Systematic Review and Meta-Analysis

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Association between TP53 gene codon72 polymorphism and prostate cancer risk

A systematic review and meta-analysis

Pei-Zhen Han, MD[a], De-Hong Cao, MD[a,b], Xue-Ling Zhang, MD[a], Zheng-Ju Ren, MD[a], Qiang Wei, MD[a,*]

Abstract

Background: TP53 gene polymorphism could increase risks of several kinds of cancer. But it remained controversial whether TP53 gene codon72 polymorphism was associated with the susceptibility to prostate cancer. Thus, we conducted a meta-analysis that evaluated the association between TP53 gene codon72 polymorphism and prostate cancer risk.

Method: A comprehensive research was performed from PubMed, Embase, Web of Science and China National Knowledge Infrastructure (CNKI) up to December 31, 2018. A random effect model was used to evaluate the effect of the outcome. The statistical analyses were performed with Review Manager 5.3.0 and Stata 14.0. The sensitivity analysis and publication bias tests were also performed to confirm the reliability of this meta-analysis.

Results: 22 studies included 3146 cases and 4010 controls were involved in this meta-analysis. Overall, no association was observed between TP53 gene codon72 polymorphism and prostate cancer risk (Arg vs Pro: odds ratio [OR] = 1.12, 95% confidence interval [CI] = 0.98–1.30; ArgArg vs ProPro: OR = 1.26, 95% CI = 0.90–1.75; ProPro vs ArgArg+ ArgPro: OR = 1.17, 95% CI = 0.86–1.57; ArgPro+ ProPro vs ArgArg: OR = 1.21, 95% CI = 0.97–1.51). Subgroup analyses, based on ethnicity, source of control and Hardy–Weinberg equilibrium (HWE) status, showed consistent results.

Conclusion: The meta-analysis we performed showed that there was no association of TP53 gene codon72 polymorphism with prostate cancer risk.

Abbreviations: CIs = confidence intervals, CNKI = China National Knowledge Infrastructure, EAF2 = ELL Associated Factor 2, HWE = Hardy–Weinberg equilibrium, NOS = Newcastle–Ottawa Scale, ORs = odds ratios.

Keywords: meta-analysis, polymorphism, prostate cancer, TP53 gene

1. Introduction

Prostate cancer is the third most common cancer in the world, and it is also the second most common cancer among men.[1] It is also the second leading reason of cancer death in American males.[2] In addition to some risk factors like age, inflammation and food factor,[3,4] previous studies showed that heritable susceptibility also played an important role in the development of prostate cancer, and several gene mutations have been reported to be associated with the development and prognosis of prostate cancer.[5–7] Some studies also suggested that TP53 gene polymorphism was a possible risk factor of prostate cancer.

TP53 gene is located on chromosome 17p13 and it consists of 11 exons.[8,9] P53 protein, the product of TP53 gene, is a tumor suppressor protein that can induce cell cycle arrest and apoptosis in response to genotoxic stress.[10] It also controls some other cellular processes, including self-renewal of stem cells, autophagy, and reprogramming of differentiated cells into metastasis, immune system or stem cells.[11,12] TP53 gene mutations were associated with several kinds of cancer, such as lung cancer, breast cancer, and colon cancer.[13–15] TP53 codon72 polymorphism (rs1042522) is an important functional polymorphic form that encodes amino acids arginine (CGC) or proline (CCC).[16] Moreover, previous studies have shown that Arg72 and Pro72 variants may lead to different biochemical and biological properties of the p53 protein.[17,18] Meanwhile, studies also reported the possible association of TP53 gene polymorphism with prostate cancer risk.

To date, there are several studies that evaluate the association between TP53 codon72 polymorphism and prostate cancer. However, most of these studies did not include large patient samples, and the results are inconclusive rather than consistent. Although there were several meta-analyses that had investigated

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[a] Department of Urology/Institute of Urology, [b] State Key Laboratory of Biotherapy and Cancer Center, West China Hospital, Sichuan University, Chengdu, China.

[*] Correspondence: Qiang Wei, Department of Urology, West China Hospital, Sichuan University, No. 37, Guoxue Alley, Chengdu, Sichuan, 610041, P.R. China (e-mail: weiqiang933@126.com, wangjiaa2002@sina.com).

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the association, results were also inconclusive.[19–21] Therefore, in this article, we conducted a comprehensive meta-analysis from all relevant scientific literatures.

2. Methods and materials

2.1. Searching strategy

Two authors independently performed a comprehensive search, using PubMed, Embase, Web of Science and China National Knowledge Infrastructure (CNKI) up to December 31, 2018. Search terms were as follows: "P53," "TP53," "polymorphism, mutation or variant," "prostate cancer." Besides, the references of reviews and several retrieved articles were also reviewed to identify other eligible studies that could be missed by the search. The search was limited to human subjects only. The search strategy flow chart is shown in Figure 1.

2.2. Inclusion criteria and exclusion criteria

Only the studies according to the following inclusion criteria were included:

(a) studies with full-text articles;
(b) case–control studies that evaluated the relationship between TP53 codon72 gene polymorphism and the susceptibility to prostate cancer;
(c) the genotype distributions were available for both cases and controls;
(d) no overlapping data.

