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# Meta-analysis demonstrates no association between p53 codon 72 polymorphism and prostate cancer risk

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**ABSTRACT.** We examined whether p53 codon 72 polymorphism confers prostate cancer risk by conducting a meta-analysis. Two investigators independently searched the Pubmed, Embase and CBM databases. This meta-analysis was made of seven case-control studies, that included 892 prostate cancer cases and 1020 healthy controls. Meta-analysis results based on all the studies showed no significant association between p53 codon 72 polymorphism and prostate cancer risk in the comparisons of Pro allele *vs* Arg allele; Pro/Pro + Pro/Arg *vs* Arg/Arg; Pro/Pro *vs* Pro/Arg + Arg/Arg; Pro/Pro *vs* Arg/Arg, and Pro/Arg *vs* Arg/Arg [odds ratio (OR) = 1.09, 95% confidence interval (CI) = 0.87-1.36, P = 0.47; OR = 1.22, 95%CI = 0.86-1.73, P = 0.27; OR = 1.03, 95%CI = 0.62-1.72, P = 0.91; OR = 1.22, 95%CI = 0.66-2.26, P = 0.52; OR = 1.25, 95%CI = 0.84-1.87, P = 0.27, respectively]. In

 

the subgroup analysis by ethnicity, no association was found between p53 codon 72 polymorphism and prostate cancer risk both in Caucasian and Asian populations. We found no association between p53 codon 72 polymorphism and prostate cancer risk.

**Key words:** Prostate cancer; p53 codon 72; Gene polymorphism; Meta-analysis

## INTRODUCTION

Prostate cancer is one of the most frequent tumors among men and is the second leading cause of cancer death among men in the USA. In 2010, prostate cancer accounted for 28% (217,730) of all newly diagnosed cancers and 11% (32,050) of all deaths in American males (Jemal et al., 2010). However, different races have different rates of this disease worldwide. Despite its high morbidity, the etiology of prostate cancer remains largely unknown (Hsing and Chokkalingam, 2006). Prostate carcinogenesis is a complex, multistep and multifactor processes, in which many factors are implicated. Advancing age, race, and a family history of prostate cancer are the only established risk factors (Lesko et al., 1996). Many studies indicate that environmental and genetic factors play a significant role in the etiology of this disease (Coughlin and Hall, 2002). It is estimated that as much as 42% of the risk of prostate cancer involves genetic influences, including individual and combined effects of rare, highly penetrant genes, more common weakly penetrant genes, and genes acting in concert with each other (Lichtenstein et al., 2000).

The p53 tumor suppressor gene, which is located on chromosome 17p13, is one of the most commonly mutated genes in all types of human cancer (Levine et al., 1991; Hollstein et al., 1991). p53 acts as a tumor suppressor gene, which induces cell cycle arrest or apoptosis, negatively regulates the cell cycle and requires loss of function mutations for tumor formation (Levine, 1997). Although p53 contains several polymorphic sites, the codon 72 polymorphism located on exon 4 is the most common candidate gene (Guimaraes and Hainaut, 2002). The polymorphism consists of a single base pair change of either arginine (Arg, CGC) or proline (Pro, CCC), which creates three distinct genotypes, including homozygous for arginine (Arg/Arg), homozygous for proline (Pro/Pro) and heterozygote (Pro/Arg; Shepherd et al., 2000). Recently, p53 codon 72 polymorphisms have been reported to be associated with prostate cancer (Henner et al., 2001). The aim of our meta-analysis was to investigate the association between p53 codon 72 polymorphism and prostate cancer risk by examining all eligible case-control studies published to date.

## MATERIAL AND METHODS

### Literature search strategy

Pubmed, Embase and CBMdisc database searches were performed to retrieve papers linking p53 codon 72 polymorphism and prostate cancer risk available up to November 2010, without language restrictions, using the following keywords: [‘p53 Gene’ or ‘Tumor Suppressor Protein p53’] and [‘Polymorphism, Genetic’ or ‘Polymorphism, Single-Stranded Con-

formational' or 'Polymorphism, Single Nucleotide' or 'Polymorphism, Restriction Fragment Length' or 'Amplified Fragment Length Polymorphism Analysis' or 'DNA Copy Number Variations'] and ['Prostate Cancer' or 'Prostate Neoplasms' or 'Prostate Tumor']. The search was included only research on human subjects. Reference lists of major textbooks, review articles, and included articles were identified through manual searches to find other potentially eligible studies.

