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hOGG1 rs1052133 Polymorphism and Prostate Cancer Risk: A Chinese Case-Control Study and Meta-Analysis

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Background: We performed a case-control study and an updated meta-analysis to assess the relationship between the hOGG1 rs1052133 polymorphism and prostate cancer (PCa) risk.

Material/Methods: We recruited 160 PCa cases and 243 healthy controls. For the meta-analysis, relevant studies were recruited from diverse databases up to April 2022. Genetic risk was evaluated by using an odds ratio (OR) with a corresponding 95% confidence interval (95% CI). The genotypes of this polymorphism were genotyped via the SNaPshot genotyping method.

Results: In the case-control study, we failed to identify any association between the hOGG1 rs1052133 polymorphism and PCa risk. Negative results were also obtained when stratified analyses were performed based on the patient's prostatic-specific antigen (PSA) level and Gleason score, as well as tumor, node, and metastasis (TNM) stage. To enlarge the sample size, we performed a restricted updated meta-analysis by recruiting 10 case-control studies (including the current one), and the results suggested that genotypes of rs1052133 polymorphism were significantly associated with an elevated risk of PCa in 2 genetic models – the heterozygote and dominant models. In the stratification analysis by population ethnicity, a significant association of this polymorphism with susceptibility to PCa was found both in the Asian populations and White populations.

Conclusions: Our case-control and updated meta-analysis study suggest that the hOGG1 rs1052133 polymorphism is a susceptibility factor for PCa, but still needs to be further verified in the Chinese population.

Keywords: Oxoguanine Glycosylase 1, Human • Polymorphism, Genetic • Prostatic Neoplasms

Full-text PDF: <https://www.medscimonit.com/abstract/index/idArt/938012>

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Background

The role of DNA damage in tumor formation and development is well established [1]. As a result of oxidative stress, inflammation, or environmental carcinogens, DNA damage can accumulate in the prostate, possibly increasing the risk for prostate cancer (PCa) [2-4]. The base excision repair (BER) pathway is the most often-used approach for removing minor damage from DNA. Despite its structural independence, it is also crucial in cellular defense against many types of DNA lesions [5,6].

The human 8-oxoguanine glycosylase 1 (hOGG1) gene, located on chromosome 3p26, plays an essential role in DNA damage repair by initiating the BER pathway [7-9]. Rs1052133 is a commonly occurring polymorphism in hOGG1, and also referred to as Ser326Cys polymorphism. Cysteine can be substituted by serine at 326 amino acids of hOGG1 protein. Notably, there is an altered susceptibility for diverse cancer types related to its genotypes [10-12].

In recent years, the hOGG1 rs1052133 polymorphism has been often investigated in relation to PCa across diverse ethnic populations, but the results were inconsistent [13-24]. Here, we assessed whether genotypes of the hOGG1 rs1052133 polymorphism were related to an elevated PCa risk in a Chinese Han population. Additionally, we performed a comprehensive updated meta-analysis of published investigations to determine the exact relationship between them.

Material and Methods

Case-Control Study

Selection of Eligible PCa Cases and Healthy Controls

We enrolled 160 PCa patients and 243 healthy controls from the First Affiliated Hospital of Anhui Medical University between January 2016 and December 2020. A biopsy or postoperative pathology of transurethral resection prostate (TURP) was used to diagnose PCa patients within 1 year of enrollment. In the present study, patients pathologically confirmed to have prostate adenocarcinoma were enrolled for subsequent analysis. Prior to invasive manipulation, PSA levels were assessed, excluding those patients who had received endocrine therapy. Gleason grades were determined by biopsy or radical prostatectomy. Based on the radical prostatectomy specimens or the results of computed tomography, magnetic resonance imaging, or bone scans, the tumor stage was determined. All the controls were cancer-free individuals who underwent regular physical examinations at the hospital. Study controls with serum PSA levels >4 ng/ml were excluded to rule out prostate cancer. The investigators excluded patients with incomplete

medical records. The Research Ethics Committee at the First Affiliated Hospital of Anhui Medical University approved the study. Furthermore, each participant signed an informed consent form in duplicate.