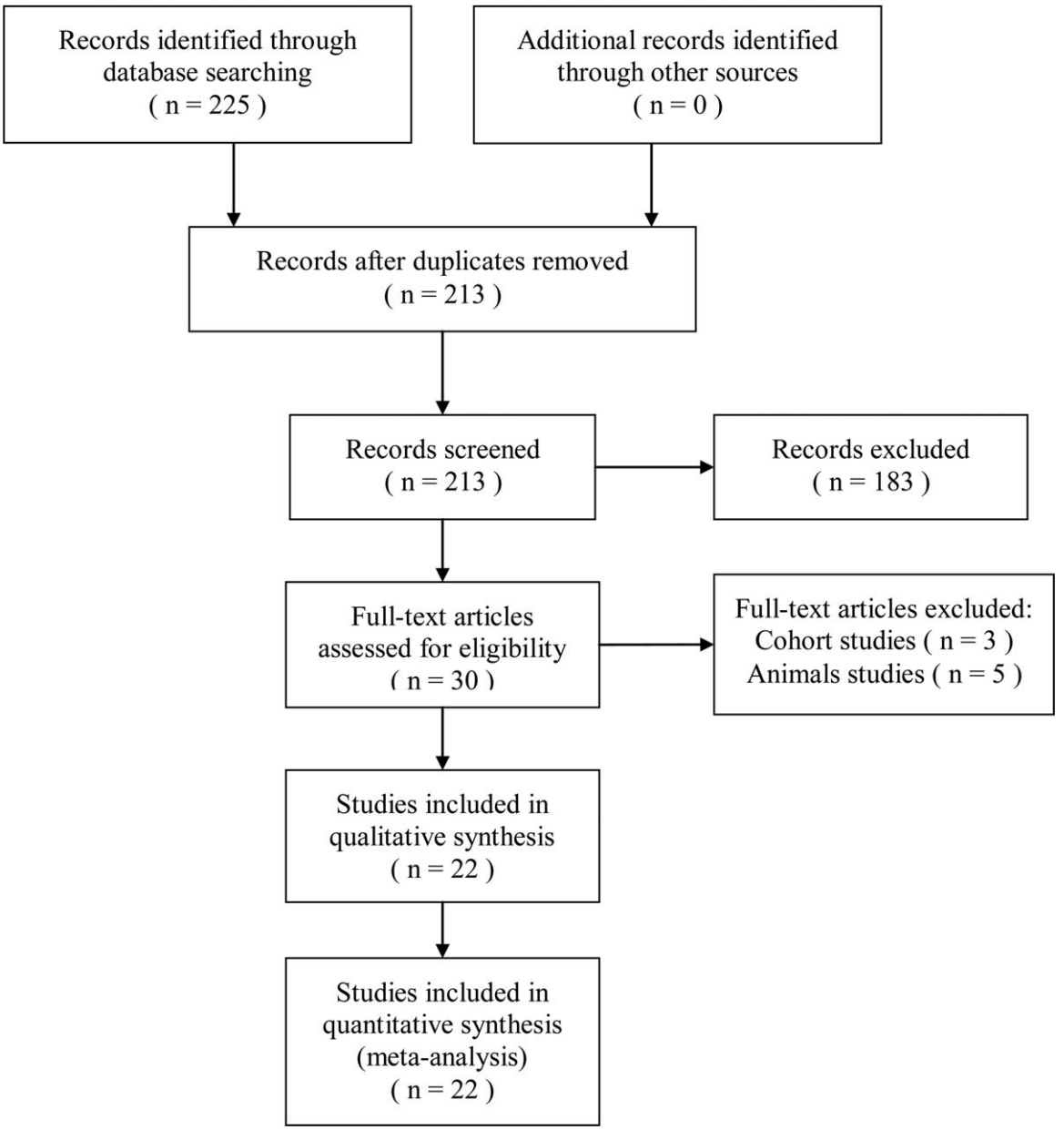

Figure 1. Flow chart of the study selection.

Studies were excluded if meeting any of the following exclusion criteria:

(a) not for the association between TP53 codon72 gene polymorphism and the risk of prostate cancer;
(b) studies with partial unusable or undefined data;
(c) animal studies, review articles, meta-analyses, conference abstracts, or editorial articles.

2.3. Quality assessment

We used the Newcastle–Ottawa Scale (NOS) to assess the quality of the included studies.[22] The NOS contains 8 parts for cohort or case–control studies. It is categorized into 3 parts including selection, comparability, and exposure for case–control studies. Selection has a maximum of 4 points, Comparability has a maximum of 2 points and Exposure has a maximum of 3 points. Scores ranged from 0 (worst) to 9 (best), and the quality of each study was graded as low (0–3), moderate (4–6), and high (7–9). Inconsistent opinions were solved by discussion and consensus.

2.4. Data extraction

Two authors reviewed the eligible scientific reports and extracted the relevant data independently according to the inclusion criteria. Then, extracted data were collected into a collection form and checked by a third author. Discrepancy was solved by discussion and consensus finding. In the meta-analysis, we collected the following information for each study:

(a) the first author's name, year of publication, country, genotyping method, races, source of control;
(b) (b)the number of people that were included in the case and control groups;
(c) the results of the Hardy–Weinberg equilibrium (HWE) test
(d) the scores evaluated by NOS.

2.5. Statistical analysis

The strength of the association between TP53 codon72 gene polymorphism and prostate cancer risk was measured by using odds ratio (OR) and corresponding 95% confidence interval (CI). The ORs were performed for 4 models, which are allele model, additive model, recessive model, and dominant model. Heterogeneity assumption was tested by the chi-square-based Q test. The heterogeneity was considered significant when $P<.10$, and I^2 values of 25%, 50%, and 75% referred to low, medium and high levels of heterogeneity, respectively. A random-effect model was used in the analysis. The significance of the pooled OR was determined by the Z-test, and when $P<.05$, it was regarded as statistically significant. The statistical analysis was performed with Reviewer Manager 5.3.0 and Stata 14.0. The potential publication bias was evaluated applying Begg test, Egger test and funnel plots. We also performed sensitivity analysis to assess the reliability of the results. The pooled ORs were estimated by removing 1 study each time to evaluate the impact of an individual study.

