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Association between the TP53 Arg72Pro Polymorphisms and Gastric Cancer Risk: An Updated Meta-Analysis and Re-Analysis of Systematic Meta-Analyses

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Abstract

Background: A latest Meta-analysis on TP53 Arg72Pro polymorphism with gastric cancer (GC) risk was published in 2015 including 20 literatures, while our study included 43 studies. Moreover, the results of previously published original studies were inconsistent and the credibility of the significant correlation between the statistical results has been ignored. Therefore, an updated Meta-analysis was conducted to further explore these associations. **Objective:** To explore whether these two gene polymorphisms are related to the risk, clinical manifestations, and pathological features of GC. **Methods:** We searched several Chinese and English databases. The crude odds ratio (OR) with 95% confidence interval (CI) was used to evaluate the correlation. In addition, false positive reporting probability (FPRP), bayesian false discovery probability (BFDP), and Venice criteria were used to assess the reliability of statistically significant correlation. **Results:** Overall, the TP53 Arg72Pro polymorphism was related to a significantly increased GC risk (AP vs. AA: OR = 1.12, 95% CI = 1.02 - 1.24; PP + AP vs. AA: OR = 1.12, 95% CI = 1.02 - 1.24; P vs. A: OR = 1.07, 95% CI = 1.00 - 1.15). However, after excluding the low quality and Hardy–Weinberg Disequilibrium (HWD) studies, significant changes were found on the TP53 Arg72Pro polymorphism with GC risk in Caucasians (PP vs. AA: OR = 1.48, 95% CI = 1.01 - 2.16) and non-gastric cancer control groups (PP vs. AP + AA: OR = 1.33, 95% CI = 1.07 - 1.64)). However, the above significant results were considered unreliable after being adjusted with Bayesian error detection probability (BFDP) and false positive

reporting probability (FPRP). These unreliable results were confirmed again, and no new reliable results were found in the further sensitivity analysis (only studies that met the quality assessment criteria). **Conclusions:** After considering the quality of the study and the reliability of the results, this Meta-analysis showed that TP53 codon 72 polymorphisms had no significant correlation with GC risk. Because of various confounding factors, the result that these polymorphisms increase GC risk is more likely to be a false positive result.

Keywords

P53, Polymorphism, Gastric Cancer, Meta-Analysis, BFDP, FPRP

1. Introduction

As we all know, gastric cancer is one of the most common malignant tumors in the world. According to statistics, there are nearly a million cases nationwide in 2020, ranking fourth and seventh among men and women respectively [1]. Among the common cancers in Chinese men, the incidence rate of gastric cancer is second only to lung cancer, and it is the fourth most common cancer among women, second only to breast cancer, lung cancer, colorectal cancer and thyroid cancer [2]. The occurrence and development of gastric cancer involves complex multi-step events, including genetic changes of multiple proton-oncogenes and tumor suppressor genes, changes in DNA repair mechanisms, and disorders of cell cycle and cell proliferation signal molecules [3].

The TP53 gene encodes a long protein composed of multiple amino acids, which is necessary for regulating the cell cycle and playing an anti-tumor role. This is achieved by coordinating the transcriptional sensitization of tumor-related genes involved in programmed cell death, maintaining genetic constancy and pathogenesis [4]. The change of TP53 has been confirmed by extensive research in a variety of malignant tumors [5] [6] [7]. The high polymorphism of TP 53 single nucleotide has been confirmed by single nucleotide polymorphism database [8]. Among them, Arg72Pro (rs1042522) is the most important and extensively studied [9].

In recent years, there have been many reports on the relationship between P53 Arg72Pro (rs 1042522) gene and gastric cancer, but the results are controversial. Thirteen related Meta-analyses have been conducted to study the association between P53 Arg72Pro polymorphism and GC risk [10]-[22]. However, the results are also controversial. In addition, the previously published Meta-analysis did not evaluate the quality of literature, nor did it evaluate the positive results to determine multiple comparisons. Therefore, this study further explored the relationship between P53 Arg72Pro and gastric cancer susceptibility by using Meta-analysis method.

2. Materials and Methods

2.1. Search Strategy

This study was performed according to the guidelines of PRISMA Group [23]. Pub Med, Em base, CNKI, International Statistical Institute (ISI), and Wan-fang databases were searched for literature retrieval, which was ended on May 1, 2022. The following search strategy was used: (SNP OR variant OR mutation OR variation OR polymorphism OR genome-wide association study OR genetic association study OR allele OR genotype) AND (gastric OR stomach) AND (p53 OR TP53). In addition, published Meta-analyses and related reviews were carefully examined.