## Inclusion and exclusion criteria

To be eligible for inclusion in this meta-analysis, the following criteria were established: 1) case-control study that addressed prostate cancer cases and healthy controls; 2) studies that evaluated the association between p53 codon 72 polymorphism and prostate cancer risk; 3) studies that included sufficient genotype data for extraction. Studies were excluded if: 1) non-case-control studies that evaluated the association between p53 codon 72 polymorphism and prostate cancer risk; 2) case reports, letters, reviews, and editorial articles; 3) studies based on incomplete raw data and no usable data reported; 4) duplicate data contained in the studies; 5) family-based design.

## Data extraction

Using a standardized form, data from published studies were extracted independently by two reviewers (Li MS and Liu JL) to populate files with the necessary information. The following information was extracted from each of the included articles: first author, year of publication, country, ethnicity, study design, source of controls, number of cases and controls, detection methods, allele and genotype frequencies of polymorphism, and evidence of Hardy-Weinberg equilibrium in controls. For conflicting evaluations, agreement was reached following discussion among the authors.

## Quality assessment of included studies

The quality of papers was also independently assessed by two reviewers (Li MS and Liu JL) based on the STROBE quality score systems (Vandenbroucke et al., 2007). Thirty items relevant to the quality appraisal were used for assessment in this meta-analysis; scores ranged from 0 to 30. Any discrepancies between the two reviewers were resolved by discussion and consultation with a third reviewer (Wang P).

## Statistical analysis

Individual or pooled odds ratios (OR) and 95% confidence intervals (CI) were calculated for each study using Review Manager Version 5.0.25 (provided by the Cochrane Collaboration, available at http://ims.cochrane.org/revman) and STATA package version 9.2 (Stata Corporation, College Station, TX, USA). The following contrasts for p53 codon 72 polymorphism were evaluated: comparison of the variant allele with the wild allele (Pro allele *vs* Arg allele); comparison of each homozygote with the other combined with heterozygote (Pro/Pro + Pro/Arg *vs* Arg/Arg; Pro/Pro *vs* Pro/Arg + Arg/Arg), comparison of wild homozygote with

heterozygote and variant homozygote (Pro/Pro *vs* Arg/Arg; Pro/Arg *vs* Arg/Arg). Between-study variations and heterogeneities were estimated using Cochran's Q-statistic (Higgins and Thompson, 2002; Zintzaras and Ioannidis, 2005). When a significant Q-statistic ($P < 0.10$) indicated heterogeneity across studies, the random effects model was used for meta-analysis, and if heterogeneity across studies was not indicated, the fixed effects model was used (Viechtbauer, 2007). We also quantified the effect of heterogeneity with the $I^2$ test. $I^2$ ranges between 0 and 100%; it represents the proportion of inter-study variability that can be attributed to heterogeneity rather than chance. $I^2$ values of 25, 50 and 75% were defined as low, moderate and high estimates, respectively. We tested whether genotype frequencies of controls were in Hardy-Weinberg equilibrium using the chi-square test. Subgroup analysis was used to explore and to explain the diversity among the results of different studies. Sensitivity analysis was mainly performed by sequential omission of individual studies. Publication bias was investigated by Begg's funnel plot, and funnel plot asymmetry was assessed by the Egger linear regression test (Peters et al., 2006); statistical significance was considered when the P value of the Egger test was <0.05. All P values were two-sided. To ensure the reliability and the accuracy of the results, two reviewers (Li and Liu) inputted the data in statistic software programs independently and obtained the same results.

## RESULTS

### Studies included in the meta-analysis

The search strategy retrieved 75 potentially relevant papers (49 in Pubmed, 20 in Embase, 6 in CBM). According to the inclusion criteria, seven studies (Henner et al., 2001; Suzuki et al., 2003; Huang et al., 2004; Wu et al., 2004; Leiros et al., 2005; Quinones et al., 2006; Ricks-Santi et al., 2010) were included in this meta-analysis and 68 studies were excluded. The flow chart of the study selection is summarized in Figure 1. These seven selected case-control studies included 892 prostate cancer cases and 1020 healthy controls. All studies were case-control studies that evaluated the association between p53 codon 72 polymorphism and prostate cancer risk. All the articles were written in English. The Hardy-Weinberg equilibrium test was performed on the genotype distribution of the controls in all included studies; all of them except Henner et al. (2001) ($P < 0.001$) and Suzuki et al. (2003) ($P = 0.03$) were in Hardy-Weinberg equilibrium. The characteristics and methodological quality of all studies are summarized in Table 1. The genotype distribution and risk allele frequency of these studies are summarized in Table 2.