3. Results

3.1. Study characteristics

The 225 articles were retrieved after the first search in PubMed, Embase, Web of Science and CNKI. The 202 articles were excluded, according to the inclusion and exclusion criteria. Finally, after the careful selection, 22 case–control studies involving 3146 cases and 4010 controls were included in this meta-analysis.[23–44] All these studies were published between 1995 and 2015. Of these, 7 studies were based on Asian, 14 studies based on Caucasian and another 2 studies were based on other races. We also conducted the HWE test for these studies, and HWE was violated in 5 studies. As for the source of control, 10 studies were hospital-based (H-B), and others were population-based (P-B). Every study's scores were moderate or better, based on NOS. The detailed characteristics of included studies were listed in Table 1. All analyses were based on previous studies, thus no ethical approval and patient consent are required.

3.2. Meta-analysis results

The influence of TP53 codon72 polymorphism on prostate cancer was totally evaluated by 22 case–control studies including 7156 individuals. Figures 2–5 show the results of the allele model (Arg vs Pro), additive model (ArgArg vs ProPro), recessive model (ProPro vs ArgArg+ ArgPro) and dominant model (ArgPro+ ProPro vs ArgArg). Overall, the result showed that there was no significant association between TP53 codon72 polymorphism and prostate cancer risk. (Arg vs Pro: OR = 1.12, 95% CI = 0.98–1.30; ArgArg vs ProPro: OR = 1.26, 95% CI = 0.90–1.75; ProPro vs ArgArg+ ArgPro: OR = 1.17, 95% CI = 0.86–1.57; ArgPro+ ProPro vs ArgArg: OR = 1.21, 95% CI = 0.97–1.51).

In the subgroup analysis by HWE status, no significant association between TP53 codon72 polymorphism and prostate cancer risk was observed in 4 models (Table 2). A weak association of TP53 gene codon72 polymorphism and prostate cancer risk was observed in the allele model in Caucasians (OR = 1.23, 95% CI = 1.00–1.52). No association was found among Asian in 4 models. (Table 2) A possible weak association was also observed in the dominant model in the population-based group (OR = 1.43, 95% CI = 1.00–2.05). In the hospital-based group, we found that TP53 gene codon72 polymorphism was not associated with prostate cancer susceptibility (Arg vs Pro: OR = 1.07, 95% CI = 0.90–1.29; ArgArg vs ProPro: OR = 1.37, 95% CI = 0.88–2.13; ProPro vs ArgArg+ ArgPro: OR = 1.42, 95% CI = 0.94–2.13; ArgPro+ ProPro vs ArgArg: OR = 0.96, 95% CI = 0.79–1.17). After all, we found no association of TP53 gene codon72 polymorphism with prostate cancer risk based on subgroup analysis. The results were shown in Table 2.

3.3. Sensitivity analysis and publication bias

Sensitivity analysis was performed by omitting 1 study each time in 4 models; the results showed that the overall pooled ORs were not influenced by any individual study, indicating the results of this meta-analysis are stable. (Fig. 6)

Begg test, Egger test, and funnel plots were conducted to assess the publication bias on TP53 codon72 polymorphism.(Fig. 7) No publication bias was observed based on funnel plots or according to Begg and Egger test for prostate cancer risk in additive model, recessive model, and dominant model. In addition, some publication bias was observed in the results of allele model according to Begg and Egger tests (Begg test: $P = .030$; Egger test $P = .046$). The results were shown in Table 3.

4. Discussion

Overall, in our meta-analysis, we found no association of TP53 gene polymorphism with prostate cancer risk in 4 models (Arg vs

Table 1

Characteristics of studies included in the meta-analysis.

Author	Country and Ethnicity	Source of control	method	Group	Sample Number (n)	Arg/Arg	Arg/Pro	Pro/Pro	Arg	Pro	HWE	NOS
Babaei 2014	Iran Caucasian	H-B	PCR	Case	40	15	15	10	45	35	>0.05	5
				Control	80	41	35	4	117	43		
Bansal 2012	India Caucasian	P-B	PCR-RFLP	Case	105	21	33	51	75	135	>0.05	7
				Control	106	22	61	23	105	107		
Behfar-jam 2015	Iran Caucasian	P-B	PCR-RFLP	Case	45	9	21	15	39	51	>0.05	6
				Control	45	16	22	7	54	36		
Doosti 2011	Iran Caucasian	H-B	PCR-RFLP	Case	187	74	98	15	246	128	<0.05	5
				Control	185	50	111	24	211	159		
Henner 2011	USA Caucasian	P-B	PCR-RFLP	Case	109	66	41	2	173	45	<0.05	6
				Control	146	93	38	15	224	68		
Hirata 2007	Japan Asian	P-B	PCR-RFLP	Case	167	56	89	22	201	133	>0.05	6
				Control	167	61	80	26	202	132		
Hirata 2009	Japan Asian	P-B	PCR-RFLP	Case	140	45	75	20	165	115	>0.05	7
				Control	167	61	80	26	202	132		
Huang 2004	China Asian	H-B	PCR-RFLP	Case	200	66	92	42	224	176	>0.05	7
				Control	247	84	109	54	277	217		
Khan 2014	Iran Caucasian	P-B	PCR-RFLP	Case	140	18	101	27	137	155	<0.05	6
				Control	97	63	28	16	154	60		
Leiros 2005	ArgentinaCaucasian	P-B	PCR-RFLP	Case	39	20	17	2	57	21	>0.05	6
				Control	48	23	23	2	69	27		
Luis A 2006	Chile Caucasian	H-B	PCR-RFLP	Case	60	22	24	14	68	52	>0.05	5
				Control	117	59	45	13	163	71		
Meyer 2012	Germany Caucasian	H-B	RT-PCR	Case	507	286	178	43	750	264	>0.05	6
				Control	470	245	202	23	692	248		
Micho-poulou 2014	Greece Caucasian	H-B	RT-PCR	Case	50	35	11	4	81	19	>0.05	5
				Control	30	23	5	2	51	9		
Mittal 2011	India Caucasian	P-B	PCR-RFLP	Case	177	86	89	2	261	93	>0.05	8
				Control	265	150	103	12	403	127		
Rogler 2011	Germany Caucasian	H-B	PCR-RFLP	Case	118	65	44	9	174	62	>0.05	6
				Control	194	104	79	11	287	101		
Sivoňová 2015	Slovak Caucasian	P-B	PCR-RFLP	Case	300	146	143	11	435	165	>0.05	7
				Control	446	200	232	14	632	260		
Salehi 2012	Iran Caucasian	H-B	PCR-RFLP	Case	68	18	37	13	73	63	>0.05	5
				Control	85	23	45	17	91	79		
Suzuki 2003	Japan Asian	H-B	PCR-RFLP	Case	114	48	46	20	142	86	<0.05	6
				Control	105	41	57	7	139	71		
Wu 1995	Japan Asian	H-B	PCR-RFLP	Case	28	12	14	2	38	18	>0.05	5
				Control	403	170	189	44	529	277		
Wu 2004	China Asian	P-B	RT-PCR	Case	92	11	61	20	83	101	<0.05	6
				Control	126	43	53	30	139	113		
Xu 2010	China Asian	P-B	PCR-RFLP	Case	209	39	129	41	207	211	>0.05	7
				Control	268	42	140	86	224	312		
Henner1 2001	USA Other	P-B	PCR-RFLP	Case	6	2	3	1	7	5	>0.05	6
				Control	35	15	14	6	44	26		
Ricks-Santi 2014	USA Other	P-B	PCR-RFLP	Case	245	37	135	73	209	281	>0.05	7
				Control	178	22	86	70	130	226		

