Association between the polymorphisms in XPG gene and gastric cancer susceptibility in Chinese populations

A PRISMA-compliant meta-analysis

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Abstract

Background: Several previous studies were carried out on the association between xeroderma pigmentosum group G (XPG) gene polymorphisms (including rs873601 G>A, rs2094258 C>T, rs2296147 T>C, and rs751402 C>T) and the risk of gastric cancer in Chinese populations. However, their conclusions were not consistent. Therefore, this meta-analysis was performed by us to investigate the association between the 4 potentially functional single nucleotide polymorphisms (SNPs) of XPG gene and gastric cancer risk.

Methods: The eligible literatures were identified through PubMed, Embase, Ovid MEDLINE, Web of Science, CNKI, and Wan fang databases up to July 2017. Finally, 5 studies for rs873601, 7 studies for rs2094258, 4 studies for rs2296147, and 8 studies for rs751402 were used for the current meta-analysis.

Results: Of the 4 included SNPs, only rs751402 was showed to be associated with the risk of gastric cancer [C vs T, odds ratio (OR)=1.16, 95% confidence interval (CI)=1.04–1.29; CC + CT vs TT, OR=1.23, 95% CI=1.00–1.52; CC vs CT + TT, OR=1.15, 95% CI=1.06–1.27; CC vs TT, OR=1.35, 95% CI=1.06–1.72; CC vs CT, OR=1.13, 95% CI=1.02–1.25].

Conclusion: The current meta-analysis demonstrated that the XPG gene polymorphism rs751402 was associated with increased susceptibility to gastric cancer in Chinese populations. However, studies with a larger number of subjects among different ethnic groups are needed to further validate the results.

Abbreviations: CI = confidence interval, ERCC5 = excision repair cross complementing group 5, HWE = Hardy–Weinberg equilibrium, MAF = minor allele frequency, NER = nucleotide excision repair, OR = odds ratio, SNP = single nucleotide polymorphism, XPG = xeroderma pigmentosum group G.

Keywords: Chinese, gastric cancer, polymorphism, susceptibility, XPG

1. Introduction

Gastric cancer is always accompanied with high mortality. According to the statistics, the incidence rate of gastric cancer is the highest in Eastern Asia including China. [1–2] Gastric carcinogenesis is a multifactor process involved in lifestyle, environmental factor, and host genetics. [3] The relationship between the former 2 factors and gastric cancer risk has been already well known. [4–5] Genetic susceptibility attracts increasing attention in recent years. [6–11]

In humans, DNA repair system plays a critical role in maintaining genome stability, which prevents carcinogenesis. [12] Nucleotide excision repair (NER) has been identified as a major DNA repair pathway. [13] One of the rate-limiting proteins in the NER mechanism is xeroderma pigmentosum group G (XPG). [14] The protein, also named the excision repair cross complementing group 5 (ERCC5), is an endonuclease. The endonuclease could cut the damaged DNA at the lesion during DNA repair process. [15] Therefore, genetic variations of XPG may affect DNA repair capacity. And it could partly explain why certain individuals have increased susceptibility to malignancies compared with others. [16]

Recently, several studies have explored the association between the polymorphisms in XPG gene (including rs873601 G>A, rs2094258 C>T, rs2296147 T>C, and rs751402 C>T) and gastric cancer risk in Chinese populations. However, the conclusions in these studies were controversial. [16–24] To clarify the association between these single nucleotide polymorphisms (SNPs) and gastric cancer risk in Chinese populations, we performed this meta-analysis of eleven published studies. Meanwhile, we will learn the roles of these SNPs in gastric carcinogenesis and illustrate the possible reasons for these
conflicting results. All of the original regions in these studies were from China and no other ethnicities or regions existed.

2. Methods

2.1. Search strategy
The potentially relevant literatures were searched in PubMed, Embase, Ovid MEDLINE, Web of Science, CNKI, and Wanfang databases up to July 2017. The search terms were “gastric cancer,” “stomach cancer,” “xeroderma pigmentosum group G,” “XPG,” “excision repair cross-complementing group 5,” “ERCC5,” “polymorphism,” “SNP,” “rs873601,” “rs2094258,” “rs2296147,” and “rs751402.” Furthermore, all references of the retrieved eligible studies were examined for additionally relevant publications.