2.2. Selection Criteria

Literature retrieval and collection strictly follows PICOS standards: 1) research based on various ethnic groups around the world; 2) literature contains sufficient genotype data or odds ratio (OR) and its 95% credibility interval (CI); 3) healthy people or non-gastric cancer people were used as the control group; 4) described the association on the P53 Arg72Pro (rs1042522) polymorphisms with GC risk; and 5) case-control or cohort studies. The exclusion criteria were: a) repetitious literature or incomplete information or data; b) no data available for relevant genotype; c) literature reviews, case reports, and letters.

2.3. Data Collection and Research Quality Scoring

All relevant data were collected independently by two researchers and examined alternately. In case of disagreement, ask the third investigator to assist in judgment. A total of 56 original articles were collected (**Supplemental Table S1**). General characteristics of literature included, including country, geographical location, race, sample size, sample source, type of control group, matching, gene frequency, adjusted OR value and adjusted confounding factors (**Supplemental Table S2**). Our study conducted a further multi-variable study on the association between TP53 Arg72Pro gene polymorphism and GC risk. Multivariate analysis included all relevant Clinicopathological characteristics, such as Helicobacter pylori infection, gender, TNM stage, differentiation type, tumor location, and histological subtypes of gastric cancer (**Supplemental Table S3**). Our study also further summarized the overall correlation between gene polymorphism and gastric cancer risk in the previously published Meta-analysis and the correlation in the subgroup analysis, and analyzed its reliability (**Supplemental Table S4**). The total score of literature quality is 18, and a total score greater than 70% is considered as low deviation risk (**Supplemental Table S5**).

2.4. Statistical Analysis and Reliability Evaluation

Crude ORs and 95% CI were used to assess the strength of the association between the P53 Arg72Pro polymorphisms and GC risk. Five genetic models were constructed including allele model, additive model, dominant model, recessive

model, and super dominant model. Q test and I^2 test based on Chi square test was used to test heterogeneity [24]. If $P \geq 0.1$ and/or $I^2 \leq 50\%$, ORs was adjoined with fixed effect model, indicating marked heterogeneity between studies. Otherwise, the random effect model was used for calculation [25]. We can determine the source of heterogeneity by Meta regression analysis of the factors that may lead to the heterogeneity of the study itself [26]. We performed sensitivity analysis by retaining high-quality and Hardy-Weinberg equilibrium (HWE) compliant studies at the same time, and judged publication bias by Begg's funnel and Egger's test [27] [28] after finding significant publication bias, these missing studies will be supplemented and added by the non-parametric "pruning and filling" method [28]. Moreover, we used the following criteria to investigate the significant results: false-positive report probability (FPRP), bayesian false discovery probability (BFDP) and the Venice criteria [29] [30] [31]. Therefore, we calculated the FPRP and BFDP in this study through Excel spreadsheet. In general, the criteria for these tests are as follows: 1) statistically significant associations were observed in at least 2 of the genetic models; 2) FPRP < 0.2 and BFDP < 0.8; 3) $I^2 < 50\%$; and 4) statistical power > 80%. If the above criteria are met, the association is considered a positive result, and all other results are considered less credible positive factors. The collected data were statistically analyzed applying Stata 12.0 software (Stata Corporation, College Station, TX).

3. Results

3.1. Search Results and Study Characteristics

Forty three studies were included in the present study (**Figure 1** and **Supplemental Table S1**). Among them, 43 studies reported TP53 Arg72Pro (13,699 cases and 18,039 controls). Moreover, 27 analyzed Asians, 11 investigated whites, two reported Indians, and three analyzed mixed populations;18 high-quality (more than 12 points) studies and 25 medium and low-quality studies; 39 studies consistent with the HWE (**Supplemental Table S2**).

3.2. Quantitative Synthesis

TP53 Arg72Pro

Overall, the Tp53 Arg72Pro polymorphism was related to a significantly increased GC risk (AP vs. AA: OR = 1.17, 95% CI = 1.04 - 1.31; PP + AP vs. AA: OR = 1.17, 95% CI = 1.04 - 1.32; P vs. A: OR = 1.09, 95% CI = 1.00 - 1.18, **Table 1** and **Supplementary Table S6**). Then, a significantly increased GC risk was also found in Asians (AP vs. AA: OR = 1.13, 95% CI = 1.02 - 1.30; PP + AP vs. AA: OR = 1.16, 95% CI = 1.03 - 1.30; P vs. A: OR = 1.10, 95% CI = 1.00 - 1.20, **Table 1**), hospital-based control (AP vs. AA: OR = 1.12, 95% CI = 1.00 - 1.25, **Table 1**), healthy control (AP vs. AA: OR = 1.13, 95% CI = 1.01 - 1.28; PP + AP vs. AA: OR = 1.15, 95% CI = 1.01 - 1.30; P vs. A: OR = 1.10, 95% CI = 1.00 - 1.21, **Table 1**), and female (PP + AP vs. AA: OR = 1.48, 95% CI = 1.04 - 2.08; P vs. A: OR = 1.32, 95% CI = 1.03 - 1.70, **Table 1**).

