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Meta Analysis

Association between the rs1042522 polymorphism in *TP53* and prostate cancer risk: An updated meta-analysis

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Abstract

Objective: The proposal of the present study was to investigate whether the *TP53* rs1042522 polymorphism confers susceptibility to prostate cancer (PCa), by performing an updated meta-analysis.
Methods: Eligible publications investigating the association between the *TP53* rs1042522 polymorphism and PCa susceptibility were selected from PubMed, Google Scholar, and Web of Science. We used STATA 12.0 software to conduct the analyses. Odds ratio (*OR*) with 95% confidence interval (*CI*) was calculated.
Results: A total of 17 case−control studies were retrieved reporting a total of 2683 cases and 2981 controls. However, no significant association was uncovered between the *TP53* rs1042522 polymorphism and PCa susceptibility in the overall population under the five genetic models. In the stratification analysis by source of control, an increased susceptibility to PCa was identified in the population-based (P-B) group (CG *vs.* GG: $OR = 1.48$, 95% *CI*: 1.24−1.77, $P < 0.01$; CC/CG *vs.* GG: $OR = 1.32$, 95% *CI*: 1.12−1.57, $P < 0.01$), whereas a decreased susceptibility was uncovered in the hospital-based (H-B) group (CG *vs.* GG: $OR = 0.67$, 95% *CI*: 0.46−0.96, $P = 0.03$; CC/CG *vs.* GG: $OR = 0.67$, 95% *CI*: 0.46−0.99, $P = 0.04$) under heterozygous and dominant model.
Conclusion: This study did not find an association between the *TP53* rs1042522 polymorphism and PCa susceptibility in the overall population and corresponding subgroup analyses except in the stratification analysis by source of control. The results suggest that the *TP53* rs1042522 polymorphism is not a risk factor for PCa.

Keywords: *TP53*; rs1042522; Polymorphism; Prostate cancer; Meta-analysis

Introduction

Prostate cancer (PCa) has been the second most common cancer in men around the world, with an estimated 220,800 newly diagnosed cases and 27,540 deaths in 2015 in the United States.[1] With the strong epidemiological evidence pointing to a hereditary component to the development of PCa, much research

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into causative genes has been explored. Linkage studies investigating possible high-risk loci leading to PCa development identified possible loci on several chromosomes. In a recent genome-wide association study (GWAS), researchers identified a total of 76 common susceptibility loci,[2] with more than 1000 additional common single nucleotide polymorphisms (SNPs) predicting susceptibility to PCa.[3,4]

Tumor protein p53 (*TP53*), which is located on chromosome 17p13, has been identified as one of the most commonly mutated genes in human cancers.[5] In addition, the rs1042522 (codon 72) polymorphism, which is located on exon 4 of *TP53*, leads to a CGC→CCC transition resulting in an Arginine (Arg) → Proline (Pro) amino acid substitution at position 72,[6] contributing to a variety of biochemical and biological features of p53. Several previous studies have elaborated the association between the *TP53* rs1042522 polymorphism and PCa susceptibility; however, the results are inconsistent. In 2014, Khan et al[7] conducted a meta-analysis comprising of 13 case–control studies and identified that the Arg coding G allele was significantly associated with an increased susceptibility to prostate adenocarcinoma in the Pakistani population ($P < 0.001$), a result consistent with another meta-analysis of six case–control studies by Zhang et al[8] that implicated the *TP53* codon 72 polymorphism in a low-penetrant susceptibility to PCa in Caucasians but not in Asians. As several more studies have been published since these meta-analyses were carried out, we conducted an updated meta-analysis to achieve a more accurate estimation of the association between the *TP53* rs1042522 polymorphism and PCa susceptibility.

Materials and methods

Selection of eligible studies

We retrieved studies from PubMed, Web of Science, and Google Scholar (the last search being made on June 5, 2016) using the search terms "*TP53*," OR "*p53*," OR "codon 72," AND "prostate," AND "carcinoma," OR "neoplasm," OR "tumor," OR "cancer," AND "polymorphism," OR "variant", OR "mutations." Our search was limited to studies written in English. In addition, we adopted the PubMed option "relevant articles" for each study to search for additional possibly eligible studies. Reference lists of Reviews or Comments related to *TP53* were also checked for additional studies.

Inclusion and exclusion criteria

Studies were included when they satisfied the following criteria: (1) studies assessing the relationship between the *TP53* rs1042522 polymorphism and PCa susceptibility, (2) studies designed in a case–control format, and (3) availability of data regarding the genotype frequency of the cases and controls. Studies were removed when they were: (1) case-only studies, review articles, comments, and case reports; (2) studies without the raw data regarding the *TP53* rs1042522 polymorphism; (3) repetitive studies; (4) animal studies.

Data extraction

Two reviewers scrutinized studies on the associations between the *TP53* rs1042522 polymorphism and PCa. We discussed any discrepancies, making sure that all the controversies reached a consensus. In addition, we extracted the following details: the name of the first author, year of publication, ethnicity of the sample, sample size for the cases and controls, genotype frequency, and *P* value for the Hardy-Weinberg equilibrium (HWE).