2.2. Inclusion criteria
The inclusion criteria for studies were as follows: evaluating the association between the SNPs of XPG gene and gastric cancer risk in Chinese populations; case-control study; and available data including the phenotype or allele frequencies of the SNPs of XPG gene in both cases and controls. More than that, unpublished articles, abstracts from conferences, case reports, and reviews were excluded.

2.3. Data extraction
Data including the following information were collected from each eligible study: the first author’s name, year of publication, region and ethnicity of the sample population, the sample sizes in case and control groups, the distribution of phenotype, and minor allele frequency (MAF). The Newcastle-Ottawa scale was used to evaluate the quality of individual studies.

2.4. Statistical analysis
Hardy–Weinberg equilibrium (HWE) in the control group of each study was examined. The association between SNP and gastric cancer risk was assessed by odds ratio (OR) and 95% confidence interval (CI) in 5 genetic models, including allelic model, recessive model, dominant model, additive model, and heterozygous comparison model. We pooled these ORs using fixed or random effect model according to heterogeneity. The Chi-square-based Q test and I² index were used to assess the presence of statistical heterogeneity. If \( P < .10 \) for the Q test or \( I^2 > 50\% \), significant heterogeneity between studies existed and the random-effect model was conducted. Otherwise, the fixed-effect model was applied. To validate the stability of the pooled results and identify the sources of heterogeneity, sensitive analysis was carried out. Moreover, the publication bias among studies was evaluated by both Begg test and Egger test. The false-positive report probability (FPRP) analysis and trial sequential analysis (TSA) are performed to confirm the results in this meta-analysis. All statistical tests were performed using STATA software, version 11.0 (STATA Corp., College Station, TX).

| Table 1 | Characteristics of 11 studies included in this meta-analysis. |
|------|------------------|
| Refs. | Region | Ethnicity | Sample size | SNPs |
| Chen et al[23] | Zhejiang | Asian | 692 | G>A + + + + 5 |
| Duan et al[16] | Liaoning | Asian | 478 | G>T + + 6 |
| Feng et al[22] | Shanxi | Asian | 177 | G>A + + + 7 |
| Guo et al[21] | Hebei | Asian | 142 | G>A + + + 6 |
| He et al[24] | Shanghai and Jiangsu | Asian | 1125 | G>A + + + 6 |
| Hu et al[25] | Guangdong, Guangxi and Hainan | Asian | 1142 | G>A + + + 5 |
| Li et al[20] | Henan | Asian | 216 | G>A + + 6 |
| Lu et al[19] | Gansu | Asian | 184 | G>A + + 6 |
| Yang et al[18] | Shandong | Asian | 155 | G>A + + 5 |
| Yang et al[25] | Henan | Asian | 337 | G>A + + 6 |
| Zhou et al[17] | Hebei | Asian | 431 | G>A + + 7 |

SNPs = single nucleotide polymorphisms.
Table 2
Genotype and allele frequencies distribution of XPG polymorphism in eleven studies included in this meta-analysis.