Genotyping

Commercially available DNA extraction kits (Cat. No. 51106; Qiagen, Inc., Valencia, CA) were used to extract DNA from each participant's blood sample. The site sequence of the hOGG1 rs1052133 polymorphism was obtained from the NCBI db SNP database. For each DNA sample, the hOGG1 rs1052133 polymorphism was detected by using the SNaPshot SNP assay by Shanghai Tianhao company (Shanghai Tianhao Industrial Co., Ltd., Shanghai, China) [25,26]. We used the Multiplex SNaPshot technology (Applied Biosystems, Foster City, CA, USA) to determine the genotype of hOGG1 gene. Primer3 online software (v.0.4.0) (<http://frodo.wi.mit.edu/primer3/>) was used to design the primers for PCR and the SNaPshot extension reactions based on the sequences provided in dbSNP (<http://www.ncbi.nlm.nih.gov/SNP>) (rs1052133F: CCAGGTGGCCCTAAAGGACTCT; rs1052133R: GTGGGATGGGAGAGAGAAGT; primer extension: TGGCTCTGAGCATGGCGG). The products were sequenced by ABI3130XL Sequencer (Applied Biosystems, Foster City, CA, USA), and GeneMapper 4.0 (Applied Biosystems, Foster City, CA, USA) was used to analyze the data. The type of nucleotide presented in the SNP locus was used to determine the genotype of each sample, which was analyzed by 1 or 2 distinct colored peaks on the graph.

Statistical Analysis for Real-World Cohort

Differences between the 2 groups were determined using the 2-tailed unpaired *t* test. We presented the data as the mean±standard deviation (mean±SD), and *P* value less than 0.05 was deemed as statistically significant. The different distribution of genotypes of rs1052133 in the subgroups of PSA, Gleason score, and TNM stage were evaluated by chi-square test. Based on simple counting, genotypic and allelic frequencies were determined. We compared Hardy-Weinberg equilibrium (HWE) test results, genotype frequencies (CC, G/C, and GG), and distributions between cases and controls. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were generated for each comparison to reveal its risk to prostate cancer. Procedures of statistical analyses were performed using SPSS version 17.0 (SPSS, Inc., Chicago, United States).

Meta-Analysis

The meta-analysis was performed following the PRISMA Statement [27]. **Figure 1** shows the whole process of the study.