Statistical analysis

We calculated odds ratios (*OR*s) with 95% confidence interval (95% *CI*s) to evaluate the strength of the association between the *TP53* rs1042522 polymorphism and PCa susceptibility. A total of five genetic models were selected, including allele contrasts (C *vs.* G), additive genetic (CC *vs.* GG & CG *vs.* GG), recessive genetic (CC *vs.* CG/GG) and dominant genetic (CC/CG *vs.* GG) models. We also conducted stratified analyses by ethnicity, source of control and the genotyping method. Heterogeneity was detected by a Chi-square based *Q* statistic test. When heterogeneity existed ($P < 0.10$, $I^2 > 50\%$), the random effects model was adopted to calculate pooled *OR*s[9]; otherwise, a fixed effects model was selected. A Chi-square goodness-of-fit test was also performed to calculate the HWE in the control groups; if the *P* value was larger than 0.05, the HWE balance was reached. Sensitivity analyses were further performed to assess the stability of the included data; this involved individual case–control studies being excluded from the pooled data to identify the influence of the respective data set on the pooled *OR*s ($P < 0.05$ was regarded as statistically significant).[10] We used Begg's funnel plot and Egger's test to look for publication bias,[11,12] with $P < 0.05$ being regarded as statistically significant. We

used STATA Version 12.0 (StataCorp, College Station, Texas, USA) to conduct all the statistical analyses, and $P < 0.05$ was considered statistically significant for any tests or genetic models.

Results

Study inclusion and study characteristics

After careful application of the inclusion criteria, a total of 17 publications were entered into our meta-analysis, including 2683 cases and 2981 controls. We present a flow chart of the study screening process in Fig. 1. The included studies and their main features are summarized in Table 1.[7,13–28] The meta-analysis included 10 studies of individuals with Caucasian ethnicity, 6 of Asian, and one of African. Thirteen studies were performed by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP), three by polymerase chain reaction (PCR) and one was conducted by TaqMan assay. The majority of the controls were sex- and age-matched. Of the studies, 10 were population-based (P-B) and 7 hospital-based (H-B). Notably, there were 5 case–control studies that deviated from the HWE (Table 1).[7,13,14,24,28]

Meta-analysis

We summarize the main results of the present meta-analysis and the heterogeneity test in Table 2. As shown in Figs. 2–6, no significant association was identified between the *TP53* rs1042522 polymorphism and PCa susceptibility in the overall population under the five genetic models (C *vs.* G: $OR = 0.94$, 95% *CI*: 0.78–1.13, $P = 0.50$; CC *vs.* GG: $OR = 0.73$, 95% *CI*: 0.49–1.09, $P = 0.13$; CG *vs.* GG: $OR = 1.06$, 95% *CI*:

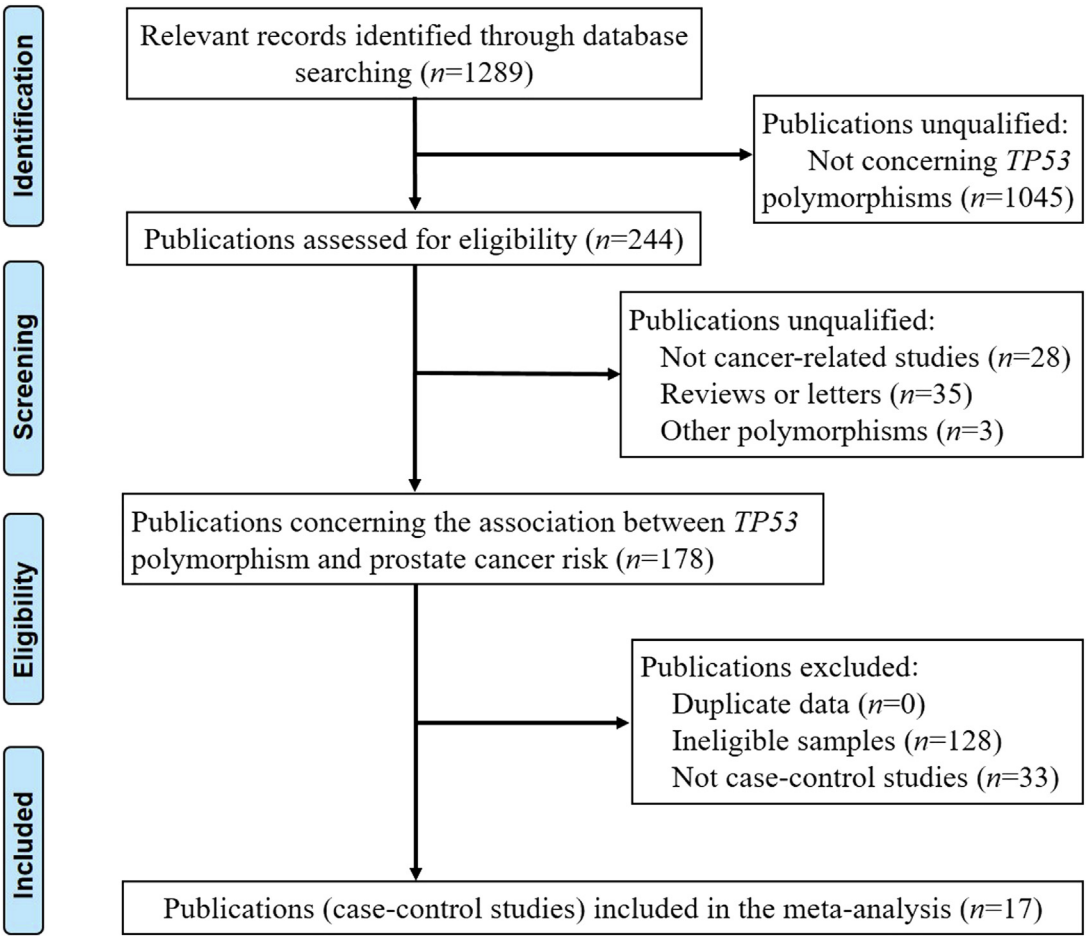

Fig. 1. Flow chart showing the study selection procedure.

Table 1
Characteristics of eligible case–control studies included in the meta-analysis.

Authors	Publication year	Ethnicity	Genotyping method	Source of control	*P* (HWE)	Case, *n*			Control, *n*		
						GG	GC	CC	GG	GC	CC
Henner et al[13]	2001	Caucasian	PCR	P-B	0.00	66	41	2	93	38	15
Suzuki et al[14]	2003	Asian	PCR-RFLP	H-B	0.03	20	46	48	7	57	41
Huang et al[15]	2004	Asian	PCR-RFLP	H-B	0.10	66	92	42	54	109	84
Wu et al[16]	2004	Asian	PCR	P-B	0.09	20	61	11	30	53	43
Leiros et al[17]	2005	Caucasian	PCR-RFLP	P-B	0.20	2	17	20	2	23	23
Quiñones et al[18]	2006	Caucasian	PCR-RFLP	H-B	0.33	14	24	22	13	45	59
Hirata et al[19]	2007	Asian	PCR-RFLP	P-B	0.98	22	89	56	26	80	61
Hirata et al[20]	2009	Asian	PCR-RFLP	P-B	0.98	20	75	45	26	80	61
Xu et al[21]	2010	Asian	PCR-RFLP	P-B	0.23	41	129	39	86	140	42
Ricks-Santi et al[22]	2010	African	PCR-RFLP	P-B	0.58	73	135	37	70	86	22
Mittal et al[23]	2011	Caucasian	PCR-RFLP	P-B	0.28	86	89	2	150	103	12
Doosti et al[24]	2011	Caucasian	PCR-RFLP	H-B	0.00	15	98	74	24	111	50
Rogler et al[25]	2011	Caucasian	PCR-RFLP	H-B	0.42	9	44	65	11	79	104
Bansal et al[26]	2012	Caucasian	PCR	P-B	0.12	21	33	51	23	61	22
Salehi et al[27]	2012	Caucasian	PCR-RFLP	H-B	0.55	18	37	13	23	45	17
Meyer et al[28]	2013	Caucasian	TaqMan	H-B	0.02	43	178	286	23	202	245
Khan et al[7]	2014	Caucasian	PCR-RFLP	P-B	0.00	27	101	18	16	28	63

HWE: Hardy-Weinberg equilibrium; PCR: polymerase chain reaction; P-B: population-based; PCR-RFLP: polymerase chain reaction-restriction fragment length polymorphism; H-B: hospital-based.

0.81–1.37, $P = 0.68$; CC/CG *vs.* GG: $OR = 0.98$, 95% *CI*: 0.78–1.25, $P = 0.89$; CC *vs.* CG/GG: $OR = 0.78$, 95% *CI*: 0.55–1.12, $P = 0.18$).

In the subgroup analysis by ethnicity, genotyping method and HWE status (Yes or No), there was also a lack of association between the *TP53* rs1042522 polymorphism and PCa susceptibility ($P > 0.05$) (Table 2).

Nevertheless, when the stratified analysis was conducted by source of control, a certain association was explored under heterozygous and dominant model. A contradictory relationship was detected between the two paired groups. Consequently, we identified an increased susceptibility in the population-based (P-B) group (CG *vs.* GG: $OR = 1.48$, 95% *CI*: 1.24–1.77, $P < 0.01$; CC/CG *vs.* GG: $OR = 1.32$, 95% *CI*: 1.12–1.57, $P < 0.01$), while a decreased susceptibility was uncovered in the hospital-based (H-B) group (CG *vs.* GG: $OR = 0.67$, 95% *CI*: 0.46–0.96, $P = 0.03$; CC/CG *vs.* GG: $OR = 0.67$, 95% *CI*: 0.46–0.99, $P = 0.04$) (Table 2).

Sensitivity analysis and publication bias

Sensitivity analyses were conducted to further evaluate the influence of the respective data on the integrated data through excluding one single data set from the pooled analyses one at a time; no single data set affected the pooled *OR*s under the allele model (Fig. 7). The similar results were obtained under the other models.