| Refs. | BB  | Bb  | bb  | BB  | Bb  | bb  | MAF Case | Control | HWE |
|-------|-----|-----|-----|-----|-----|-----|----------|---------|-----|
| rs873601 | G>A |     |     |     |     |     |          |         |     |
| Chen et al[23] | 172 | 333 | 187 | 205 | 396 | 170 | 0.511 | 0.477 | 0.415 |
| He et al[24] | 274 | 560 | 291 | 327 | 605 | 264 | 0.508 | 0.474 | 0.616 |
| Hua et al[26] | 311 | 557 | 274 | 323 | 598 | 252 | 0.484 | 0.470 | 0.424 |
| Yang et al[25] | 96  | 163 | 78  | 91  | 164 | 91  | 0.473 | 0.500 | 0.333 |
| Zhou et al[17] | 115 | 215 | 101 | 132 | 200 | 100 | 0.484 | 0.463 | 0.152 |
| rs2094258 | C>T |     |     |     |     |     |          |         |     |
| Chen et al[23] | 287 | 304 | 101 | 291 | 368 | 112 | 0.366 | 0.384 | 0.803 |
| Feng et al[22] | 15  | 75  | 87  | 15  | 96  | 127 | 0.703 | 0.735 | 0.577 |
| He et al[24] | 457 | 518 | 150 | 457 | 560 | 179 | 0.364 | 0.384 | 0.728 |
| Hua et al[26] | 499 | 508 | 135 | 527 | 524 | 122 | 0.341 | 0.327 | 0.623 |
| Lu et al[19] | 17  | 67  | 100 | 13  | 72  | 127 | 0.726 | 0.762 | 0.605 |
| Yang et al[18] | 71  | 74  | 10  | 121 | 111 | 14  | 0.303 | 0.283 | 0.076 |
| Yang et al[25] | 131 | 149 | 57  | 145 | 166 | 36  | 0.390 | 0.343 | 0.252 |
| rs2296147 | T>C |     |     |     |     |     |          |         |     |
| Chen et al[23] | 442 | 217 | 33  | 475 | 264 | 32  | 0.204 | 0.213 | 0.535 |
| Duan et al[16] | 257 | 122 | 24  | 260 | 132 | 11  | 0.211 | 0.191 | 0.232 |
| He et al[24] | 700 | 371 | 54  | 742 | 398 | 56  | 0.213 | 0.213 | 0.779 |
| Hua et al[26] | 725 | 364 | 53  | 746 | 388 | 39  | 0.206 | 0.199 | 0.182 |
| Yang et al[25] | 208 | 105 | 24  | 196 | 110 | 41  | 0.227 | 0.277 | 0.001* |
| rs751402 | C>T |     |     |     |     |     |          |         |     |
| Chen et al[23] | 286 | 313 | 93  | 351 | 331 | 89  | 0.361 | 0.330 | 0.416 |
| Duan et al[16] | 172 | 181 | 47  | 206 | 165 | 29  | 0.344 | 0.279 | 0.605 |
| Feng et al[22] | 70  | 83  | 24  | 101 | 107 | 28  | 0.370 | 0.345 | 0.967 |
| Guo et al[21] | 47  | 73  | 22  | 117 | 136 | 21  | 0.412 | 0.325 | 0.029* |
| Hua et al[26] | 426 | 555 | 161 | 433 | 551 | 189 | 0.384 | 0.396 | 0.537 |
| Li et al[19] | 88  | 106 | 22  | 95  | 103 | 18  | 0.347 | 0.322 | 0.174 |
| Lu et al[19] | 69  | 91  | 24  | 87  | 97  | 22  | 0.378 | 0.342 | 0.510 |
| Yang et al[18] | 49  | 73  | 33  | 103 | 111 | 32  | 0.448 | 0.356 | 0.807 |
| Zhou et al[17] | 174 | 196 | 61  | 193 | 193 | 46  | 0.369 | 0.330 | 0.827 |

HWE = Hardy–Weinberg equilibrium, MAF = minor allele frequency. *P < 0.05.

Table 3
Meta-analysis of XPG polymorphism and the risk of gastric cancer in Chinese populations.

| Genetic comparison | $P_0$ | F, % | 95% CI | $P_2$ | Model |
|--------------------|-------|------|--------|-------|-------|
| rs873601 G>A       | .336  | 12.30| 1.09 (1.02–1.16) | .010* | Fixed |
| GG+AG vs AA        | .263  | 23.70| 1.16 (1.04–1.28) | .007* | Fixed |
| GG vs AA+AA        | .578  | 0.00 | 1.08 (0.98–1.20) | .121  | Fixed |
| GG vs AA           | .333  | 12.60| 1.18 (1.04–1.34) | .009* | Fixed |
| GG vs AG           | .663  | 0.00 | 1.04 (1.03–1.16) | .478  | Fixed |
| rs2094258 C>T      | .133  | 38.90| 0.98 (0.92–1.05) | .618  | Fixed |
| CC+CT vs TT        | .119  | 40.80| 1.01 (0.93–1.14) | .801  | Fixed |
| CC vs CT+TT        | .409  | 2.10 | 0.96 (0.89–1.00) | .413  | Fixed |
| CC vs CT           | .083  | 46.40| 1.00 (0.90–1.25) | .974  | Random |
| CC vs CT           | .734  | 0.00 | 0.95 (0.86–1.05) | .286  | Fixed |
| rs2296147 T>C      | .687  | 0.00 | 1.02 (0.94–1.10) | .678  | Fixed |
| TT+CT vs CC        | .264  | 24.50| 1.27 (1.01–1.60) | .045* | Fixed |
| TT vs CT+CC        | .866  | 0.00 | 0.98 (0.89–1.08) | .721  | Fixed |
| TT vs CC           | .281  | 21.50| 1.25 (0.99–1.58) | .065  | Fixed |
| TT vs CT           | .885  | 0.00 | 0.95 (0.86–1.05) | .337  | Fixed |
| rs751402 C>T       | .045  | 51.20| 1.16 (1.04–1.29) | .008* | Random |
| CC+CT vs TT        | .079  | 45.10| 1.23 (1.00–1.52) | .047* | Random |
| CC vs CT+TT        | .375  | 7.20 | 1.15 (1.05–1.27) | .003* | Fixed |
| CC vs TT           | .035  | 53.70| 1.35 (1.06–1.72) | .018* | Random |
| CC vs CT           | .878  | 0.00 | 1.13 (1.02–1.29) | .015* | Random |