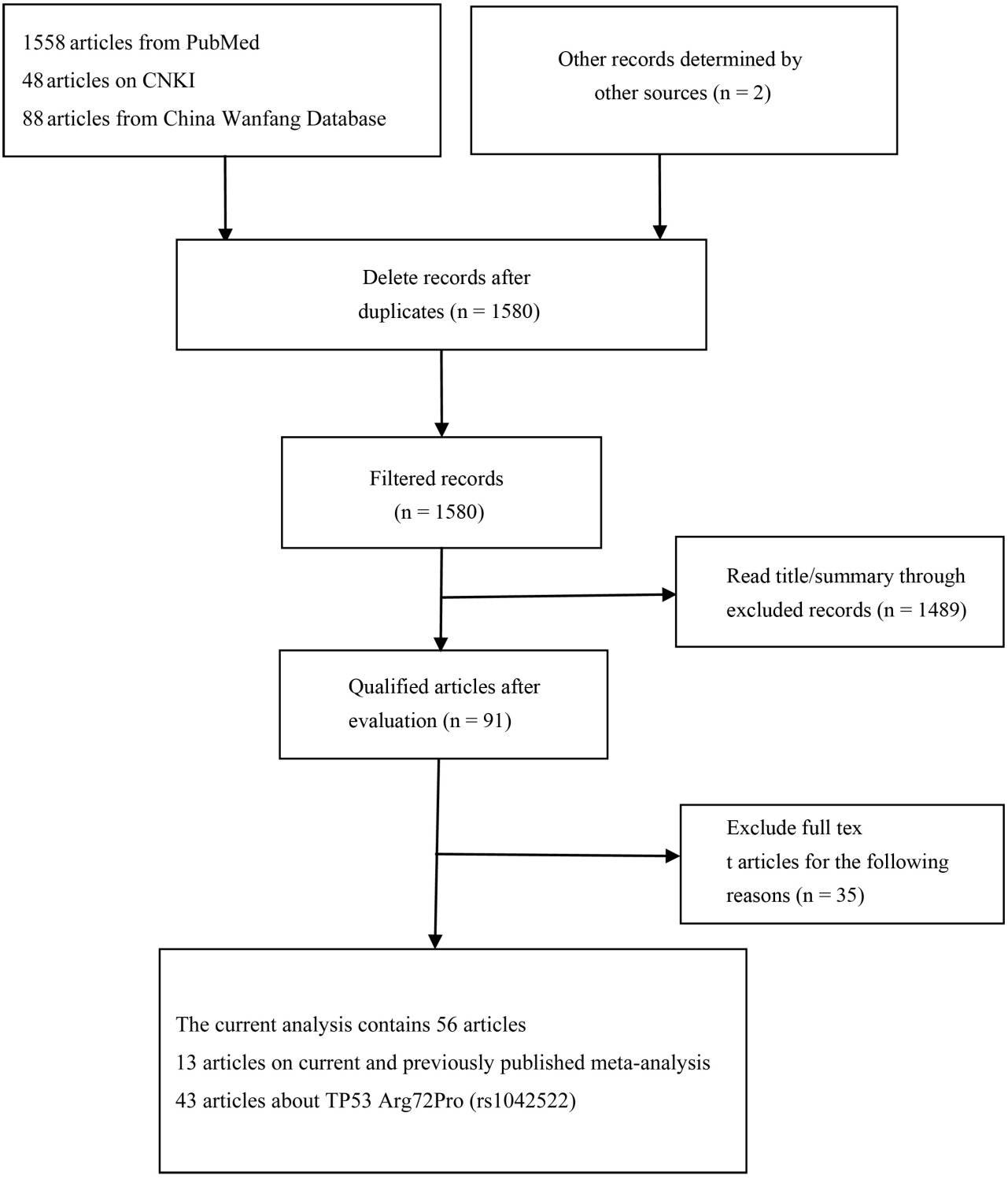

Figure 1. Flow chart of document retrieval.

3.3. Adjust ORs Analyses

Our Meta-analysis also creatively carried out Adjust ORs analyses. The results are as follows: regarding TP53 Arg72Pro polymorphism, after considering confounding factors in the overall analysis, only (PP vs. AA: OR = 1.33, 95% CI =

Table 1. Meta-analysis of the association of TP53 Arg72Pro polymorphism with risk of gastric cancer.