In addition, no significant publication bias was identified by the Begg's (C *vs.* G: $Z = 1.03$, $P = 0.30$; CC *vs.* GG: $Z = 0.04$, $P = 0.97$; CG *vs.* GG: $Z = 1.44$, $P = 0.15$; CC/CG *vs.* GG: $Z = 1.77$, $P = 0.08$; CC *vs.* CG/GG: $Z = 0.87$, $P = 0.39$) and Egger's test (C *vs.* G: $t = -0.87$, $P = 0.40$; CC *vs.* GG: $t = -0.69$, $P = 0.50$; CG *vs.* GG: $t = -1.42$, $P = 0.18$; CC *vs.* CG/GG: $t = -2.16$, $P = 0.06$; CC/CG *vs.* GG: $t = -1.60$, $P = 0.13$).

Discussion

Several studies have implicated the tumor suppressor gene *TP53* in the progression of many cancer types.[29,30] In addition, the polymorphism in codon 72 of *TP53* has been associated with susceptibility to a variety of diseases, including cancers.[31–36] This mutation is a G→C substitution at nucleotide position 313 that results in a change of Arg (CGC) to Pro (CCC). An *in vitro* study has shown that the TP53 Arg/Arg variant stimulates apoptosis and prevents proper transformation, compared to the Pro/Pro genotype.[37]

Although the association between the *TP53* polymorphism and PCa susceptibility has been investigated by several studies, results have been inconclusive. Khan et al[7] identified that Arg coding G allele was significantly associated with an increased susceptibility to prostate adenocarcinoma in the Pakistani population. This is consistent with Ricks-Santi et al's[22] finding that the p53 polymorphism may be associated with an increased risk of PCa. However, Henner et al[13] found

that men with the p53 codon 72 Pro/Pro genotype were at reduced risk of prostate cancer. Subsequently, three meta-analyses examined the association between the *TP53* rs1042522 polymorphism and PCa susceptibility.

Table 2
Results of meta-analysis for *TP53* rs1042522 polymorphism and prostate cancer risk.

Comparison	Subgroup	*n*	P_H	P_Z	*OR* (95% *CI*)
C *vs.* G	Overall	17	0.00	0.50	0.94 (0.78−1.13)
	Asian	6	0.00	0.33	0.88 (0.68−1.14)
	Caucasian	10	0.00	0.69	0.95 (0.72−1.25)
	PCR	3	0.00	0.96	1.02 (0.55−1.87)
	PCR-RFLP	13	0.00	0.43	0.92 (0.73−1.14)
	H-B	7	0.00	0.38	0.90 (0.70−1.14)
	P-B	10	0.00	0.83	0.97 (0.74−1.27)
	N	5	0.00	0.39	0.83 (0.54−1.28)
	Y	12	0.00	0.91	0.90 (0.81−1.20)
CG *vs.* GG	Overall	17	0.00	0.68	1.06 (0.81−1.37)
	Asian	6	0.00	0.80	1.07 (0.65−1.75)
	Caucasian	10	0.00	0.94	0.99 (0.69−1.41)
	PCR	3	0.07	0.58	1.19 (0.65−2.20)
	PCR-RFLP	13	0.00	0.45	1.12 (0.84−1.48)
	H-B	7	0.09	0.03	0.67 (0.46−0.96)
	P-B	10	0.39	<0.01	1.48 (1.24−1.77)
	N	5	0.00	0.84	0.93 (0.47−1.86)
	Y	12	0.02	0.36	1.13 (0.87−1.46)
CC/CG *vs.* GG	Overall	17	0.00	0.89	0.98 (0.78−1.25)
	Asian	6	0.00	0.83	0.95 (0.58−1.55)
	Caucasian	10	0.07	0.68	0.94 (0.71−1.25)
	PCR	3	0.99	0.49	1.13 (0.80−1.59)
	PCR-RFLP	13	0.00	0.96	0.99 (0.74−1.33)
	H-B	7	0.04	0.04	0.67 (0.46−0.99)
	P-B	10	0.59	<0.01	1.32 (1.12−1.57)
	N	5	0.02	0.40	0.81 (0.49−1.32)
	Y	12	0.01	0.63	1.07 (0.82−1.40)
CC *vs.* GG	Overall	17	0.00	0.13	0.73 (0.49−1.09)
	Asian	6	0.00	0.30	0.74 (0.41−1.32)
	Caucasian	10	0.00	0.18	0.65 (0.35−1.21)
	PCR	3	0.00	0.55	0.62 (0.13−2.96)
	PCR-RFLP	13	0.00	0.23	0.75 (0.48−1.20)
	H-B	7	0.01	0.12	0.67 (0.41−1.11)
	P-B	10	0.00	0.38	0.77 (0.42−1.39)
	N	5	0.00	0.13	0.49 (0.19−1.24)
	Y	12	0.00	0.50	0.87 (0.57−1.32)
CC *vs.* CG/GG	Overall	17	0.00	0.18	0.78 (0.55−1.12)
	Asian	6	0.00	0.14	0.75 (0.51−1.10)
	Caucasian	10	0.00	0.36	0.75 (0.42−1.35)
	PCR	3	0.00	0.60	0.57 (0.07−4.55)
	PCR-RFLP	13	0.00	0.19	0.77 (0.53−1.14)
	H-B	7	0.00	0.87	0.97 (0.70−1.35)
	P-B	10	0.00	0.17	0.64 (0.33−1.21)
	N	5	0.00	0.25	0.58 (0.23−1.46)
	Y	12	0.00	0.44	0.87 (0.61−1.24)

P_H: *P* value of *Q* test for heterogeneity test; P_z: *P* value of *Z* test; *OR*: odds ratio; *CI*: confidence interval; PCR: polymerase chain reaction; PCR-RFLP: polymerase chain reaction-restriction fragment length polymorphism; H-B: hospital-based; P-B: population-based; Y: studies conformed to Hardy-Weinberg equilibrium; N: studies not conformed to Hardy-Weinberg equilibrium.

