Association between TP53 gene codon72 polymorphism and prostate cancer risk
A systematic review and meta-analysis

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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.6 It is also the second leading reason of cancer death in American males.7 In addition to some risk factors like age, inflammation and food factors,8 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.8−10 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.11−13 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
the association, results were also inconclusive.\cite{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.

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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.125,126 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 2 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) 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. Heteroge-
neity assumption was tested by the chi-square-based Q test. The
additive model, recessive model, and dominant model. Heteroge-
neity was considered significant when P < .10, and I²
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
Rev 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.12,23–44 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 popula-
tion-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 = 0.03; 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
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: 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 polymorphism and prostate cancer risk was not significant in the current meta-analysis.
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 2. Forest plot of the studies evaluating the association of TP53 codon72 polymorphism with prostate cancer risk (Allele model: Pro vs Arg).

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).
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 prostate cancer. Table 3 and Table 2 summarize the publication bias tests and meta-analysis of the association of TP53 codon72 polymorphism with prostate cancer risk.

**Table 3**

| Comparisons         | Coefficient | Egger test P value | 95% CI          | Begg test P value |
|---------------------|-------------|--------------------|-----------------|------------------|
| Arg vs Pro          | 2.201       | .046               | −0.042 to 4.359 | .360             |
| ProPro vs ArgArg    | 0.628       | .552               | −1.534 to 2.799 | .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**

| 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]              | 0.88[0.64, 1.51]                      | 1.43[0.60, 2.09]                      |
| HWE < .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 > .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.
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.

I² 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.

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Conceptualization: Zheng-Ju Ren.
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Writing – original draft: Pei-Zhen Han.
Writing – review & editing: Pei-Zhen Han.

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