CI = confidence interval. *P < 0.05.
2.5. Ethical review

The current meta-analysis was performed on the base of previous studies. Thus, the ethical approval was not required.

3. Results

3.1. Study selection and characteristics

The study selection process in this meta-analysis is shown in Fig. 1. A total of 97 studies were found in the initial search (PubMed: 40, Embase: 18, Web of Science: 19, CNKI: 16, and Wan fang: 4). Of these, 29 studies were duplicated. Therefore, 68 articles were retrieved based on the search criteria. Among these studies, 2 review articles, 2 abstracts from conferences, and 53 irrelevant studies were excluded. Finally, the remaining eleven studies were selected and the data in them were extracted.  

Of them, 3 studies were medium quality and the other studies were high quality (Table 1). The genotype and allele frequencies distribution of XPG gene polymorphisms in all studies are listed in Table 2. However, phenotype distribution of rs2296147 in Yang et al’s study[25] and rs751402 in Guo et al’s study[21] departed from HWE (Table 2). Their data were excluded and not used for further meta-analysis. Therefore, 5 studies for rs873601, 7 studies for rs2094258, 4 studies for rs2296147, and 8 studies for rs751402 were used for the final meta-analysis.

3.2. Meta-analysis results

For rs873601 and rs2296147, no significant heterogeneity was observed in 5 genetic models, and the fixed-effect model was used to calculate the ORs and 95% CIs (Table 3). We found that rs873601 was significantly associated with the increased gastric cancer risk in
allelic, recessive, and additive models. However, no obvious association between rs873601 and gastric cancer susceptibility was detected in dominant model or heterozygous model (Table 3 and Fig. 2). Furthermore, our data indicated that rs2296147 was significantly associated with the elevated risk of gastric cancer in recessive model, but not in other models (Table 3 and Fig. 3).

For rs2094258, the significant heterogeneity was present in additive model. Therefore, the random-effect model was used in this genetic model and the fixed-effect model was used for other genetic models. No association between rs2094258 and gastric cancer susceptibility was found using the 5 genetic models in this meta-analysis (Table 3 and Fig. 4).

For rs751402, the heterogeneity in dominant and heterozygous models was not statistically significant, and the fixed-effect model was selected. Meanwhile, the random-effect model was used for other genetic models. Our data showed that rs751402 was associated with the increased susceptibility to gastric cancer in all genetic models (Table 3 and Fig. 5).

3.3. Heterogeneity and sensitivity analyses

Meta-regression was performed for rs2094258 and rs751402 to explore the source of heterogeneity. The publication year was considered as possible covariate. However, the result indicated that publication year was not the main factor responsible for the heterogeneity in any genetic model (Table 4).

Sensitivity analysis showed that the pooled ORs for rs2094258 were not considerably affected by omitting any single study in the 5 genetic models (Table 5). However, for rs873601 and rs2296147, certain study included in this meta-analysis might influence the whole results (Table 5). More than that, after omitting any single study for rs751402, the result of the SNP was
stable in allelic and dominant models, but not in other genetic models (Table 5).