In Zhang et al's[8] meta-analysis, they identified that *TP53* codon 72 polymorphism might be a low-penetrant risk factor for developing PCa in Caucasians but not in Asians. In the study conducted by Lu et al,[38] they concluded that Pro/Pro genotype of p53 codon 72 polymorphism was associated with increased risk for PCa, especially among Caucasians. Conversely, no association was explored between *TP53* polymorphism and PCa risk by Li et al.[39] However, their findings needed further validation in a larger population. Therefore, we performed the present meta-analysis to more conclusively determine whether the rs1042522 polymorphism in *TP53* was implicated in PCa. Nevertheless, no association between the *TP53* rs1042522 polymorphism and PCa susceptibility was identified in the overall population under the five genetic models, a result that is consistent with that of a previous study.[39] However, when the stratified analyses were conducted by source of control, we identified an increased susceptibility in the P-B group, while a decreased susceptibility was uncovered in the H-B group under co-dominant and dominant models. We suggest that the discrepancy was possibly due to the relatively small sample sizes of existing studies that may be underpowered to identify a marginal influence. In addition, several random factors, including the matching standard, selection bias, adjustments in statistical analyses and publication bias may all be implicated. We also conducted a stratification analyses by ethnicity and genotyping method, but identified no association.

Although we performed a comprehensive search for all eligible publications, there are several limitations that should be considered concerning the present meta-analysis. Firstly, we included a limited number of case−control studies with small sample sizes, leading to insufficient power to identify a potential marginal influence of the polymorphism on PCa. Secondly, the majority of the included studies had enrolled individuals from the Caucasian population, with only one study of the African population eligible for inclusion in this study. Thirdly, the controls in these studies were not uniformly defined. Several studies were designed as P-B while others were H-B, which might not be representative of the general population. Fourthly, the language of included studies was restricted to English, which may have resulted in a potential bias. In addition, because of the lack of raw data, we could not conduct further analyses to assess the roles of several specific environmental or lifestyle factors, such as diet, alcohol consumption, and smoking status.

Taken together, no association was explored in overall population as well as the corresponding

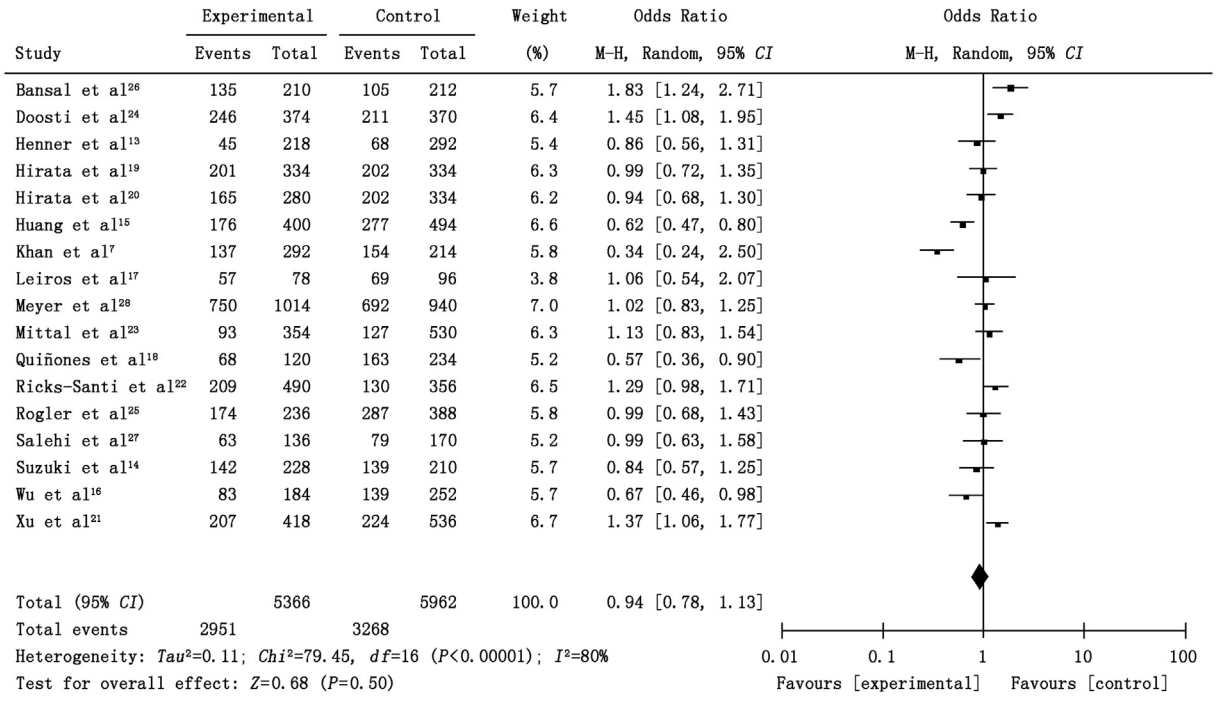

Fig. 2. Forest plot for the meta-analysis of the association between *TP53* rs1042522 polymorphism and prostate cancer risk under allele model (C *vs.* G).