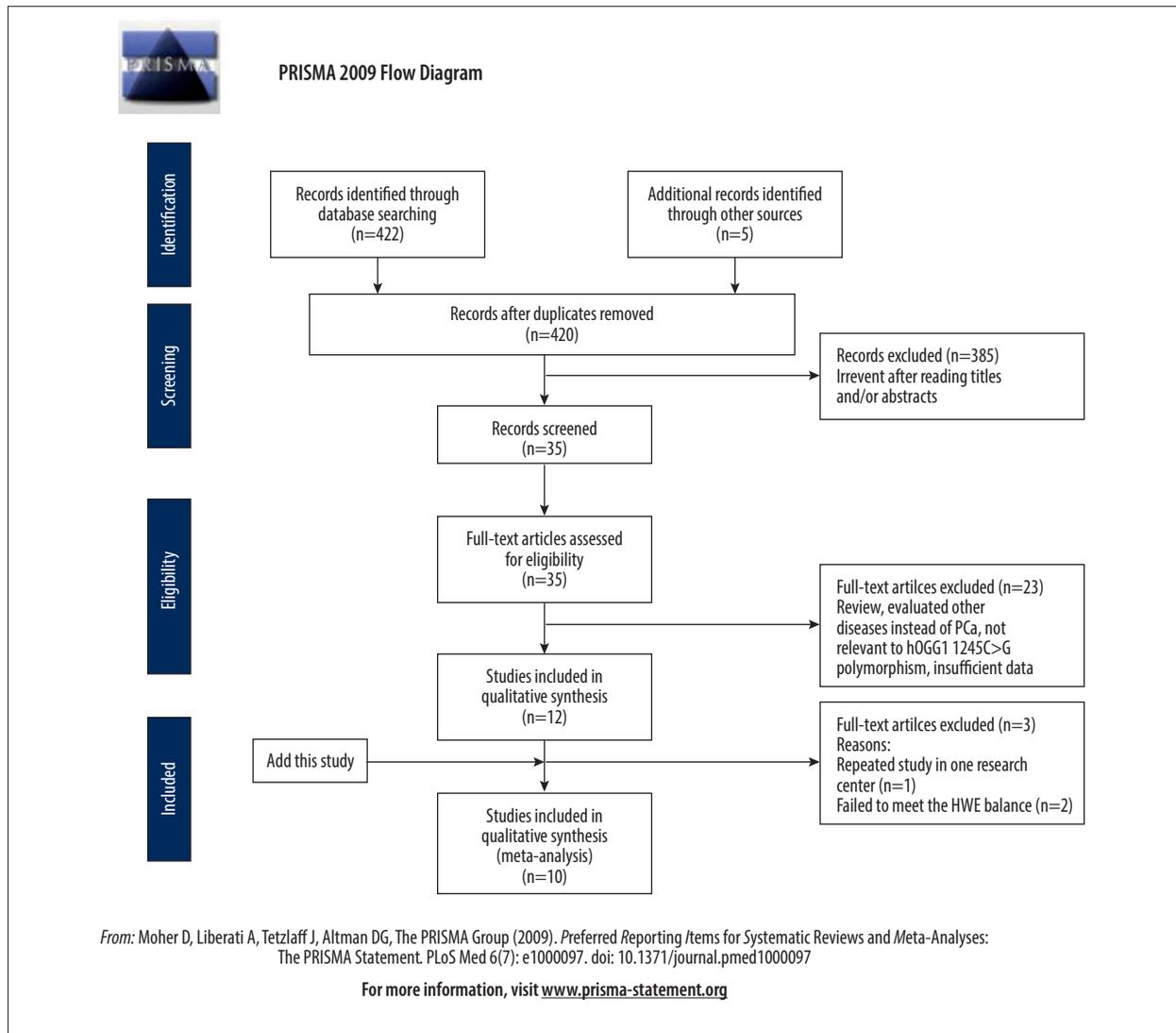


Figure 1. Flowchart of our meta-analysis study. (PowerPoint, v2020, Microsoft Co. Ltd.).

Publication Search

Our electronic literature search utilized PubMed, Web of Science, and EMBASE to find all eligible studies that evaluated the risk associated between the hOGG1 rs1052133 polymorphism and the risk of PCa up to April 2022. In this search, the following MeSH terms and keywords were employed: (“PCa” OR “prostate cancer” OR “prostate tumor” OR “prostate adenocarcinoma” OR “prostate neoplasm”) AND (“hOGG1” OR “human 8-oxoguanine DNA glycosylase 1”) AND (“gene” OR “polymorphism” OR “variant” OR “allele” OR “mutation”) AND (“rs1052133” OR “Ser326Cys” OR “1245C>G” OR “C8069G”). The entire search process was conducted in English. If the same population was presented in multiple publications, only the publication with the largest sample size was enrolled.

Inclusion and Exclusion Criteria

Eligible studies were recruited to the meta-analysis when the following criteria were reached: (1) a case-control study; (2) a cohort study; (3) evaluation of the presence of the rs1052133 polymorphism and the risk of PCa; (3) adequate data were available; and (4) genotype distributions following Hardy-Weinberg equilibrium (HWE).