3.4. Publication bias

For rs751402, the publication bias existed in recessive and additive models, but not in other genetic models. No obvious publication bias was obtained in any genetic model for the other 3 SNPs (Table 6).

3.5. False-positive report probability analysis and trial sequential analysis

The false-positive report probability analysis and trial sequential analysis were performed for the results of rs751402. All significant findings remained significant at a prior probability of .1 and the FPRP values were less than .20 with the exception of the recessive genetic model of rs751402 C>T (Table 7). More than that, our data indicated that the cumulative Z-curve crossed the trial sequential monitoring boundary, suggesting that the sample size was sufficient and no further analysis was required to confirm the results of rs751402 in allelic, dominant, additive, and heterozygous models (Fig. 6). In recessive genetic model, the cumulative Z-curve crossed the conventional threshold value, but it did not cross the trial sequential monitoring boundary or the required information size line.

4. Discussion

As we all known, stomach is always exposed to various endogenous and exogenous mutagens. If the capability of DNA
repair is insufficient during the process, stomach cells will fail to repair the acquired DNA damage. DNA mutations will accumulate, and eventually gastric cancer is more likely to occur.\cite{16}

Therefore, DNA repair system plays a critical role in maintaining genome stability, which prevents gastric carcinogenesis.\cite{12}

XPG has been demonstrated to play an important role in DNA repair system.\cite{13,14} The 1186 amino-acid protein encoded by XPG gene functions as a structure-specific endonuclease involved in 2 incision steps, which are critical to correct the excision repair deficiency.\cite{27,28} During the process of DNA repair, the DNA at the 3' terminus could be cut by the endonuclease via the amino acids located at the N-terminus of XPG protein.\cite{15,29} Therefore, the protein is critical to elimination of the damaged DNA.\cite{30}

Genetic variations of XPG may lead to emergence of the corresponding mutated protein, resulting in alteration of DNA repair.\cite{30}
Table 5

Sensitivity analysis of the meta-analysis.