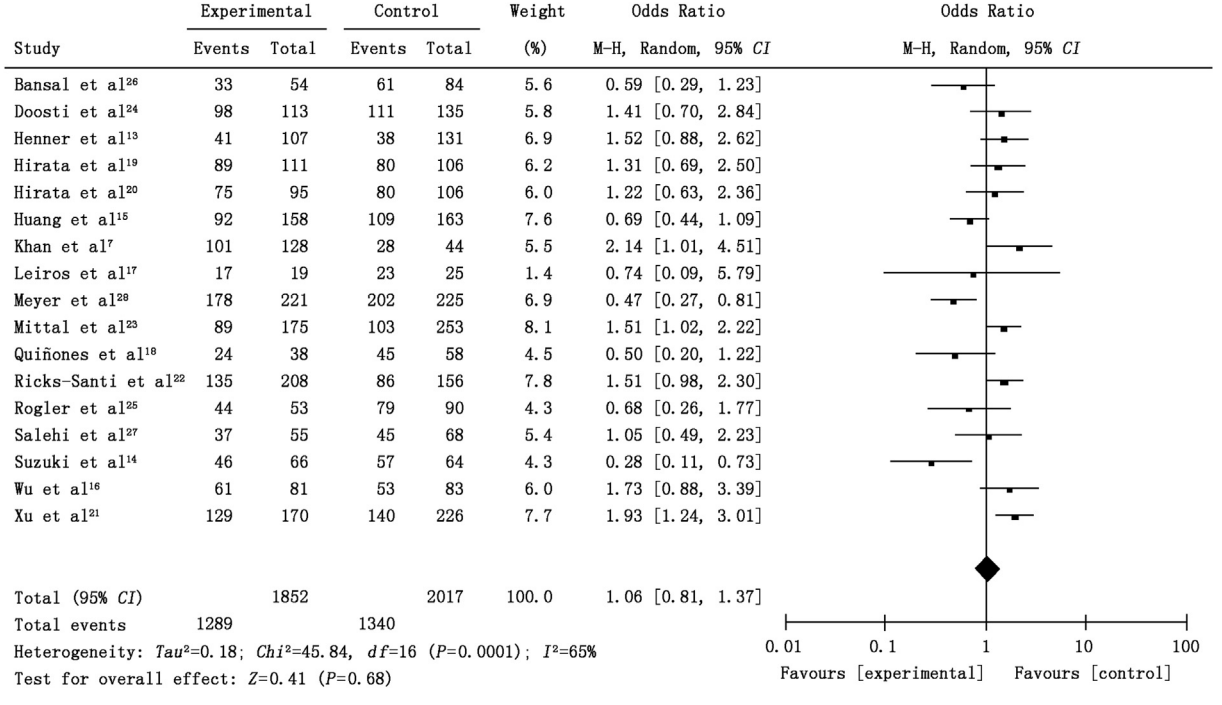

Fig. 3. Forest plot for the meta-analysis of the association between *TP53* rs1042522 polymorphism and prostate cancer risk under heterozygous model (CG *vs.* GG).