Variable	n (Cases/ Controls)	PP vs. AA		AP vs. AA		PP+AP vs. AA		PP vs. AP+AA		P vs. A	
		OR (95% CI)	Ph/I^2 (%)	OR (95% CI)	Ph/I^2 (%)	OR (95% CI)	Ph/I^2 (%)	OR (95% CI)	Ph/I^2 (%)	OR (95% CI)	Ph/I^2 (%)
Overall	43 (10610/13645)	1.17 (0.98 - 1.40)	0.000/77.6	**1.17 (1.04 - 1.31)**	0.000/66.2	**1.17 (1.04 - 1.32)**	0.000/73.8	1.01 (0.93 - 1.09)	0.069/25.6	**1.09 (1.00 - 1.18)**	0.000/78.0
Ethnicity											
Asian	27 (5187/8340)	119 (0.99 - 1.44)	0.000/75.2	**1.13 (1.02 - 1.25)**	0.000/46.2	**1.16 (1.03 - 1.30)**	0.000/64.8	1.09 (0.94 - 1.26)	0.000/70.5	**1.10 (1.00 - 1.20)**	0.000/75.9
Caucasian	11 (3931/3645)	1.02(0.75 - 1.37)	0.176/28.2	1.04 (0.75 - 1.44)	0.000/73.0	1.03 (0.79 - 1.33)	0.002/64.6	0.96 (0.70 - 1.33)	0.042/47.1	1.01 (0.89 - 1.14)	0.231/22.3
Mixed	3 (653/851)	-	-	-	-	-	-	-	-	-	
Source of control											
HB	32 (8570/10172)	1.08 (0.93 - 1.26)	0.000/56.9	**1.12 (1.00 - 1.25)**	0.001/51.0	1.11 (0.99 - 1.26)	0.000/57.4	1.00 (0.88 - 1.12)	0.002/47.4	1.04 (0.96 - 1.12)	0.000/56.4
PB	10 (1748/3257)	1.39 (0.88 - 2.19)	0.000/80.9	1.12 (0.86 - 1.46)	0.003/63.7	1.18 (0.90 - 1.54)	0.000/71.5	1.33 (0.90 - 1.95)	0.000/80.7	1.20 (0.96 - 1.49)	0.000/81.4
Type of control											
Healthy	28 (7357/9387)	1.19 (0.97 - 1.47)	0.000/74.1	**1.13 (1.01 - 1.28)**	0.001/51.6	**1.15 (1.01 - 1.30)**	0.000/62.9	1.10 (0.93 - 1.30)	0.000/72.0	**1.10 (1.00 - 1.21)**	0.000/73.6
Non-gastric cancer	15 (3253/4258)	1.10 (0.90 - 1.35)	0.066/38.3	1.10 (0.91 - 1.32)	0.004/56.3	1.08 (0.91 - 1.29)	0.004/56.8	1.02 (0.86 - 1.21)	0.144/28.5	1.04 (0.94 - 1.15)	0.071/37.5
H-pylori	5 (1962/2082)										
Positive		1.36 (0.97 - 1.91)	0.252/25.4	1.10 (0.88 - 1.36)	0.548/0.0	1.15 (0.93 - 1.41)	0.398/1.5	1.22 (0.97 - 1.54)	0.372/6.1	1.15 (0.99 - 1.33)	0.326/13.8
Negative		1.12 (0.71 - 1.75)	0.469/0.0	0.93 (0.65 - 1.32)	0.507/0.0	0.96 (0.67 - 1.38)	0.353/9.3	1.20 (0.86 - 1.68)	0.735/0.0	1.04 (0.82 - 1.32)	0.286/20.2
Gendering	6 (982/1455)										
Male		1.13 (0.6 - 1.95)	0.108/50.5	1.15 (0.85 - 1.55)	0.574/0.0	1.13 (0.84 - 1.53)	0.355/7.6	1.10 (0.68 - 1.78)	0.011/66.2	1.07 (0.83 - 1.39)	0.119/48.8
Female		1.67 (0.91 - 3.04)	0.248/27.3	1.43 (0.99 - 2.05)	0.846/0.0	**1.48 (1.04 - 2.08)**	0.676/0.0	1.47 (0.78 - 2.78)	0.317/14.9	**1.32 (1.03 - 1.70)**	0.305/17.3
Tumor Location	7 (1412/2548)										
Cardia		1.23 (0.67 - 2.26)	0.066/49.2	1.07 (0.72 - 1.59)	0.065/49.4	1.10 (0.72 - 1.69)	0.017/61.1	1.05 (0.58 - 1.89)	0.022/59.4	1.06 (0.75 - 1.49)	0.002/70.6
Non-cardia		1.00 (0.72 - 1.38)	0.208/28.9	1.16 (0.94 - 1.45)	0.224/26.8	1.12 (0.90 - 1.40)	0.154/35.9	0.93 (0.74 - 1.16)	0.524/0.0	1.03 (0.88 - 1.21)	0.138/38.2
Histologicsubtype	8 (1378/1605)										
Intestinal type		1.12 (0.69 - 1.83)	0.01/62.3	0.90 (0.64 - 1.26)	0.026/56.1	0.94 (0.67 - 1.33)	0.008/63.5	1.27 (0.84 - 1.93)	0.035/53.6	1.03 (0.80 - 1.33)	0.004/66.8
Diffuse type		1.33 (0.87 - 2.03)	0.095/42.4	1.10 (0.85 - 1.41)	0.305/15.8	1.15 (0.91 - 1.44)	0.318/14.3	1.23 (0.84 - 1.80)	0.051/50.0	1.13 (0.92 - 1.38)	0.070/46.5