H-B = hospital-based, P-B = population-based, PCR-RFLP = polymerase chain reaction-restriction fragment length polymorphism, RT-PCR = reverse transcription-polymerase chain reaction.

Pro: OR = 1.12, 95% CI = 0.98–1.30; ArgArg vs ProPro: OR = 1.26, 95% CI = 0.90–1.75; ProPro vs ArgArg+ ArgPro: OR = 1.17, 95% CI = 0.86–1.57; ArgPro+ ProPro vs ArgArg: OR = 1.21, 95% CI = 0.97–1.51). In subgroup analyses by ethnicity, source of control and HWE status, no significant association was observed between prostate cancer risk and TP53 gene polymorphism. (Table 2)

Studies showed that TP53 gene mutations could have an impact on 50% of human cancers,[45] and several studies have been taken to study the underlying mechanism of the association between TP53 gene and prostate cancer, as well. For example, Ashkari et al reported that p53 may translocate to the cytoplasm by androgen-mediated induction of G3BP2, a newly described direct target gene of androgen receptor, which played a central role in prostate cancer progression.[46] Potential gene–gene interaction could also play a vital role in the association of TP53 gene polymorphism and prostate cancer risk. Wang et al demonstrated that ELL Associated Factor 2 (EAF2) gene and TP53 gene may functionally interact in prostate tumor suppression and the simultaneous inactivation of EAF2 and TP53 may drive prostate carcinogenesis, based on their findings on mice.[47] However, the association between TP53 gene codon72 polymor-

