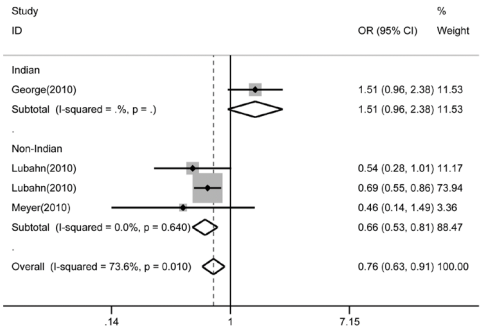

Figure 3. Forest Plot of Odd Ratios (ORs) of D302H Polymorphism Dominant Model (DH+HH *vs.* DD) Associated with PCa Stratified by Ethnicity Using a Fixed-Effect Mode

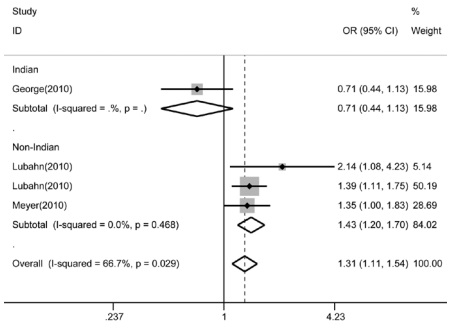

Figure 4. Forest Plot of Odd Ratios (ORs) of D302H Polymorphism Over-Dominant Model (DD+HH *vs.* DH) Associated with PCa Stratified by Ethnicity Using a Fixed-Effect Mode

over-dominant (DD+HH *vs*. DH) genetic models. On the other hand, subgroup analysis stratified by ethnicity demonstrated that the D302H polymorphism was a highly protective allele for PCa in the Non-Indian population in the dominant model (OR=0.66; 95% CI=0.53-0.81; $P<0.001$; $P_{bon}=0.02$; $P_{fdr}=0.01$; Figure 4) and over-dominant model (OR=1.43; 95% CI=1.20-1.70; $P<0.001$; $P_{bon}<0.001$; $P_{fdr}<0.001$; Figure 4). The detailed data are presented in Table 4.

Sensitivity analysis

Because eligible studies were not available for sensitivity analysis of the D302H polymorphism, a one-way sensitivity analysis across all ethnic groups was performed to evaluate the stability of the -652 6N del polymorphism data. The results of this analysis showed

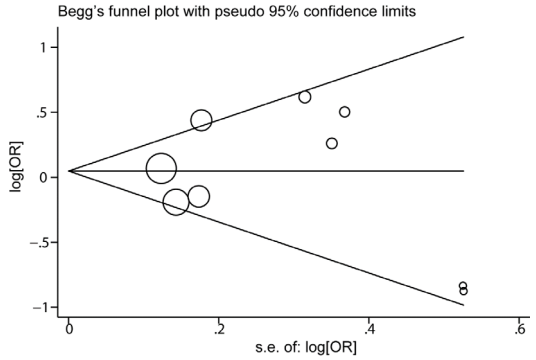

Figure 5. Begg's Funnel Plot for Publication Bias Test of -652 6N del (ins/del *vs.* del/del)

that statistical significance was not changed when any single study was omitted (data not shown). The results of the sensitivity analysis demonstrated that the -652 6N del polymorphism data in this meta-analysis were relatively stable and credible.

Publication bias

In the -652 6N studies, both the Begg's funnel plot (Figure 5) and Egger's test were performed to estimate publication bias. Because of the limited number of D302H studies, only Egger's test was performed. The results did not show any statistical evidence of publication bias (all $P>0.05$). Results of the publication bias test are shown in Table 3.

Discussion

To date, our study is the first meta-analysis to determine the association of CASP8 -652 6N del and D302H SNPs with PCa. The association of CASP8 -652 6N del and D302H SNPs with PCa risk was evaluated in 8196 and 4201 subjects, respectively. The lack of significant results in the pooled analysis suggested the absence of robust associations between the 2 SNPs and PCa. In the pooled analysis, both SNPs showed substantial heterogeneity in all the genetic models. The subgroup analyses based on ethnicity yielded more homogeneous genetic effects than the pooled analyses. The sensitivity analysis of the -652 6N del polymorphism indicated that our results were relatively robust.