Continued

Sensitivity analysis											
HWE and Quality score > 12											
Overall	16 (5513/7792)	1.08 (0.86 - 1.36)	0.000/68.5	1.06 (0.94 - 1.19)	0.049/40.1	1.07 (0.93 - 1.23)	0.001/59.1	1.04 (0.87 - 1.24)	0.001/60.2	1.04 (0.94 - 1.16)	0.000/69.5
Ethnicity											
Asian	10 (3017/4643)	1.13 (0.84 - 1.52)	0.000/80.0	1.05 (0.90 - 1.23)	0.033/52.2	1.08 (0.90 - 1.30)	0.000/71.9	1.10 (0.88 - 1.36)	0.000/72.1	1.07 (0.92 - 1.23)	0.000/80.4
Caucasian	4 (634/1874)	0.93 (0.63 - 1.35)	0.374/3.7	1.01 (0.76 - 1.34)	0.132/46.6	0.99 (0.75 - 1.31)	0.116/49.3	0.92 (0.64 - 1.30)	0.488/0.0	0.98 (0.81 - 1.20)	0.167/40.8
Source of control											
HB	10 (4122/5068)	1.13 (0.89 - 1.44)	0.012/57.2	1.05 (0.94 - 1.17)	0.326/12.7	1.07 (0.93 - 1.23)	0.076/42.3	1.06 (0.87 - 1.30)	0.019/54.8	1.04 (0.93 - 1.17)	0.007/60.6
PB	6 (1391/2724)	1.03 (0.63 - 1.69)	0.000/79.5	1.07 (0.81 - 1.42)	0.012/65.8	1.08 (0.79 - 1.49)	0.001/76.2	1.00 (0.71 - 1.42)	0.005/69.9	1.06 (0.83 - 1.34)	0.000/80.7
Type of control											
Healthy	11 (4574/6218)	1.04 (0.80 - 1.36)	0.000/72.5	1.06 (0.92 - 1.23)	0.030/49.7	1.06 (0.90 - 1.25)	0.002/63.4	1.00 (0.81 - 1.23)	0.001/66.8	1.03 (0.91 - 1.17)	0.000/72.4
Non-gastric cancer	5 (939/1574)	1.26 (0.85 - 1.88)	0.170/37.7	1.09 (0.88 - 1.35)	0.331/12.9	1.09 (0.82 - 1.45)	0.097/49.1	**1.33 (1.07 - 1.64)**	0.427/0.0	1.08 (0.86 - 1.35)	0.054/57.0
Egger's test											
P_E		0.627		0.369		0.317		0.419		0.739	

HWE = Hardy-Weinberg equilibrium, OR = odds ratio, HB = hospital-based studies, PB = population-based studies.

1.09 - 1.61; PP + AP vs. AA: OR = 1.36, 95% CI = 1.04 - 1.77). The results showed that TP53 Arg72Pro polymorphism still increased the risk of gastric cancer after excluding confounding factors. This phenomenon can also be observed in further subgroup analysis (Table 2).

3.4. Heterogeneity and Sensitivity Analyses

Meta regression analysis was used to test the heterogeneity. It was not found in TP53 Arg72Pro.

We conducted sensitivity analysis to determine the impact of individual data sets on the pooled or and the stability of pooled data by eliminating hardy Weinberg disequilibrium and low-quality research at the same time. For the TP53 Arg72Pro, when we only selected studies with high quality scores and HWE, the overall results changed significantly, then, significant associations were observed only in non-gastric cancer control groups (PP vs. AP + AA: OR = 1.33, 95% CI = 1.07 - 1.64, Table 1).

3.5. Publication Bias

We did not observe publication bias.

Table 2. Meta analysis of the association between TP53 Arg72Pro polymorphism and gastric cancer risk previously published.