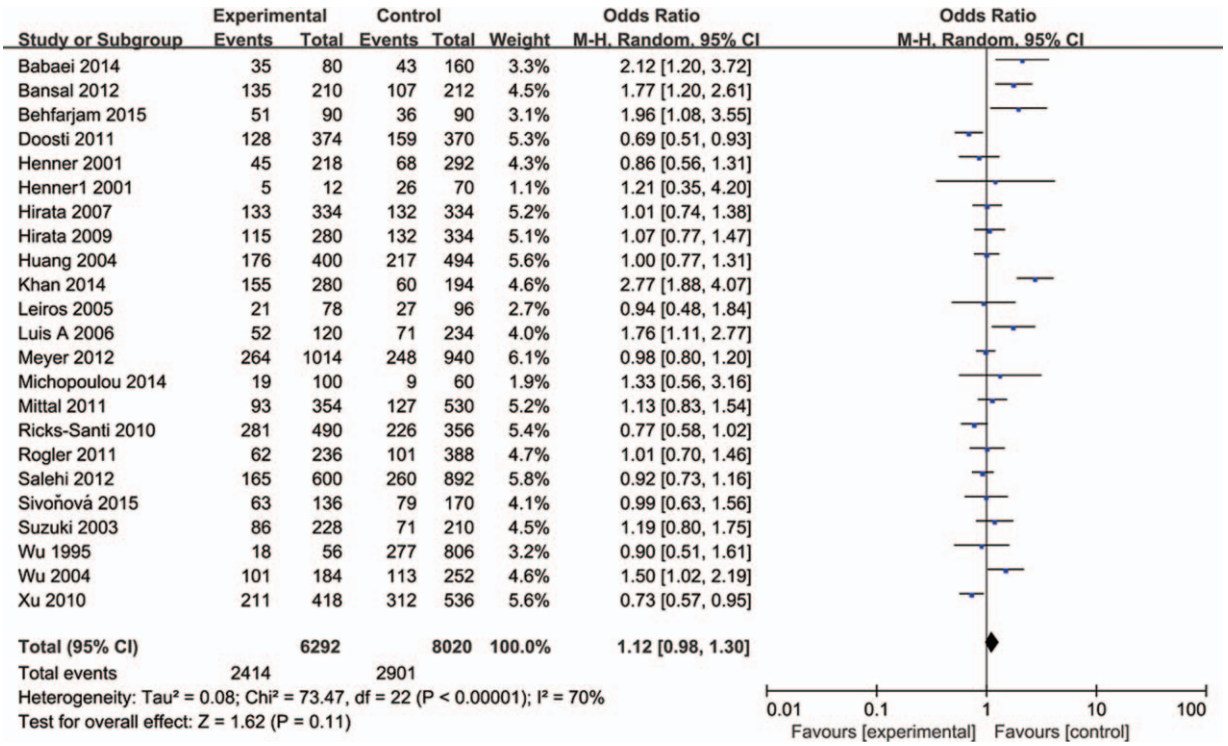

Figure 2. Forest plot of the studies evaluating the association of TP53 codon72 polymorphism with prostate cancer risk (Allele model: Pro vs Arg).

phism and prostate cancer risk remained unclear. To draw a better comprehensive understanding, we conducted this meta-analysis to evaluate the association of TP53 gene codon72 polymorphism with prostate cancer risk. And the result of our meta-analysis implied no association between TP53 gene codon72 polymorphism and the risk of prostate cancer.

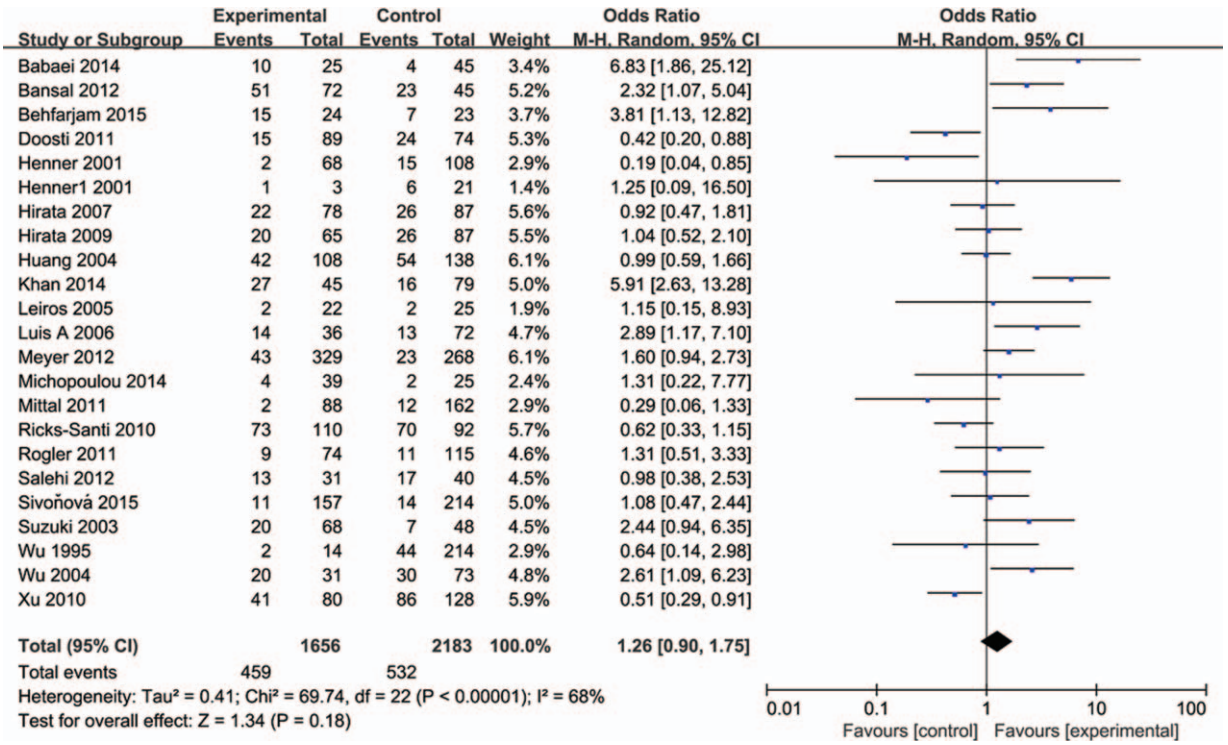

Figure 3. Forest plot of the studies evaluating the association of TP53 codon72 polymorphism with prostate cancer risk (Additive model: ProPro vs ArgArg).