### Main results, subgroup and sensitivity analysis

A summary of the meta-analysis findings of the association between p53 codon 72 polymorphism and prostate cancer risk is shown in Table 3. Meta-analysis results showed that there was no association between p53 codon 72 polymorphism and prostate cancer risk in the comparisons of Pro allele *vs* Arg allele; Pro/Pro + Pro/Arg *vs* Arg/Arg; Pro/Pro *vs* Pro/Arg + Arg/Arg; Pro/Pro *vs* Arg/Arg, and Pro/Arg *vs* Arg/Arg (OR = 1.09, 95%CI = 0.87-1.36, P = 0.47; OR = 1.22, 95%CI = 0.86-1.73, P = 0.27; OR = 1.03, 95%CI = 0.62-1.72, P = 0.91; OR = 1.22, 95%CI = 0.66-2.26, P = 0.52; OR = 1.25, 95%CI = 0.84-1.87, P = 0.27, respectively)

(Figure 2). In the subgroup analysis based on ethnicity, the studies included were divided into Caucasian and Asian populations. No significant association was found between p53 codon 72 polymorphism and prostate cancer risk both in Caucasian and Asian populations in all comparisons (P > 0.10).

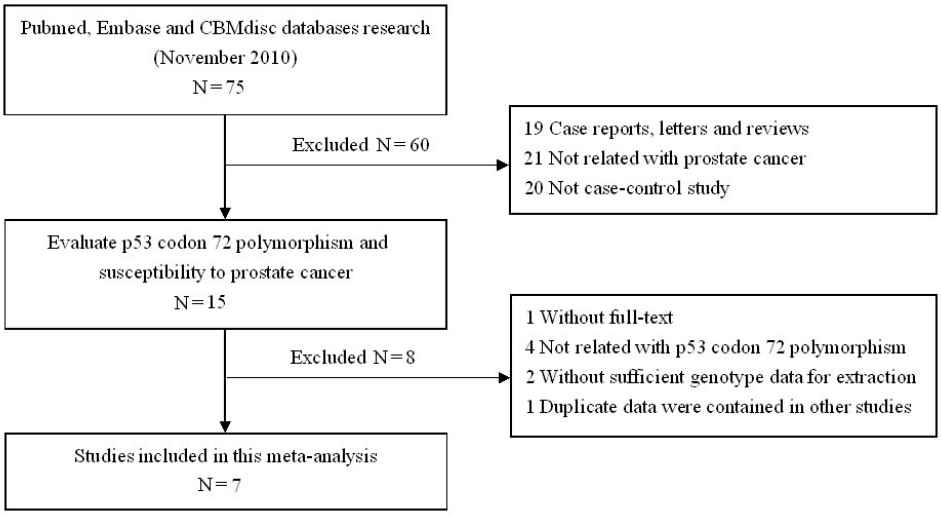


**Figure 1.** Flow chart showing the study selection procedure.

**Table 1.** Baseline characteristics of studies included in the meta-analysis.

| First author | Year | Country | Ethnicity | Source of controls | Number of subjects | | Detection method | Quality scores |
|---|---|---|---|---|---|---|---|---|
| | | | | | Cases | Controls | | |
| Henner et al. | 2001 | Poland | Caucasian | Population-based | 115 | 181 | PCR-RFLP | 19 |
| Wu et al. | 2004 | China, Taiwan | Asian | Population-based | 92 | 126 | PCR-SSP | 21 |
| Suzuki et al. | 2003 | Japan | Asian | Population-based | 114 | 105 | PCR-RFLP | 14 |
| Huang et al. | 2004 | China, Taiwan | Asian | Population-based | 200 | 247 | PCR-RFLP | 11 |
| Leiros et al. | 2005 | Germany | Caucasian | Population-based | 39 | 48 | PCR-RFLP | 20 |
| Quinones et al. | 2006 | Chile | Caucasian | Population-based | 60 | 117 | PCR-SSP | 19 |
| Ricks-Santi et al. | 2010 | American | Caucasian | Population-based | 266 | 189 | PCR-RFLP | 15 |