Variable	n	PP vs. AA		AP vs. AA		PP+AP vs. AA		PP vs. AP+AA	
		aOR (95% CI)	Ph/I^2 (%)	aOR (95% CI)	Ph/I^2 (%)	aOR (95% CI)	Ph/I^2 (%)	aOR (95% CI)	Ph/I^2 (%)
Overall	**16**	**1.33 (1.09 - 1.61)**	0.026/46.1	1.17 (0.97 - 1.41)	0.002/60.5	**1.36 (1.04 - 1.77)**	0.526/0.0	-	-
Ethnicity									
Asian	10	**1.38 (1.15 - 1.66)**	0.144/34.3	**1.22 (1.05 - 1.42)**	0.118/37.7	1.39 (0.99 - 1.95)	0.258/22.0	-	-
Caucasian	4	1.01 (0.48 - 2.13)	0.046/62.6	0.37 (0.07 - 1.89)	0.005/87.5	-	-	-	-
Source of control									
HB	12	1.25 (0.97 - 1.61)	0.024/50.1	1.13 (0.88 - 1.44)	0.002/65.4	**1.73 (1.02 - 2.94)**	0.662/0.0	-	-
PB	3	1.42 (0.98 - 2.06)	0.695/0.0	1.28 (0.87 - 1.88)	0.265/19.6	-	-	-	-
Type of control									
Healthy	11	**1.43 (1.18 - 1.72)**	0.172/29.7	**1.21 (1.03 - 1.41)**	0.129/34.9	1.39 (0.99 - 1.95)	0.258/22.0	-	-
Non-GC	5	1.09 (0.65 - 1.81)	0.05/57.9	0.72 (0.23 - 2.23)	0.000/87.3	-	-	-	-

aOR = adjust odds ratio, HB = hospital-based studies, PB = population-based studies, GC = gastric cancer.

3.6. The Credibility of Genetic Association

Our research creatively applied three methods to test the reliability of current and previously published Meta-analyses, including: 1) false positive reporting probability (FPRP), 2) Bayesian false discovery probability (BFDP) and Venice standard. First, FPRP, BFDP and Venice standards were used to evaluate the reliability of previously published Meta-analyses. All major findings were considered "less credible". All statistically significant associations were considered "less credible" (Supplementary Table S4). Therefore, we conducted an updated Meta-analysis to confirm this result. At the same time, the reliability of our research was also evaluated, and no statistically significant correlation was observed in the genetic model we studied. Therefore, the current results are considered false positive, and detailed reliability assessment results are listed (Table 3).

4. Discussion

GC is the main cause of cancer deaths worldwide, causing more than 700,000 deaths every year [32] [33]. The incidence rate of gastric cancer varies in different geographical locations [34]. These regional differences are attributed to helicobacter pylori infection, lifestyle (such as drinking, smoking, etc) and genetic risk [35]. Due to the joint effect of genetic factors, environment and helicobacter pylori, when oncogenes, tumor suppressor genes and genes involved in cell regulation mechanism mutate, cancer will be triggered [36]. Many important evidences indicate that p53 gene polymorphism (Arg72Pro) may be a potential

Table 3. False-positive report probability values and Bayesian-false discovery probability values for the statistically significant associations in current meta-analysis.

Variables	OR (95% CI)	I^2 (%)	Statistical power		Prior probability of 0.001		Prior probability of 0.001
			OR = 1.2	OR = 1.5	OR = 1.2	OR = 1.5	
TP53 Arg72Pro							
Overall							
AP vs. AA	**1.17 (1.04 - 1.31)**	66.2	0.908	1.000	0.970	0.967	0.999
PP + AP vs. AA	**1.17 (1.04 - 1.32)**	73.8	0.908	1.000	0.970	0.967	0.999
P vs. A	**1.09 (1.00 - 1.18)**	78.0	0.999	1.000	0.985	0.985	1.000
Asian							
AP vs. AA	**1.13 (1.02 - 1.25)**	46.2	0.878	1.000	0.952	0.946	0.999
PP + AP vs. AA	**1.16 (1.03 - 1.30)**	64.8	0.720	1.000	0.937	0.914	0.997
P vs. A	**1.10 (1.00 - 1.20)**	75.9	0.975	1.000	0.970	0.969	0.999
HB							
AP vs. AA	**1.12 (1.00 - 1.25)**	51.0	0.891	1.000	0.980	0.977	0.999
Healthy							
AP vs. AA	**1.13 (1.01 - 1.28)**	51.6	0.828	1.000	0.985	0.982	0.999
PP + AP vs. AA	**1.15 (1.01 - 1.30)**	62.9	0.752	1.000	0.971	0.962	0.999
P vs. A	**1.10 (1.00 - 1.21)**	73.6	0.963	1.000	0.981	0.980	0.999
Gendering							
Female							
PP + AP vs. AA	**1.48 (1.04 - 2.08)**	0.0	0.114	0.531	0.995	0.978	0.997
P vs. A	**1.32 (1.03 - 1.70)**	17.3	0.230	0.839	0.993	0.974	0.998
HWE and Quality score > 12							
Non-gastric cancer							
PP vs. AP + AA	**1.33 (1.07 - 1.64)**	0.0	0.168	0.870	0.978	0.898	0.994