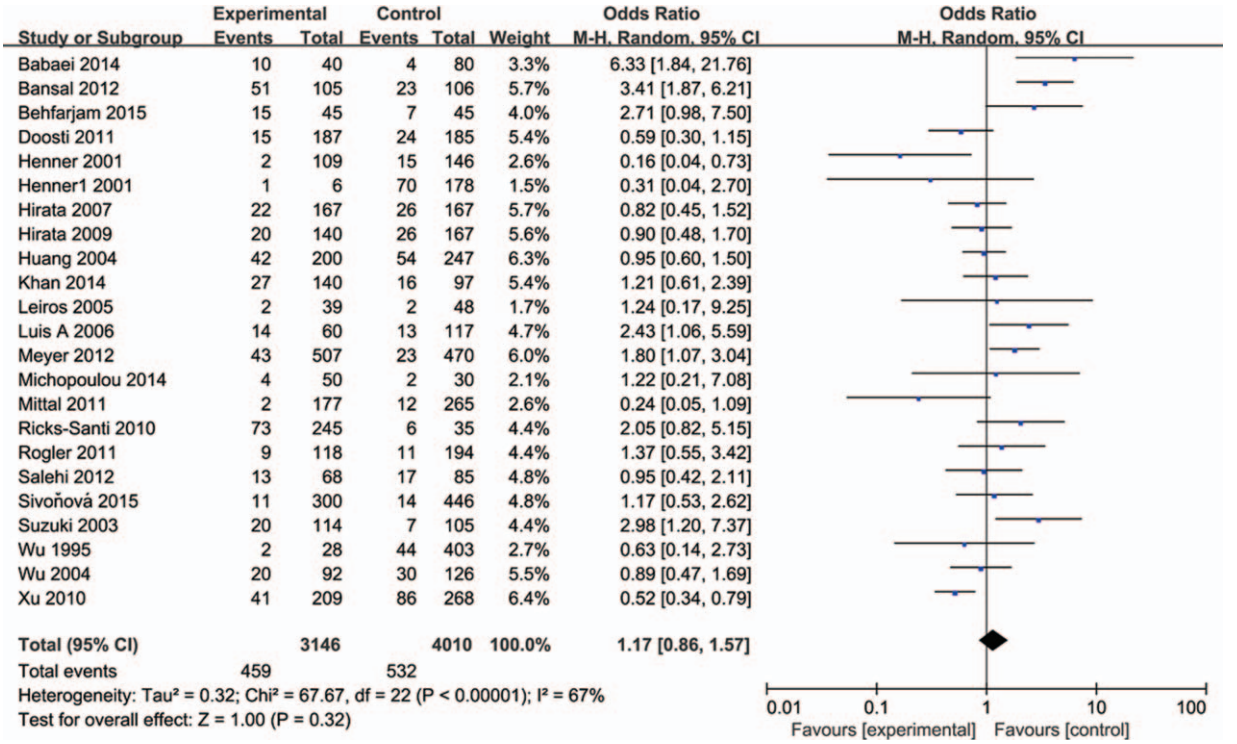

Figure 4. Forest plot of the studies evaluating the association of TP53 codon72 polymorphism with prostate cancer risk (Recessive model: ProPro vs ArgArg +ArgPro).

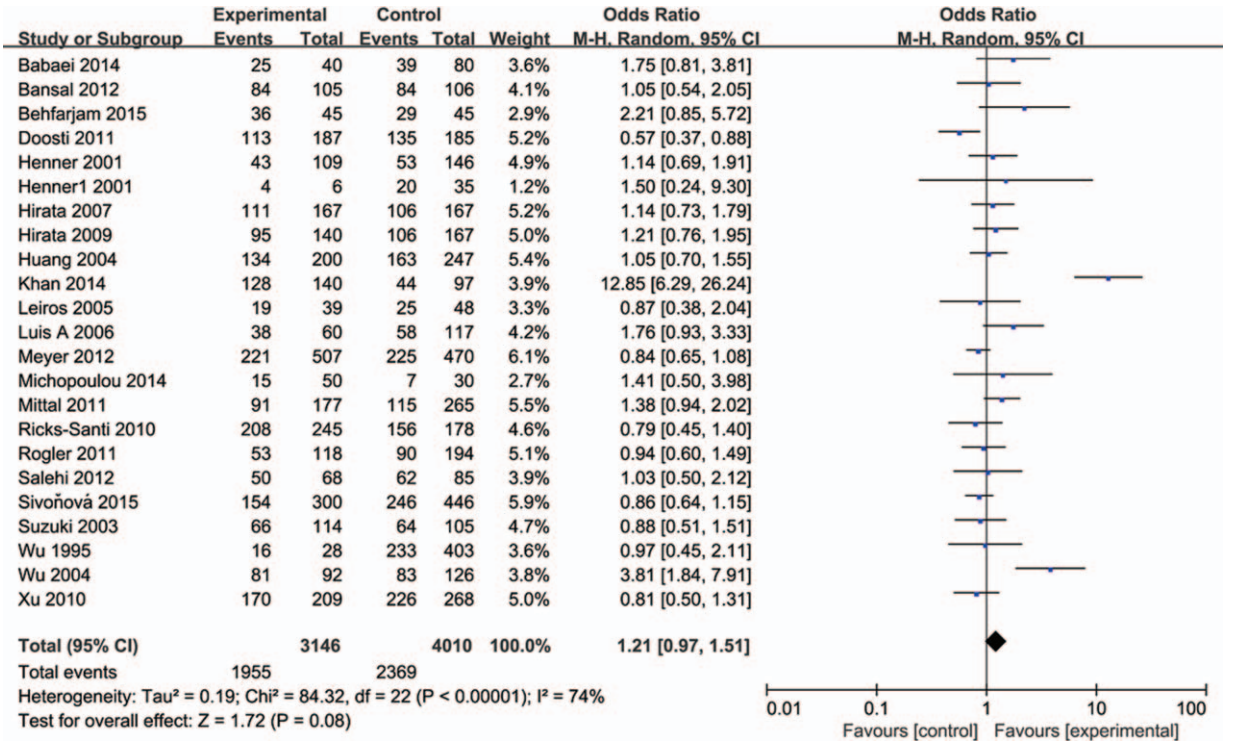

Figure 5. Forest plot of the studies evaluating the association of TP53 codon72 polymorphism with prostate cancer risk (Dominant model: ProPro+ArgPro vs ArgArg).

Table 3

Publication bias tests for the TP53 codon72 polymorphism.

Comparisons	Coefficient	Egger test *P* value	95% CI	Begg test *P* value
Arg vs Pro	2.201	.046	−0.042 to 4.359	.030
ProPro vs ArgArg	0.628	.552	−1.534 to 2.789	.369
ProPro+ArgPro vs ArgArg	2.098	.052	−0.021 to 4.217	.057
ArgArg+ArgPro vs ProPro	0.873	.453	−3.244 to 1.499	.712

Table 2

Meta-analysis of the association of TP53 codon72 polymorphism with prostate cancer risk.