**Table 2.** Genotype distribution and risk allele frequency of all included studies.

| First author | Year | Cases | | | | | | | Controls | | | | | | HWE test | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Total | Arg/Arg | Pro/Arg | Pro/Pro | Arg | Pro | RF | Total | Arg/Arg | Pro/Arg | Pro/Pro | Arg | Pro | Total | $\chi^2$ | P value |
| Henner et al. | 2001 | 109 | 66 | 41 | 2 | 173 | 45 | 0.79 | 146 | 93 | 38 | 15 | 224 | 68 | 0.77 | 10.97 | <0.001 |
| Wu et al. | 2004 | 92 | 11 | 61 | 20 | 83 | 101 | 0.45 | 126 | 43 | 53 | 30 | 139 | 113 | 0.55 | 2.82 | 0.09 |
| Suzuki et al. | 2003 | 114 | 48 | 46 | 20 | 142 | 86 | 0.62 | 105 | 41 | 57 | 7 | 139 | 71 | 0.66 | 4.73 | 0.03 |
| Huang et al. | 2004 | 200 | 66 | 92 | 42 | 224 | 176 | 0.56 | 247 | 84 | 109 | 54 | 277 | 217 | 0.56 | 2.68 | 0.10 |
| Leiros et al. | 2005 | 39 | 20 | 17 | 2 | 57 | 21 | 0.73 | 48 | 23 | 23 | 2 | 69 | 27 | 0.72 | 1.65 | 0.20 |
| Quinones et al. | 2006 | 60 | 22 | 24 | 14 | 68 | 52 | 0.57 | 117 | 59 | 45 | 13 | 163 | 71 | 0.70 | 0.95 | 0.33 |
| Ricks-Santi et al. | 2010 | 245 | 37 | 135 | 73 | 209 | 281 | 0.43 | 178 | 22 | 86 | 70 | 130 | 226 | 0.37 | 0.32 | 0.57 |

RF = risk allele frequency.

Sensitivity analysis was performed by sequential omission of individual studies. The significance of pooled ORs in all individual and subgroup analyses was not influenced excessively by omitting any single study.

**Table 3.** Meta-analysis of the association between p53 codon 72 polymorphism and prostate cancer risk.

| Comparisons | OR | 95%CI | P value | Heterogeneity | | Effects model* |
|---|---|---|---|---|---|---|
| | | | | $I^2$ | P value | |
| Pro allele *vs* Arg allele | 1.09 | 0.87-1.36 | 0.47 | 58% | 0.03 | Random |
| Caucasian | 1.01 | 0.69-1.47 | 0.97 | 68% | 0.03 | |
| Asian | 1.17 | 0.93-1.48 | 0.18 | 30% | 0.24 | |
| Pro/Pro + Pro/Arg *vs* Arg/Arg | 1.22 | 0.86-1.73 | 0.27 | 61% | 0.02 | Random |
| Caucasian | 1.10 | 0.78-1.54 | 0.60 | 18% | 0.30 | |
| Asian | 1.45 | 0.68-3.05 | 0.33 | 82% | 0.003 | |
| Pro/Pro *vs* Pro/Arg + Arg/Arg | 1.03 | 0.62-1.72 | 0.91 | 69% | 0.003 | Random |
| Caucasian | 0.80 | 0.29-2.19 | 0.67 | 76% | 0.006 | |
| Asian | 1.23 | 0.66-2.29 | 0.51 | 63% | 0.06 | |
| Pro/Pro *vs* Arg/Arg | 1.22 | 0.66-2.26 | 0.52 | 69% | 0.003 | Random |
| Caucasian | 0.83 | 0.27-2.55 | 0.74 | 75% | 0.007 | |
| Asian | 1.68 | 0.84-3.40 | 0.14 | 60% | 0.08 | |
| Pro/Arg *vs* Arg/Arg | 1.25 | 0.84-1.87 | 0.27 | 66% | 0.007 | Random |
| Caucasian | 1.20 | 0.87-1.65 | 0.27 | 0% | 0.52 | |
| Asian | 1.43 | 0.57-3.61 | 0.44 | 87% | 0.0004 | |

*Using random effects model; OR = odds ratio; 95%CI = 95% confidence interval.