Accordingly, we excluded studies with the following characteristics: (1) cross-sectional cohort studies published in other languages, non-original studies, dissertations, and thesis studies; (2) insufficient data or studies lacking genotype distribution data; and (3) study was not relevant to hOGG1 rs1052133 or the PCa polymorphism. Author(s), publication date, country, ethnicity, examined genes (SNPs), sample number, genotyping method used, genotypic frequencies, and allelic frequencies

were collected. Two reviewers (HJX and MZ) independently evaluated the qualities of enrolled studies in our meta-analysis. The qualities of the included studies were assessed by the Newcastle-Ottawa Scale (NOS) score method [28] from the different aspects, including selection, comparability, exposure/outcome (**Supplementary Table 1**).

Meta-Analysis

Genotype models (the heterozygote, homozygote, dominant, and recessive genetic models) were employed to determine the correlation of the hOGG1 rs1052133 polymorphism with PCa risk by using the crude OR with related 95% CI.

We determined the methods to calculate the OR from the χ^2 -based Q-test and checked the heterogeneity of the current study. If $P>0.1$ indicated that the Q-tests were not heterogeneous, then the ORs were obtained by using the Mantel-Haenszel method (fixed effects). As an alternative, the DerSimonian and Laird model was used to check the significance of a pooled OR. We performed a stratification analysis by ethnicity (White, Asian, and mixed populations). Moreover, a visual assessment of publication bias was performed by inspecting Begg’s funnel plot for asymmetry, as well as the Egger’s linear regression test. There is a possibility of publication bias when $P\leq 0.05$ and the scheme is considered to be asymmetric. We used STATA 12.0 software (Stata Corp., College Station, TX) to conduct the statistical analyses. We considered two-sided P values <0.05 to be statistically significant.

Results

Case-Control Study

Demographic Features

The average age in the PCa group was 70.09 ± 7.14 years compared to 71.30 ± 8.80 years in the negative control group (t test, $P=0.148$). In the PCa group, 46 (28.75%) subjects showed a

Table 1. Comparison of clinical pathological characteristics between prostate cancer cases and controls.

Characteristics	Controls	Cases	P-value*
Number	243	160	
Age, (years \pm SD)	71.30 \pm 8.80	70.09 \pm 7.14	0.148
PSA level (n)			
4<n<10 ng/ml	/	46 (28.75)	
10 \leq n \leq 20 ng/ml	/	50 (31.25)	
>20 ng/ml	/	64 (40.00)	
Gleason score (n)			
6	/	29	
7		70	
8		30	
9		26	
10	/	5	
TNM stage (n)			
T1N0M0		5	
T2N0M0		104	
T2N0M1		4	
T2N1M0		7	
T2N1M1		1	
T3N0M0		15	
T3N0M1		3	
T3N1M0		9	
T3N1M1		4	
T3NxM0		1	
T3NxM1		1	
T4N1M0		1	
T4N0M1		1	
T4N1M1		5	
T4NxM1		1	

* t-test. PSA – prostatic specific antigen; SD – standard deviation; n – number; TNM – Tumor, Nodes, Metastases.

Table 2. hOGG1 (rs1052133) gene polymorphism in patients with prostate cancer and controls.

Parameter	Control N (%)	Case N (%)	OR (95% CI)	P-value
C/C	40 (16.46)	20 (12.50)	1 (Ref.)	
C/G	109 (44.86)	85 (53.13)	1.56 (0.86, 2.90)	0.151
G/G	94 (38.68)	55 (34.37)	1.17 (0.63, 2.23)	0.626
C/G+G/G	203 (83.54)	140 (87.50)	1.38 (0.78, 2.50)	0.276
C allele	189 (38.89)	125 (39.06)	1 (Ref.)	
G allele	297 (61.11)	195 (60.94)	0.99 (0.74, 1.33)	0.961

N – number; Ref. – reference.

Table 3. Correlation between hOGG1 (rs1052133) genotypes and different clinicopathological features of prostate cancer.