| Refs. | Genetic comparison | $P_0$ | $F_\alpha$, % | 95% CI | $P_1$ | Model |
|-------|--------------------|-------|---------------|--------|-------|-------|
| rs2094258 C>A | Chen et al[23] | G vs A | .263 | 24.70 | 1.07 (1.00–1.15) | .046 | Fixed |
| | | G vs AG vs AA | .268 | 23.90 | 1.12 (1.00–1.26) | .057 | Fixed |
| | | G vs AG + AA | .412 | 0.00 | 1.08 (0.97–1.21) | .175 | Fixed |
| | | G vs AA | .263 | 24.80 | 1.16 (1.00–1.33) | .045 | Fixed |
| | | G vs AG | .514 | 0.00 | 1.05 (0.93–1.18) | .436 | Fixed |
| | He et al[24] | G vs A | .329 | 12.80 | 1.06 (0.99–1.15) | .115 | Fixed |
| | | G vs AG vs AA | .201 | 35.10 | 1.12 (0.99–1.28) | .072 | Fixed |
| | | G vs AG + AA | .577 | 0.00 | 1.05 (0.93–1.18) | .433 | Fixed |
| | | G vs AA | .330 | 12.60 | 1.13 (0.97–1.32) | .112 | Fixed |
| | | G vs AG | .597 | 0.00 | 1.01 (0.89–1.15) | .839 | Fixed |
| | Hua et al[26] | G vs A | .236 | 29.40 | 1.10 (1.02–1.19) | .014 | Fixed |
| | | G vs AG vs AA | .155 | 42.80 | 1.16 (1.02–1.31) | .024 | Fixed |
| | | G vs AG + AA | .536 | 0.00 | 1.12 (0.99–1.28) | .079 | Fixed |
| | | G vs AG | .226 | 31.10 | 1.21 (1.04–1.40) | .015 | Fixed |
| | | G vs AG | .653 | 0.00 | 1.07 (0.94–1.22) | .281 | Fixed |
| | Yang et al[25] | G vs A | .764 | 0.00 | 1.11 (1.04–1.18) | .003 | Fixed |
| | | G vs AG vs AA | .616 | 0.00 | 1.19 (1.07–1.33) | .002 | Fixed |
| | | G vs AG + AA | .675 | 0.00 | 1.10 (0.99–1.23) | .067 | Fixed |
| | | G vs AG | .770 | 0.00 | 1.23 (1.08–1.40) | .002 | Fixed |
| | | G vs AG | .556 | 0.00 | 1.05 (0.94–1.18) | .397 | Fixed |
| | Zou et al[17] | G vs A | .207 | 34.20 | 1.09 (1.02–1.16) | .015 | Fixed |
| | | G vs AG vs AA | .210 | 33.70 | 1.17 (1.05–1.31) | .005 | Fixed |
| | | G vs AG + AA | .516 | 0.00 | 1.07 (0.96–1.19) | .233 | Fixed |
| | | G vs AA | .207 | 34.30 | 1.19 (1.04–1.36) | .013 | Fixed |
| | | G vs AG | .773 | 0.00 | 1.02 (0.91–1.14) | .779 | Fixed |
| rs2094258 G>T | Chen et al[23] | C vs T | .108 | 44.50 | 1.00 (0.93–1.07) | .963 | Fixed |
| | | C vs CT vs TT | .072 | 50.60 | 1.03 (0.83–1.28) | .782 | Random |
| | | C vs CT + TT | .462 | 0.00 | 0.99 (0.89–1.10) | .845 | Fixed |
| | | C vs TT | .054 | 53.90 | 1.03 (0.77–1.36) | .860 | Random |
| | | CC vs CT | .835 | 0.00 | 0.98 (0.88–1.09) | .671 | Fixed |
| | Feng et al[25] | C vs T | .111 | 44.10 | 0.99 (0.93–1.06) | .772 | Fixed |
| | | C vs CT vs TT | .100 | 45.90 | 1.03 (0.90–1.17) | .656 | Fixed |
| | | C vs CT + TT | .350 | 10.30 | 0.97 (0.86–1.08) | .472 | Fixed |
| | | CC vs TT | .068 | 51.20 | 1.03 (0.82–1.17) | .788 | Random |
| | | C vs CT | .649 | 0.00 | 0.95 (0.86–1.05) | .319 | Fixed |
| | He et al[24] | C vs T | .161 | 36.90 | 1.01 (0.94–1.10) | .734 | Fixed |
| | | C vs CT vs TT | .149 | 38.50 | 1.07 (0.92–1.24) | .374 | Fixed |
| | | C vs CT + TT | .375 | 6.60 | 0.99 (0.88–1.11) | .850 | Fixed |
| | | CC vs CT | .126 | 41.90 | 1.08 (0.91–1.29) | .390 | Fixed |
| | | CC vs CT | .629 | 0.00 | 0.96 (0.85–1.08) | .461 | Fixed |
| | | CC vs CT | .173 | 35.10 | 0.95 (0.89–1.03) | .231 | Fixed |
| | | CC vs CT vs TT | .119 | 43.00 | 0.97 (0.84–1.12) | .672 | Fixed |
| | | CC vs CT + TT | .482 | 0.00 | 0.92 (0.82–1.03) | .161 | Fixed |
| | | CC vs TT | .097 | 46.40 | 0.96 (0.73–1.26) | .770 | Random |
| | | CC vs CT | .783 | 0.00 | 0.91 (0.81–1.03) | .139 | Fixed |
| | Lu et al[33] | C vs T | .125 | 42.00 | 0.99 (0.93–1.06) | .790 | Fixed |
| | | C vs CT vs TT | .101 | 45.70 | 1.03 (0.90–1.17) | .658 | Fixed |
| | | C vs CT + TT | .366 | 3.10 | 0.97 (0.88–1.06) | .491 | Fixed |
| | | CC vs CT | .081 | 49.10 | 1.04 (0.83–1.30) | .752 | Random |
| | | CC vs CT | .690 | 0.00 | 0.95 (0.86–1.05) | .332 | Fixed |
| | | CC vs T | .099 | 45.90 | 0.98 (0.88–1.08) | .639 | Random |
| | Yang et al[18] | C vs T | .074 | 50.20 | 1.02 (0.85–1.23) | .842 | Random |
| | | CC vs CT vs TT | .372 | 6.90 | 0.95 (0.87–1.05) | .319 | Fixed |
| | | CC vs CT vs TT | .052 | 54.40 | 0.99 (0.78–1.28) | .943 | Fixed |
| | | CC vs CT | .731 | 0.00 | 0.94 (0.85–1.04) | .213 | Fixed |
| | | CC vs T | .348 | 10.60 | 0.96 (0.90–1.03) | .277 | Fixed |
| | | CC vs CT | .594 | 0.00 | 0.96 (0.84–1.10) | .559 | Fixed |
| | | CC vs CT vs TT | .419 | 0.00 | 0.95 (0.86–1.04) | .269 | Fixed |
| | | CC vs TT | .383 | 5.30 | 0.94 (0.81–1.09) | .414 | Fixed |
| | | CC vs CT | .626 | 0.00 | 0.94 (0.85–1.05) | .268 | Fixed |