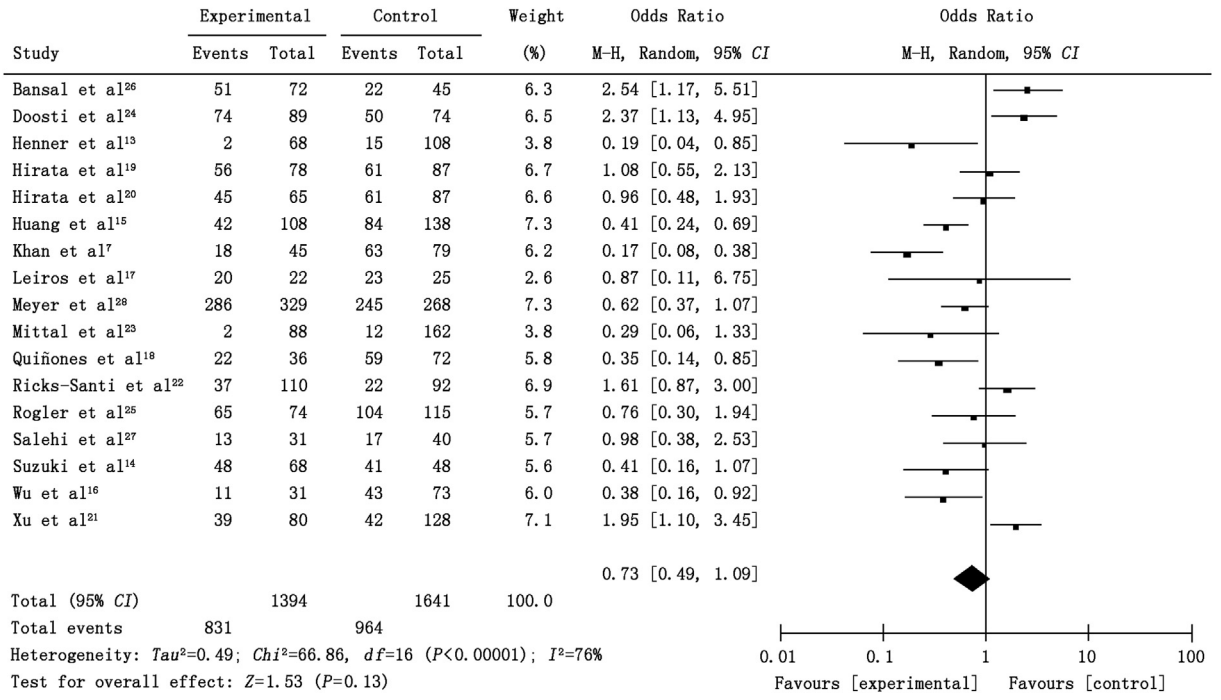

Fig. 4. Forest plot for the meta-analysis of the association between *TP53* rs1042522 polymorphism and prostate cancer risk under homozygous model (CC *vs.* GG).

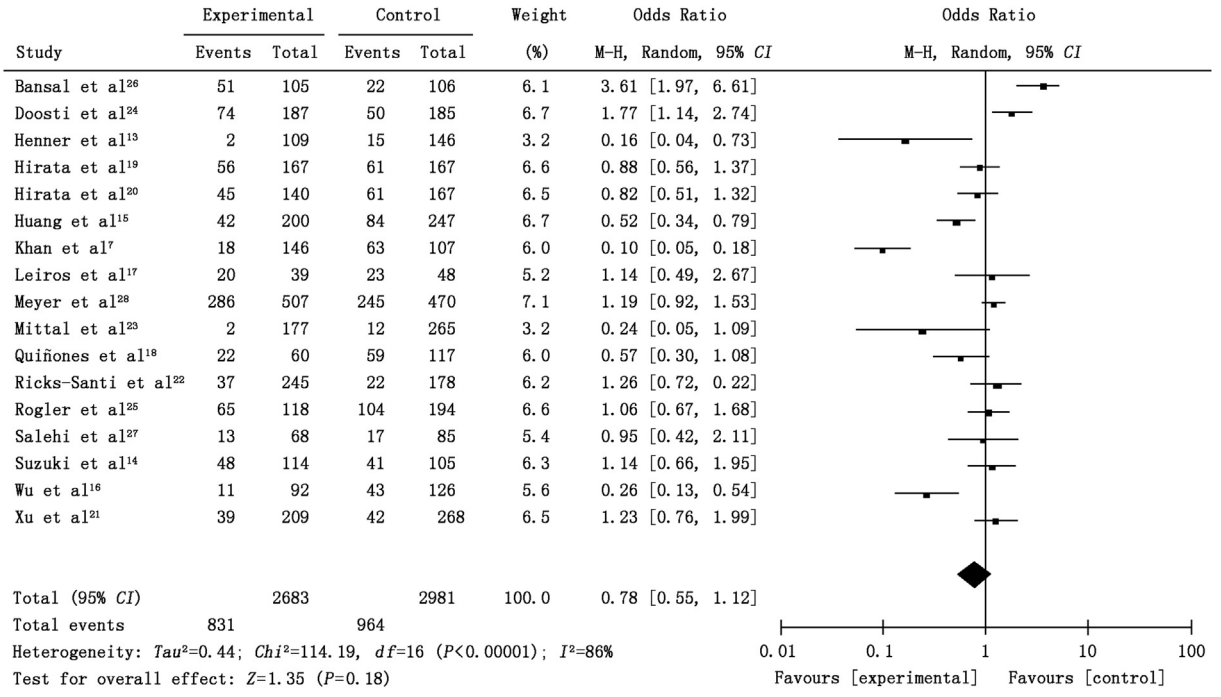

Fig. 5. Forest plot for the meta-analysis of the association between *TP53* rs1042522 polymorphism and prostate cancer risk under recessive model (CC *vs.* CG/GG).