Genotype	PSA level, ng/ml					Gleason score				TNM			
	<10 (%)	10-20 (%)	>20 (%)	OR (95% CI)	P-value	≤7 (%)	>7 (%)	OR (95% CI)	P-value	≤T3 (%)	>T3 (%)	OR (95% CI)	P-value
CC	5 (10.9)	9 (14.1)	6 (12.0)	1 (Ref.)		11 (11.1)	9 (14.8)	1 (Ref.)		13 (10.9)	7 (17.1)	1 (Ref.)	
CG	23 (50.0)	40 (62.5)	22 (44.0)	1.02 (0.41, 2.53)	0.974	53 (53.5)	32 (52.5)	0.74 (0.28, 2.01)	0.545	63 (52.9)	22 (53.7)	0.65 (0.23, 1.91)	0.414
GG	18 (39.1)	15 (23.4)	22 (44.0)	0.57 (0.22, 1.46)	0.240	35 (35.4)	20 (32.8)	0.70 (0.25, 2.00)	0.498	43 (36.1)	12 (29.3)	0.52 (0.17, 1.64)	0.250
CG+GG	41 (89.1)	55 (85.9)	44 (88.0)	0.8 (0.33, 1.9)	0.609	88 (88.9)	52 (85.2)	0.72 (0.28, 1.90)	0.500	106 (89.1)	34 (82.9)	0.60 (0.22, 1.70)	0.308
C allele	33 (35.9)	58 (45.3)	34 (34.0)	1 (Ref.)		75 (37.9)	50 (41.0)	1 (Ref.)		89 (37.4)	36 (43.9)	1 (Ref.)	
G allele	59 (64.1)	70 (54.7)	66 (66.0)	0.71 (0.47, 1.08)	0.114	123 (62.1)	72 (59.0)	0.88 (0.55, 1.39)	0.580	149 (62.6)	46 (56.1)	0.76 (0.46, 1.27)	0.298

PSA – prostatic specific antigen; TNM – tumor node metastasis; OR – odds ratio; Ref. – reference; CI – confidential interval.

Table 4. Major features of eligible case-control studies recruited in the updated meta-analysis.

Author (ref.)	Date	Country	Race	Method	Case			Control			HWE
					CC	CG	GG	CC	CG	GG	
Xu et al	2002	USA	Mix	PCR	182	106	10	96	63	15	Y
Chen et al	2003	USA	Caucasian	RT-PCR	49	29	6	185	63	3	Y
Nam et al	2005	Canada	Mix	MS	593	350	53	617	386	89	N
Nock et al	2006	USA	Mix	PCR	280	135	24	305	142	31	N
Zhang et al	2010	USA	Mix	MS	126	61	4	118	71	7	Y
Lavender et al	2010	USA	African	TaqMan-PCR	132	58	4	452	173	21	Y
Dhillon et al	2011	Australia	Caucasian	PCR	38	57	21	69	50	12	Y
Mittal et al	2012	India	Asian	PCR	98	83	14	136	100	14	Y
Yun et al	2012	Korea	Asian	PCR	54	119	93	68	131	67	Y
Zhou et al	2013	China	Asian	PCR-RFLP	22	52	26	29	57	14	Y
Gong et al	2022	USA	Mix	PCR	354	227	33	423	229	37	Y
Xu et al	2022	China	Asian	Mass ARRAY	20	85	55	40	109	94	Y

Mix – from more than two races; HWE – Hardy-Weinberg equilibrium (Y means study consistent to HWE, and N means study did not consistent to HWE); PCR – Polymerase Chain Reaction; RT-PCR – real-time PCR; MS – mass spectrometry; PCR-RFLP – PCR-restriction fragment length polymorphism.

Table 5. Summary risk estimations for the relationship of the hOGG1 polymorphism and prostate cancer risk.