(continued)
| Refs.  | Genetic comparison          | P₀   | χ², % | 95% CI          | P₂  | Model |
|--------|-----------------------------|------|-------|-----------------|-----|-------|
|        | rs2296147 T>C               |      |       |                 |     |       |
| Chen et al[23] | T vs C                      | .674 | 0.00  | 1.04 (0.94–1.14) | .462 | Fixed |
|        | TT + CT vs CC               | .146 | 47.70 | 1.30 (1.05–1.60) | .045 | Fixed |
|        | TT vs CT + CC               | .972 | 0.00  | 1.00 (0.90–1.12) | .061 | Fixed |
|        | TT vs CC                    | .167 | 44.10 | 1.29 (0.99–1.68) | .061 | Fixed |
|        | TT vs CT                    | .950 | 0.00  | 0.97 (0.87–1.09) | .609 | Fixed |
|        | T vs C                      | .719 | 0.00  | 1.00 (0.92–1.10) | .933 | Fixed |
|        | TT + CT vs CC               | .541 | 0.00  | 1.18 (0.92–1.51) | .187 | Fixed |
|        | TT vs CT + CC               | .741 | 0.00  | 0.98 (0.88–1.08) | .646 | Fixed |
|        | TT vs CC                    | .554 | 0.00  | 1.16 (0.91–1.49) | .238 | Fixed |
|        | TT vs CT                    | .728 | 0.00  | 0.95 (0.86–1.06) | .388 | Fixed |
|        | rs751402 C>T                |      |       |                 |     |       |
| Chen et al[23] | C vs T                      | .028 | 57.70 | 1.16 (1.02–1.33) | .022 | Random |
|        | CC + CT vs TT               | .049 | 52.50 | 1.26 (0.98–1.63) | .074 | Random |
|        | CC vs CT + TT               | .281 | 19.50 | 1.14 (1.03–1.27) | .014 | Fixed |
|        | CC vs TT                    | .020 | 59.90 | 1.38 (1.02–1.86) | .035 | Random |
|        | CC vs CT                    | .807 | 0.00  | 1.13 (1.01–1.26) | .040 | Fixed |
|        | Duan et al[16]               |      |       |                 |     |       |
|        | C vs T                      | .100 | 43.60 | 1.09 (1.01–1.17) | .025 | Fixed |
|        | CC + CT vs TT               | .131 | 39.10 | 1.10 (1.05–1.27) | .215 | Fixed |
|        | CC vs CT + TT               | .704 | 0.00  | 1.12 (1.01–1.24) | .025 | Fixed |
|        | CC vs TT                    | .921 | 0.00  | 1.11 (1.00–1.26) | .026 | Fixed |
|        | Feng et al[22]               |      |       |                 |     |       |
|        | C vs T                      | .026 | 58.20 | 1.16 (1.03–1.31) | .013 | Random |
|        | CC + CT vs TT               | .047 | 52.90 | 1.25 (0.99–1.58) | .058 | Random |
|        | CC vs CT + TT               | .274 | 20.40 | 1.15 (1.05–1.27) | .004 | Fixed |
|        | CC vs TT                    | .019 | 60.30 | 1.37 (1.04–1.79) | .023 | Random |
|        | Hua et al[26]               |      |       |                 |     |       |
|        | C vs T                      | .669 | 0.00  | 1.21 (1.11–1.31) | <.001 | Fixed |
|        | CC + CT vs TT               | .804 | 0.00  | 1.35 (1.15–1.61) | <.001 | Fixed |
|        | CC vs CT + TT               | .867 | 0.00  | 1.24 (1.11–1.40) | <.001 | Fixed |
|        | CC vs TT                    | .691 | 0.00  | 1.48 (1.22–1.78) | <.001 | Random |
|        | Li et al[20]                |      |       |                 |     |       |
|        | C vs T                      | .026 | 58.20 | 1.16 (1.03–1.31) | .013 | Random |
|        | CC + CT vs TT               | .049 | 52.60 | 1.24 (0.99–1.56) | .063 | Random |
|        | CC vs CT + TT               | .274 | 20.40 | 1.15 (1.05–1.27) | .004 | Fixed |
|        | CC vs TT                    | .020 | 60.10 | 1.36 (1.04–1.77) | .025 | Random |
|        | CC vs CT                    | .801 | 0.00  | 1.13 (1.02–1.26) | .017 | Fixed |
|        | Lu et al[19]                |      |       |                 |     |       |
|        | C vs T                      | .027 | 57.90 | 1.16 (1.03–1.30) | .015 | Random |
|        | CC + CT vs TT               | .049 | 52.50 | 1.24 (0.99–1.56) | .065 | Random |
|        | CC vs CT + TT               | .280 | 19.60 | 1.15 (1.04–1.27) | .005 | Fixed |
|        | CC vs TT                    | .021 | 59.90 | 1.35 (1.03–1.77) | .027 | Fixed |
|        | Yang et al[14]              |      |       |                 |     |       |
|        | C vs T                      | .103 | 43.10 | 1.09 (1.02–1.17) | .013 | Fixed |
|        | CC + CT vs TT               | .141 | 37.80 | 1.10 (0.95–1.27) | .190 | Fixed |
|        | CC vs CT + TT               | .483 | 0.00  | 1.13 (1.03–1.25) | .011 | Fixed |
|        | CC vs TT                    | .082 | 46.50 | 1.26 (1.03–1.60) | .049 | Random |
|        | Zhou et al[17]              |      |       |                 |     |       |
|        | C vs T                      | .931 | 56.80 | 1.15 (1.02–1.31) | .022 | Random |
|        | CC + CT vs TT               | .068 | 48.90 | 1.22 (0.97–1.54) | .006 | Fixed |
|        | CC vs CT + TT               | .279 | 19.70 | 1.15 (1.04–1.27) | .008 | Fixed |
|        | CC vs TT                    | .027 | 57.90 | 1.34 (1.01–1.76) | .040 | Random |
|        | CC vs CT                    | .800 | 0.00  | 1.13 (1.02–1.26) | .022 | Fixed |