HWE = Hardy-Weinberg equilibrium, OR = odds ratio, HB = hospital-based studies, PB = population-based studies.

genetic factor of gastric cancer. TP53 protein has the functions of cell cycle regulation, programmed cell death and DNA repair [37] [38]. Therefore, the status of mutant TP53 is of great significance in predicting the clinical prognosis of tumor. Therefore, it is worth further discussion. Therefore, the purpose of this study is to clarify the relationship between genetic polymorphism and the risk of gastric cancer and clinicopathological characteristics by systematically analyzing the relationship between GC and TP53 gene polymorphism. The current Meta-analysis includes 13,699 cases of TP53 Arg72Pro polymorphism and 18039 controls [39]-[81]. The following is a summary of the strength of the relationship between this gene polymorphism and the risk of gastric cancer.

With regard to the polymorphism of TP53 codon 72, the overall analysis showed that the polymorphism of codon 72 would affect GC risk. In further subgroup analyses, the comprehensive results after excluding the HWE violation group and the low-quality study showed the opposite conclusion. Comparative studies of Asian race subgroup, healthy control subgroup, female and Hb source subgroup showed that codon 72 polymorphism significantly increased the risk of GC, while no significant results were found in other subgroup analysis and final sensitivity analysis, indicating that studies with relatively high quality of combined data tended to indicate that codon 72 polymorphism increased the risk of gastric cancer. No susceptibility of GC to codon 72 polymorphism was found in HP infection, tumor site and histological type. Although 43 studies have described the relationship between codon 72 polymorphism and the risk of gastric cancer, more high-quality studies are still needed to draw more convincing conclusions.

In the current Meta-analysis, the data of TP53 polymorphisms on the clinical and pathological characteristics of GC were collected and statistically analyzed. Codon 72 polymorphism was significantly increased in female patients, and there was no correlation in male patients. There was no significant correlation among the presence or absence of Helicobacter pylori infection, tumor site and histological subtype. Only one study on TP53 Arg 72 polymorphism under different case characteristics [16] reported that TP53 Arg 72 polymorphism was associated with high risk of intestinal type gastric cancer and non cardiac gastric cancer in Asians and Non-cardia. However, this conclusion is not certain, because the control group of the sample does not meet HWE and other limitations in the studied procedure. Our Meta-analysis also creatively carried out Adjust ORs analyses. The results showed that TP53 Arg72Pro polymorphism still increased the risk of gastric cancer after excluding confounding factors. This phenomenon can also be observed in further subgroup analysis. In addition, the reliability analysis, including bayesian error detection probability (BFDP), false positive report probability (FPRP) and Venice standard, was used. The results showed that there was no significant difference (correlation in the overall analysis and any subgroup analysis).

The current Meta-analysis has some advantages over previously published meta-analyses: 1) we explored credibility using FPRP and BFDP; 2) The quality of eligible studies was evaluated; 3) The sample size is larger, and the data collected is more detailed than previous meta-analyses: in 2015, the published meta-analysis with the largest sample size was conducted to detect the relationship between TP53 codon 72 (21 studies, including 6463 cases and 7435 controls), has GC risk. The number of studies and sample size in the current Meta-analysis (43 studies, including 13699 GC cases and 18039 controls at codon 72) were larger than those in the published meta-analysis. 4) More subgroup analyses were performed according to control type, matching, and quality score. 5) Our study also further summarized the adjusted OR values and adjusted confounders in the previously published Meta-analysis.

The published Meta-analysis results of the association between TP53 codon 72 polymorphisms and GC risk are shown in **Supplementary Table S4**. Published Meta-analyses [10] [13] [15] [16] [17] [19] [21] [22] showed that TP53 codon 72 polymorphism significantly increased GC risk in the overall analysis; In one of the studies [19], it can be seen that in the meta-analysis published by studies from China, South Korea, Japan, the United States and Italy, there is significant inconsistency in ethnic classification; Moreover, only two studies [16] [19] have carried out analysis according to clinicopathological characteristics; Another five published Meta-analyses [11] [12] [14] [18] [20] did not carry out model calculation. Compared with the current study, previous studies have some limitations. First, the previous Meta-analysis has not conducted literature quality evaluation. Secondly, 10 Meta-analyses did not report HWE inclusion in the study, and only 4 [10] [17] [20] [21] excluded studies that violated HWE. In addition, in the past, only three Meta-analyses [13] [15] [21] have carried out the Begg test, and one of them [15] has also carried out the egger test. Third, all previous Meta-analyses [10]-[22] did not adjust the positive results of multiple comparisons, nor did they conduct subgroup analyses of clinical manifestations. Fourth, some published Meta-analyses have not carried out sensitivity analyses. Finally, due to improper retrieval strategies and a large number of updated original research, the published Meta-analysis included incomplete research.