Comparison	Subgroup	N	P_H	P_Z	Random	Fixed
G vs C	Overall	10	0.000	0.102	1.173 (0.969-1.420)	1.142 (1.042-1.252)
GG vs CC	Overall	10	0.001	0.241	1.326 (0.828-2.126)	1.316 (1.052-1.645)
GC vs CC	Overall	10	0.216	0.014	1.172 (1.032-1.331)	1.172 (1.033-1.330)
GC+GG vs CC	Overall	10	0.019	0.047	1.227 (1.003-1.500)	1.182 (1.047-1.334)
GG vs GC+CC	Overall	10	0.002	0.427	1.177 (0.788-1.759)	1.175 (0.970-1.423)
G vs C	Asian	4	0.306	0.008	1.216 (1.033-1.432)	1.217 (1.052-1.409)
GG vs CC	Asian	4	0.541	0.004	1.593 (1.160-2.189)	1.593 (1.160-2.187)
GC vs CC	Asian	4	0.850	0.116	1.214 (0.951-1.549)	1.215 (0.953-1.550)
GC+GG vs CC	Asian	4	0.933	0.027	1.298 (1.030-1.637)	1.299 (1.030-1.638)
GG vs GC+CC	Asian	4	0.057	0.174	1.335 (0.880-2.024)	1.290 (1.012-1.645)
G vs C	Caucasian	3	0.000	0.317	1.395 (0.727-2.676)	1.238 (1.005-1.526)
GG vs CC	Caucasian	3	0.000	0.472	1.924 (0.323-11.461)	1.405 (0.850-2.322)
GC vs CC	Caucasian	3	0.025	0.186	1.430 (0.842-2.429)	1.309 (0.993-1.725)
GC+GG vs CC	Caucasian	3	0.001	0.242	1.500 (0.761-2.955)	1.313 (1.012-1.705)
GG vs GC+CC	Caucasian	3	0.000	0.559	1.612 (0.325-7.993)	1.239 (0.760-2.021)
G vs C	Mix	2	0.101	0.670	0.975 (0.709-1.342)	1.036 (0.881-1.219)
GG vs CC	Mix	2	0.316	0.891	0.971 (0.613-1.540)	0.969 (0.615-1.526)
GC vs CC	Mix	2	0.117	0.438	1.019 (0.704-1.474)	1.084 (0.884-1.327)
GC+GG vs CC	Mix	2	0.092	0.972	0.993 (0.674-1.463)	1.067 (0.878-1.297)
GG vs GC+CC	Mix	2	0.420	0.747	0.932 (0.594-1.461)	0.929 (0.593-1.454)

N – number; P_H – P -value of heterogeneity test; P_Z – P -value of Z-test; Mix – from two more races.

PSA level <10 ng/ml, 50 (31.25%) subjects showed a PSA level of 10-20 ng/ml, and 64 (40.00%) subjects showed a PSA level >20 ng/ml. The number of PCa cases whose Gleason score ≤ 7 was 99 (61.88%), and the number with a Gleason score >7 was 61 (38.12%). Moreover, there were 119 (74.38%) patients and 41 (25.62%) patients with stage <T3 and \geq T3, respectively. We summarized these features in **Table 1**.

Association of hOGG1 Genotypes with PCa Risk

The prevalence of the hOGG1 rs1052133 polymorphism in healthy controls followed HWE ($P=0.380$). As indicated, hOGG1 polymorphism was not correlated with an increased risk of PCa in the 4 genetic models in our case-control study (**Table 2**). We further analyzed the correlation between subgroups (PSA level, Gleason score, and TNM stage) in PCa cases to validate the correlation with the predictive risk of PCa (**Table 3**). However, none of these differences were statistically significant, which was possibly due to the limited sample size.

Meta-Analysis

Eligible Studies

Twelve eligible studies were found by using the selected keywords (**Table 4**) [13-24]; however, 1 repeated study was removed [19], and 2 studies that failed to meet the HWE balance were excluded [20,21]. Finally, 10 studies were included in the meta-analysis, including the data that were generated from the present case-control study.