TP53 rs1042522	N	Arg vs Pro (OR, 95% CI)	ArgArg vs ProPro (OR, 95% CI)	ArgArg+ArgPro vs ProPro (OR, 95% CI)	ProPro+ArgPro vs ArgArg (OR, 95% CI)
Overall	23	1.12 [0.98, 1.30]	1.26[0.90, 1.75]	1.17[0.86, 1.57]	1.21[0.97, 1.51]
Caucasian	14	1.23 [1.00, 1.52]	1.45[0.88, 2.40]	1.34[0.88, 2.04]	1.29[0.94, 1.78]
Asian	7	1.02 [0.86, 1.21]	1.07[0.70, 1.64]	0.89[0.62, 1.27]	1.16[0.86, 1.56]
Other	2	0.79 [0.60, 1.04]	0.64[0.35, 1.18]	1.04[0.17, 6.19]	0.84[0.49, 1.44]
H-B	10	1.05 [0.89, 1.25]	1.37[0.88, 2.13]	1.42[0.94, 2.13]	0.96[0.79, 1.17]
P-B	13	1.17 [0.94, 1.47]	1.16[0.70, 1.92]	0.98[0.64, 1.51]	1.43[1.00, 2.05]
HWE <0.05	5	1.23 [0.75, 2.02]	1.33[0.41, 4.30]	0.89[0.45, 1.75]	1.89[0.69, 5.23]
HWE >0.05	18	1.08 [0.95, 1.22]	1.19[0.87, 1.61]	1.26[0.89, 1.78]	1.02[0.91, 1.14]

HWE = Hardy–Weinberg equilibrium.

In previous studies, some of the researchers thought that TP53 codon72 polymorphism was significantly associated with prostate cancer risk. Mittal et al[35] observed that individuals with heterozygous genotype of TP53 codon72 polymorphism demonstrated prostate cancer risk (OR = 1.5, 95% CI = 1.00–2.199). Similarly, Xu et al[44] also found that the frequencies of TP53 codon72 between the case group and control group were significantly different ($P < .01$), after adjusting some potential covariates.

However, some other studies' conclusions were inconsistent. For example, Huang et al,[30] one of the studies included, found no significant association between p53 polymorphism and risk of

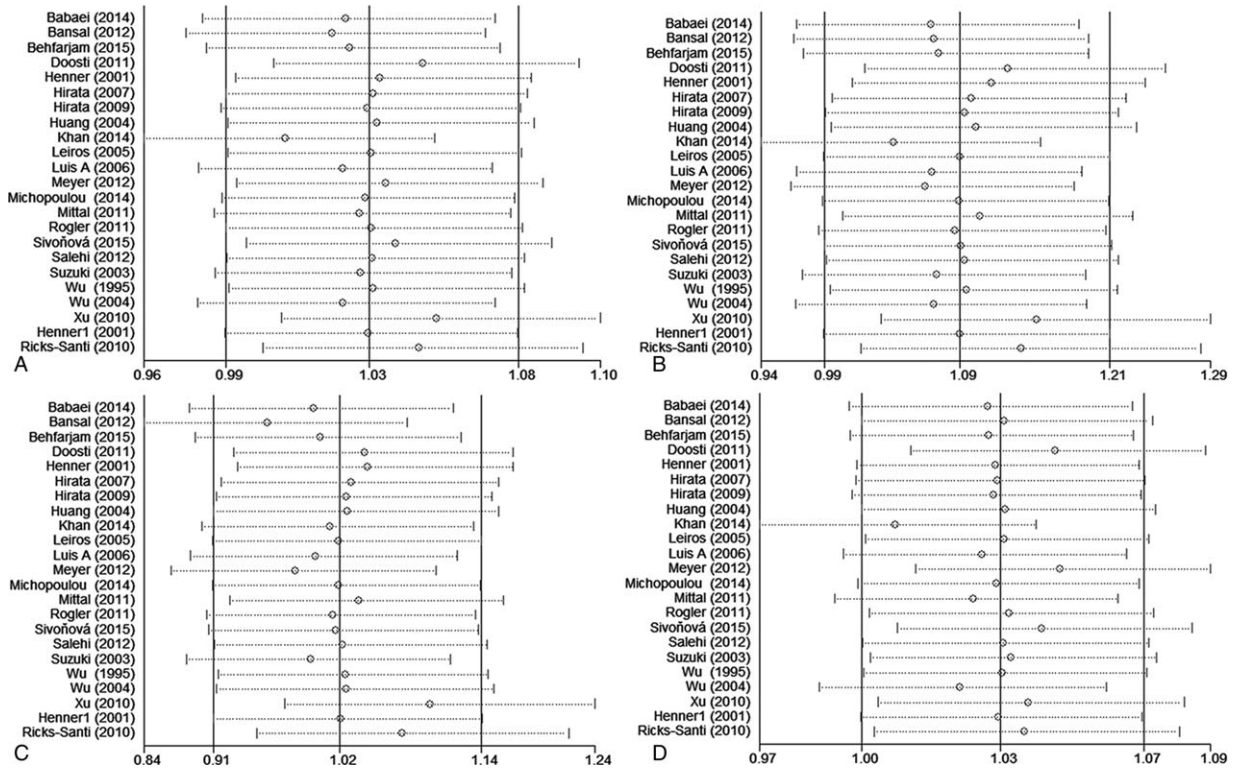

Figure 6. Sensitivity analysis diagram for each study used to evaluate the relative risk estimated for the TP53 codon72 polymorphism and prostate cancer risk in all of the included studies (A. allele model: Pro vs Arg; B. additive model: ProPro vs ArgArg; C. recessive model: ProPro vs ArgArg+ArgPro; D. dominant model: ProPro +ArgPro vs ArgArg).