Therefore, we conducted an updated Meta-analysis to further explore the association between TP53 codon 72 polymorphisms and GC risk. In the current Meta-analysis, we used a larger sample size. In addition, we evaluated the quality of relevant studies and considered the epidemiological characteristics of the studies included in this Meta-analysis (**Table 1**, **Supplement Table S2** and **Supplement Table S3**). In addition, Meta regression analysis has been used to explore sources of heterogeneity (including geographical region, race, sample size, control source, case source, cancer determination, control determination, matching, HWE, and adjustment for confounders and quality scores). In addition, we conducted stratified analysis based on epidemiology, especially sensitivity analysis. After considering the research process comprehensively, we selected high-quality studies with high comprehensive scores and HWE compliance (to avoid random errors and confounding bias that may distort the results of molecular epidemiology research). In addition, the subgroup analyses with clinical manifestations were performed in this Meta-analysis. Finally, BFDP and FPRP methods have been used to correct for significant results.

Although a variety of strategies have been adopted to improve the problems of previous studies, this study still has some limitations. First, the current Meta-analysis only includes studies published in English or Chinese, which may omit irrelevant or negative findings in other languages and generate certain publication bias, although it cannot be detected using Begg funnel plot and egger test. Second, in our study, there were few Indian ethnic groups, so we could not evaluate the impact of these polymorphisms on this ethnic group, so more and more large sample studies are needed to estimate the impact of gene polymor-

phisms (Arg72Pro). Third, the few cases and controls in certain specific subgroups, especially the Indian population and the mixed population, may not provide sufficient statistical power to evaluate the relationship between gene polymorphisms (Arg72Pro) and gastric cancer harm in these populations. Fourth, in different studies, the inclusion criteria of the control group are also different. Some were selected from asymptomatic individuals who were not diagnosed by examination, and some were selected from non cancer patients who were clearly diagnosed by gastroscopy. Such classification criteria may lead to miscalculation bias, which makes it impossible to exclude some case-control cases with potential cancer risk. Last but not least, so far, there is no rich data to support our Meta-analysis to further explore the interaction between these two genes and between genes and the environment. As we all know, besides genetic factors, smoking, drinking, eating habits, family history and age are also the main risk factors for GC; however, due to the limited coverage of such relevant data in the selected studies, we did not perform subgroup analyses on smokers or non-smokers, drinkers or non drinkers, and whether there was a family genetic history. Therefore, when sufficient data are available in the future, more accurate analysis should be carried out.

5. Conclusion

In conclusion, biological, epidemiological, and clinical characteristics confirmed the correlation between p53 (Arg72Pro) polymorphism and GC risk. Our study intensely suggests that p53 Arg72Pro gene polymorphisms are associated with the risk of GC, especially in Asians. However, it was a great pity that all statistically significant associations were considered as "less reliable" results. Therefore, based on these deficiencies, we need more research to verify and enrich our future research results and further explore the interaction between the two genes.

6. Data Availability

All data have been included in the article and attached table. **Supplementary Table S1** details the research in this study and the previously published Meta-analysis; **Supplementary Table S2** and **Supplementary Table S3** summarize the general situation and specific data of all genotype of P53 Arg72Pro; **Supplementary Table S4** shows the reliability results of previously published Meta-analyses; **Supplementary Table S5**: All the quality scoring standards included in the study; **Supplementary Table S6** provides a forest map of the meta-analysis results.

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Author's Contribution

Li-Li Huo: research design and performance, data collection, data analysis, paper

writing.

Yu-Wei Wang: data collection.

Di Wang and Jingyi Chen: data recheck.

Chang-Qing Yang and Xiao-Feng He: research design and paper review.

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Competing Interests

The authors of this study declare that there is no other competitive interest in this manuscript.

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Supplementary

Supplementary Table S1: https://kdocs.cn/l/cakU8Edss6Yu
Supplementary Table S2: https://kdocs.cn/l/cb77blKzvksM
Supplementary Table S3: https://kdocs.cn/l/cpZAA7CZRJyM
Supplementary Table S4: https://kdocs.cn/l/cjFRh0Lcxjih
Supplementary Table S5: https://kdocs.cn/l/cctxv87OpHb4
Supplementary Table S6: https://kdocs.cn/l/cvs5hbfRh5XA