Meta-Analysis

The detailed associations of the hOGG1 rs1052133 polymorphism with PCa susceptibility in all of the genetic models are presented in **Table 5**. The results showed that rs1052133 polymorphism was significantly related to an elevated PCa risk in 2 genetic models, including heterozygote (OR: 1.172, 95% CI: 1.033-1.330, $P=0.014$) and dominant models (OR: 1.227, 95% CI: 1.003-1.500, $P=0.047$). In the stratification

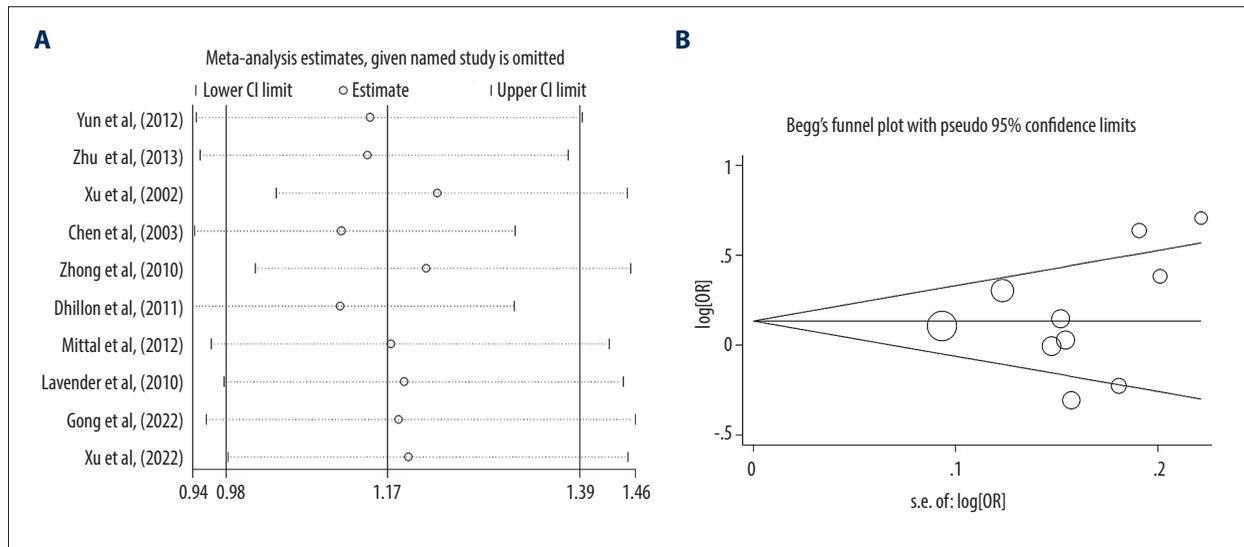


Figure 2. Sensitivity analysis and publication bias evaluation. (A) Sensitivity analysis plot (G vs C); (B) Begg's funnel plot (G vs C). (STATA, v12.0, StataCorp LP).

analysis by ethnicity, we observed a significant association of the rs1052133 polymorphism with susceptibility to PCa risk in Asian population in 3 genetic models, including allele (OR: 1.217, 95% CI: 1.052-1.409, $p=0.008$), heterozygote (OR: 1.593, 95% CI: 1.160-2.187, $P=0.004$), and dominant models (OR: 1.299, 95% CI: 1.030-1.638, $P=0.027$), and in White populations in all of the genetic models, but it should be noted that there were 2 studies with small sample sizes that were included (Table 5).

Moreover, the findings were stable and robust, which was supported by the sensitivity analysis after removing any of the individual studies (Figure 2A). Both the plot of Begg's funnel (Figure 2B) and test of Egger's regression analysis ($P>|t|=0.478$) suggested that no publication bias existed.

Discussion

In developed and developing countries alike, PCa is a malignancy that is strongly influenced by genetic factors. According to Yamane et al [29], the hOGG1 gene is an integral component of the DNA repair pathway. hOGG1-Cys326 (also termed rs1052133) was much less effective at preventing mutations in human cells than hOGG1-Ser326. Studies have suggested that the hOGG1 rs1052133 polymorphism may be important in determining PCa susceptibility. There is disagreement over the relationship between the rs1052133 polymorphism in hOGG1 and PCa susceptibility.