Nowadays a number of studies have investigated association between CASP8 gene polymorphisms and risk of cancer. It is reported that CASP8 -652 6N del and D302H polymorphisms play a vital role in diversity tumors, such as lung cancer (Son et al., 2006), breast cancer (Cybulski. et al., 2007; Frank et al., 2008) and colorectal cancer (Wu et al., 2013). Sun et al. reported that the del allele of -652 6N del reduces T lymphocyte apoptosis by inhibiting the binding site for the transcriptional activator stimulatory protein 1 in the CASP8 promoter (Sun et al., 2007). This function of -652 6N del has been associated with increased immune surveillance (Sun et al., 2007). Therefore, individuals with the del allele may be less susceptible to tumorigenesis. However, different ethnicities may have distinct genetic backgrounds; therefore, tumor susceptibility can be influenced by ethnicity (Hirschhorn et al., 2002). The subgroup analyses revealed that the association of -652 6N del with PCa susceptibility was paradoxical among the different ethnicities. The subgroup analysis stratified by ethnicity indicated that -652 6N del was associated with increased PCa risk in subjects of Indian descent and with reduced PCa risk in subjects of East Asian descent. The -652 6N del polymorphism was not significantly associated with PCa susceptibility in subjects of Caucasian descent under any genetic model. With regard to D302H polymorphism, its functional effect is yet unknown. Between mouse and human, D302H map to an evolutionarily conserved region. This suggests that this variant can directly influence PCa rather than depending on an unknown linkage disequilibrium causative variant (Bethke et al., 2009). It has been suggested that the D302H polymorphism may affect the interaction of CASP8 with regulatory proteins (MacPherson et al., 2004; Bethke et al., 2009). Previous meta-analyses of the association of the D302H polymorphism with cancer risk have been inconclusive (Bethke et al., 2009; Sergentanis and Economopoulos, 2010). Meanwhile, Michailidou (Michailidou et al., 2013) and Turnbull (Turnbull et al., 2010) indicated that D302H variant in CASP8 may be a false positive association through recent GWAS studies. In the present meta-analysis, the protective effect of the D302H polymorphism for PCa risk was observed only in the Non-Indian population under over-dominant, heterogeneous co-dominant, and dominant models.

Given the complex etiology of cancer, PCa risk cannot be attributed to a single factor. Demographic patterns, lifestyle, hormonal influences, inflammation, Statin drugs, cholesterol, and genome wide variation play a role in prostate carcinogenesis. Considering the multitude of factors associated with PCa risk, the varied results of CASP8 polymorphisms and PCa risk among the different ethnicities in our meta-analysis is not surprising. It's worth noting that the rare allele of -652 6N del and D302H of CASP8 all have a trend of an increased risk of PCa in the Indian population. Meanwhile the rare allele of -652 6N del has a positive association with PCa in the Indian population, but a negative observation in the East Asian population. Previous studies on genetic association suggested that the characteristics of Indian population might be different from other Asian populations. A meta-analysis of p53 codon 72 polymorphism conducted by Zhou et al. indicated that Pro carrier showed significant associations with increased risk of cervical cancer among Indian populations, but not among Chinese, Japanese and Korean populations (Zhou et al., 2012). However, the study on KCNQ1 rs2237892 C→T gene polymorphism and type 2 diabetes mellitus in the Asian population demonstrated that a significant association was found in Chinese, Korean and Malaysia population, but not in Indian population (Li et al., 2014). The prevalence of prostate cancer and the allele frequencies differ across populations (Zhao et al., 2013), and some genes are specific in region and race, any conclusion concerning genetic effects should be carefully interpreted.

The limitations of our meta-analysis should be noted. First, although 9 -652 6N del studies were included in

the meta-analysis, the subgroup analysis was limited to 3 studies after stratification by ethnicity. The limited number of D302H studies in the subgroup analysis may have increased the risk of bias in the meta-analysis. Second, given that PCa is a multifactorial disease, confounding factors, such as age, tobacco smoking, PSA levels, clinical aggressiveness, and Gleason score, may have affected the associations between the 2 CASP8 polymorphisms and PCa risk. Finally, our analysis was based on unadjusted estimates. Adjusted ORs for the above risk factors should also be pooled to provide exact summary estimates. We were unable to perform these analyses because of the lack of individual data.

In conclusion, our meta-analysis demonstrated that the association of CASP8 -652 6N del and D302H polymorphisms with PCa risk may be influenced by ethnicity. The association of the -652 6N del polymorphism with PCa susceptibility was different among subjects of Asian descent. -652 6N del polymorphism was positively associated with PCa risk in the Indian population and negatively associated with PCa risk in the East Asian population. D302H polymorphism was associated with reduced PCa risk in the Non-Indian population. Given the limitations of our meta-analysis, confirmation of our findings in larger multicenter studies is warranted, especially between the Indian and East Asian populations.

Acknowledgements

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