## Heterogeneity and publication bias

Between-study heterogeneity was found in all comparisons of p53 codon 72 polymorphism; the random effects model was used to minimize the impact of biases (Table 3). The publication bias of the meta-analysis of the association between p53 codon 72 polymorphism and prostate cancer risk was detected by Begg's funnel plot and the Egger linear regression test. All graphical funnel plots of the included studies appeared to be symmetrical. The Egger test also showed that there was non-significance in all evaluations of publication bias. Information concerning the Egger publication bias test is given in Table 4.

**Table 4.** Egger publication bias test for p53 codon 72 polymorphism.

| Comparisons | Coefficient | Standard error | *t* | P > \|t\| | 95%CI |
|---|---|---|---|---|---|
| Pro allele *vs* Arg allele | 2.13 | 2.20 | 0.97 | 0.38 | [-3.53 ~ 7.78] |
| Pro/Pro + Pro/Arg *vs* Arg/Arg | 2.54 | 2.68 | 0.95 | 0.39 | [-4.34 ~ 9.42] |
| Pro/Pro *vs* Pro/Arg + Arg/Arg | 0.79 | 1.66 | 0.48 | 0.65 | [-3.47 ~ 5.05] |
| Pro/Pro *vs* Arg/Arg | 0.40 | 1.97 | 0.20 | 0.85 | [-4.66 ~ 5.46] |
| Pro/Arg *vs* Arg/Arg | 2.33 | 3.12 | 0.75 | 0.49 | [-5.70 ~ 10.35] |