The first evidence for the increased prostate cancer risk of men with the CC genotype (Ser326) was presented by Xu et al [13] in 2002, which compared this genotype with homozygous GG men.

Similar findings have been confirmed in the Korean population [22] and White population [14]. Moreover, Dhillon et al [17] found that only G allele of the rs1052133 polymorphism was related to an elevated risk of PCa. In 2 studies that were conducted in the Chinese Han population, one study demonstrated that the hOGG1 rs1052133 polymorphism was correlated with an enhanced malignant potential of PCa [23], whereas the other study reported that this polymorphism was more associated with the risk of low-grade prostate cancer [24]. Lavender et al. [16] and Mittal et al. [18] proposed contrasting opinions that they failed to observe any significant association between the HOGG1 genotypes and PCa risk. These discordant and conflicting results may be due to limited sample sizes and different genetic backgrounds.

Several meta-analysis studies have made efforts to test the relationship of the hOGG1 rs1052133 polymorphism with PCa risk. Notably, our results are slightly different from those published studies via the improvement of some flaws [30-32]. In 2012, Zhu et al [30] performed a meta-analysis study, and they found that the rs1052133 polymorphism was related to an elevated risk of PCa in both Whites and Asians. However, in the study by Agalliu et al. [33], they focused on the rs3218997 polymorphism and PCa risk, which was incorrectly recruited and synthesized in the study by Zhu et al. [30]. In 2015, Chen et al [32] performed an updated meta-analysis comprising 11 studies. However, in the pooled analysis, their results failed to show any correlation between the rs1052133 polymorphism and PCa risk. Significant associations were only found in the Asian population. Two studies with duplicated samples were both enrolled, which would cause a potential bias [18,19]. Furthermore, for those studies that failed, the HWE balance should be removed from the pooled analysis. Thus, we aimed

to perform a case-control study and comprehensive updated meta-analysis to reveal the associations. In our case-control study, we failed to identify any positive results between the genotypes and PCa risk, which is a result consistent with most previous studies. Notably, based on the newly generated data from our case-control study, we performed a more rigorous and updated meta-analysis to determine the association of the rs1052133 polymorphism and PCa risk. Finally, we recruited 10 case-control studies, including 2218 PCa cases and 2946 controls. As a result, we obtained a positive correlation between the hOGG1 rs1052133 polymorphism and an elevated risk of PCa. Our meta-analysis identified a statistically significant correlation between the rs1052133 and PCa risk.

However, there were several shortcomings to be addressed in this study. First, this was a case-control study based in a hospital; thus, a selection bias should be considered. Additionally, our case-control study only analyzed the Chinese Han population

with small sample size; therefore, more research is needed to confirm these findings. Finally, the biological function of this polymorphism during the progression of PCa has not been investigated.

Conclusions

Our study indicates that the rs1052133 polymorphism in hOGG1 is related to an elevated risk of PCa. However, more studies are necessary to examine their precise effects and the genuine associations between them in different countries and ethnicities.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors, who confirm that the images are original with no duplication and have not been previously published in whole or in part.

Supplementary Table

Supplementary Table 1. The NOS scores of the included eleven studies.

Study	Selection		Comparability		Exposure/outcome	
	Researcher 1	Researcher 2	Researcher 1	Researcher 2	Researcher 1	Researcher 2
Chen et al, 2003	***	****	**	**	**	***
Xu et al, 2002	**	***	**	*	***	***
Zhang et al, 2010	***	***	**	**	**	**
Lavender et al, 2010	****	****	**	**	***	***
Dhillon et al, 2011	***	***	**	**	***	**
Mittal et al, 2012	***	***	**	**	***	**
Yun et al, 2012	***	***	*	*	**	**
Zhou et al, 2013	***	***	**	**	**	**
Gong et al, 2022	***	***	**	**	***	***
Xu et al, 2022	***	***	**	**	**	**

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