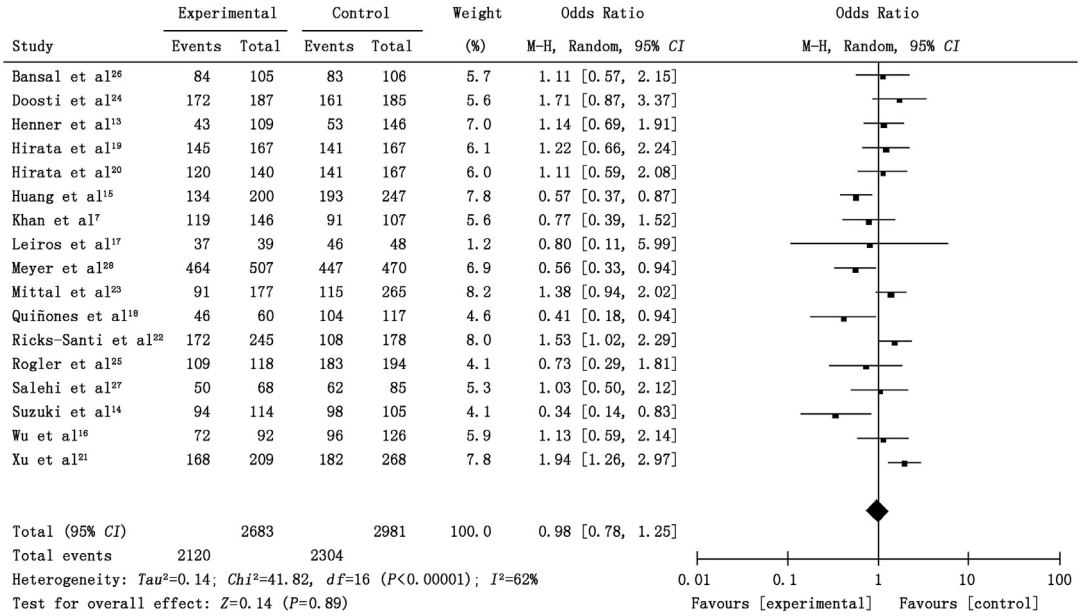

Fig. 6. Forest plot for the meta-analysis of the association between *TP53* rs1042522 polymorphism and prostate cancer risk under dominant model (CC/CG *vs.* GG).

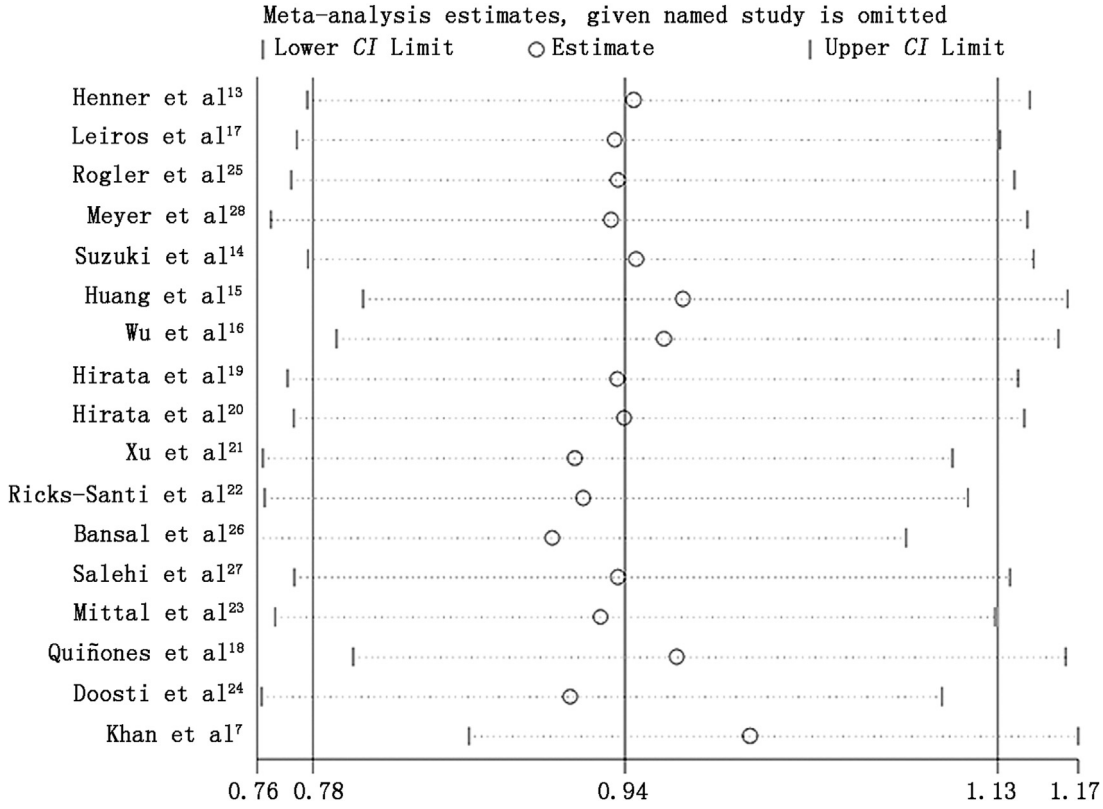

Fig. 7. Sensitivity analysis of overall odds ratio (*OR*) co-efficient for the *TP53* rs1042522 polymorphism under allele model (C *vs.* G). Results were calculated by omitting each study in turn. The two ends of the dotted lines represent the 95% confidence interval.

subgroup analyses except by source of control. The present study suggests that the *TP53* rs1042522 polymorphism might not be a risk factor for PCa. However, some other well-designed prospective studies with large cohort size and various SNPs are urgently necessary to check the current findings in advanced research.

Conflicts of interest

The authors declare no conflicts of interests.

Acknowledgments

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