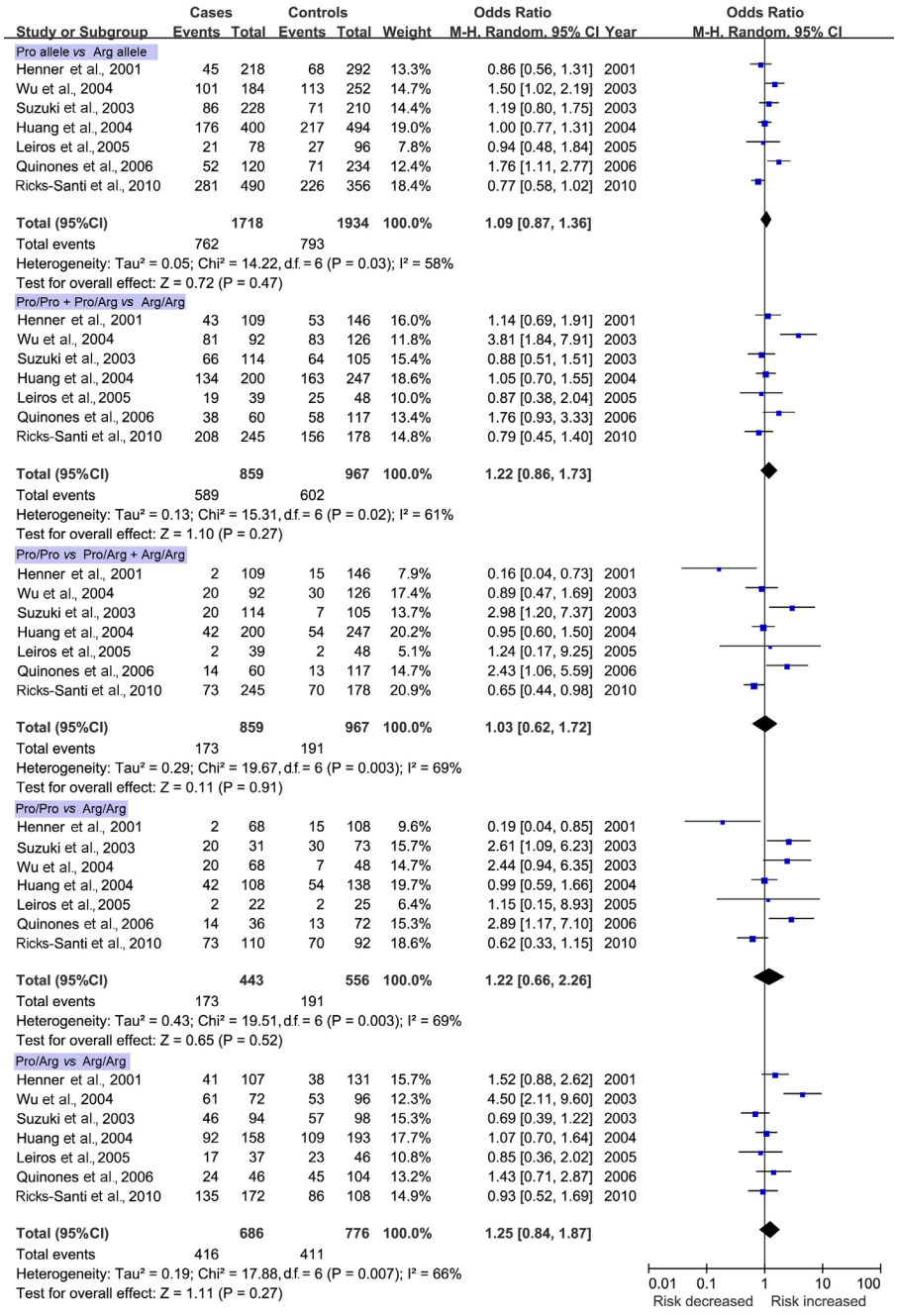


**Figure 2.** Forest plot of prostate cancer risk associated with p53 codon 72 polymorphism. The squares and horizontal lines correspond to the study-specific odds ratios (OR) and 95% confidence intervals (CI). The area of the squares reflects the study-specific weight (inverse of the variance). The diamonds represent the pooled ORs and 95%CI. M.H. = Mantel-Haenszel.

## DISCUSSION

Few studies have investigated the association between p53 codon 72 polymorphism and prostate cancer risk in the last two decades. Wu et al. (1995) found no association between p53 codon 72 polymorphism and prostate cancer risk ($\chi^2$ = 0.448, P = 0.799) in Japanese males. However, due to the small sample size, a definite conclusion could not be drawn. Subsequently, Henner et al. (2001) found that men with Pro/Pro have a significantly lower risk of prostate cancer (OR = 0.14; 95%CI = 0.03-0.71, P = 0.017) than those with Arg/Arg. However, the distribution of p53 codon 72 genotypes violated the rule of Hardy-Weinberg equilibrium. Our meta-analysis based on five studies found that although controls conformed to Hardy-Weinberg equilibrium, there was no association between p53 codon 72 polymorphism and prostate cancer risk in the comparisons of Pro allele *vs* Arg allele; Pro/Pro + Pro/Arg *vs* Arg/Arg; Pro/Pro *vs* Pro/Arg + Arg/Arg; Pro/Pro *vs* Arg/Arg, and Pro/Arg *vs* Arg/Arg.

Relationships between p53 codon 72 polymorphism and cancer development have been found for several cancers, including ovarian (Pegoraro et al., 2003), lung (Mechanic et al., 2007), cervical (Klug et al., 2009), and colon (Katkoori et al., 2009) cancers. Different races also have different genotype frequencies; Zhou et al. (2007) found that patients with gastric cancer had a significantly lower frequency of Arg/Arg than noncancer patients among Asians. In all studies, people with different nationalities have different genotype frequencies; however, in the subgroup meta-analysis by ethnicity, no association was found between p53 codon 72 polymorphism and prostate cancer risk both in Caucasian and Asian populations. Relationships between genotypes and pathological grade or clinical stage or prognosis have been reported for lung cancer (Wang et al., 1999) and nasopharyngeal carcinoma (Tsai et al., 2002). Suzuki et al. (2003) found that Pro/Pro genotype is associated with increased risk of prostate cancer but decreased risk of aggressive disease. However, even though Hardy-Weinberg equilibrium was confirmed, we observed no correlation between genotypes and pathological grade or clinical stage or prognosis in prostate cancer.

There were also some limitations in our meta-analysis. First, because of incomplete raw data or publication limitations, some relevant studies could not be included in our analysis. Secondly, we were not able to address the sources of heterogeneity that existed among studies for each polymorphism. We could not perform further subgroup stratification analysis because of the limited number of published studies. In addition, the small sample size was not ideal for detecting small genetic effects. Finally, our systematic review was based on unadjusted data, as the genotype information stratified for the main confounding variables was not available in the original papers and also the confounding factors addressed across the different studies were variable.

In conclusion, our meta-analysis suggests no association between p53 codon 72 polymorphism and prostate cancer risk. As few studies are available in this field and current evidence remains limited, it should be emphasized that there is a necessity to conduct large-scale studies with adequate methodological quality, properly controlling for possible confounding effects in order to come to a definitive conclusion.

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