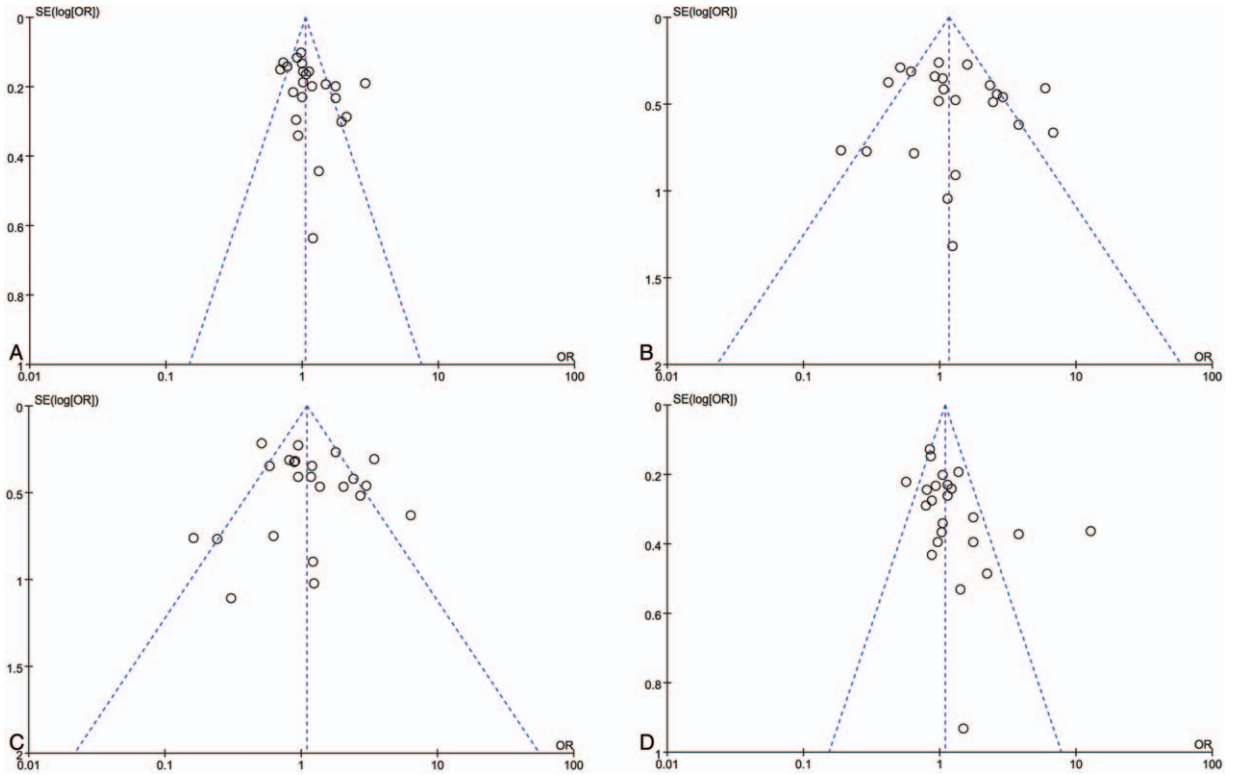

Figure 7. Funnel plots for the TP53 codon72 polymorphism and prostate cancer risk. (A. allele model: Pro vs Arg; B. additive model: ProPro vs ArgArg; C. recessive model: ProPro vs ArgArg+ArgPro; D. dominant model: ProPro+ArgPro vs ArgArg).

prostate cancer. Michopolou et al[34] observed no statistically significant association between the HPV presence and TP53 codon 72 polymorphism, and in that case, they did not think that TP53 polymorphism status at codon 72 was associated with prostate cancer. It is possible to lead to the inconsistence, because of the scale of samples or other environmental factors that were not considered.

Thus, these conclusions needed further validation based on a larger population. Meanwhile, other factors, like ethnicity, should be taken in consideration. Therefore, we conducted this meta-analysis. And the results showed no association between TP53 polymorphism and prostate cancer risk, which was consistent with a previous study.[19] However, in this meta-analysis, we included more studies than before. In addition, we also used NOS to evaluate the methodological quality of the studies included, and it helped us to pick out and evaluate eligible articles.

I^2 statistics and Q test were performed to evaluate the significance of heterogeneity in this meta-analysis. Significant heterogeneity among the including studies was found in all 4 models. After subgrouped by ethnicity, source of control, and HWE status, the heterogeneity remained obvious. Therefore, we considered the heterogeneity may result from the variety of countries that studies were published and other confounding factors. Moreover, some limitations of this meta-analysis should be taken in consideration. First, we did not estimate some latent hereditary factors, like the potential gene-gene and gene-environment interactions, because of the lack of information available in the original studies included. Second, subject age, sample quality, and some other clinical data, were not considered here, due to the lack of information. Third, publication bias existed in the allele model, which indicated that more studies should be taken and included.

5. Conclusion

In conclusion, this meta-analysis suggested no association between TP53 codon72 polymorphism and prostate cancer risk. Nevertheless, more large and representative case-control studies are needed for the validation of our conclusion.

Author contributions

Conceptualization: Zheng-Ju Ren.
Data curation: Xue-Ling Zhang.
Formal analysis: Pei-Zhen Han.
Funding acquisition: Qiang Wei.
Investigation: Pei-Zhen Han.
Methodology: Xue-Ling Zhang.
Resources: Zheng-Ju Ren.
Software: Zheng-Ju Ren.
Supervision: De-Hong Cao, Qiang Wei.
Visualization: Xue-Ling Zhang.
Writing – original draft: Pei-Zhen Han.
Writing – review & editing: Pei-Zhen Han.

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