CI = confidence interval.
repair capacity. Therefore, compared with others, certain individuals carrying more XPG variations have the increased susceptibility to gastric cancer.\[16\]

Several studies have showed that XPG gene polymorphism is significantly associated with not only the risk of cancer but also the efficacy of chemotherapy in cancer patients. For example, platinum-based chemotherapeutics is the most common regimen for various cancers. To today, XPG gene polymorphism has been demonstrated to influence the efficacy of chemotherapy in many types of cancers, such as, nonsmall cell lung cancer, osteosarcoma cancer, and ovarian cancer.\[31–35\] Additionally, certain leukemia subline is resistant to F11782, a novel dual catalytic inhibitor of topoisomerases with DNA repair-inhibitory properties. Further research indicated that NER activity was decreased 3-fold in these cells companied with a decreased (67%) level of XPG.\[37\]

Thus far, several published studies have focused on the association between XPG gene polymorphisms (including rs873601, rs2094258, rs2296147, and rs751402) and gastric cancer susceptibility in Chinese populations.\[16–26\] However, the conclusions in these literatures were not consistent or even contradictory, which might be due to the relatively small sample size in a single study. To resolve this controversy, we performed the current meta-analysis.

Our results indicated that no association between rs2094258 and gastric cancer risk was observed. Although rs873601 and rs2296147 were associated with high gastric cancer risk in certain genetic models, these results should nonetheless be applied cautiously due to the instability. Additionally, our data showed that rs751402 was associated with increased susceptibility to gastric cancer in allelic and dominant models. The results of rs751402 in allelic and dominant models were robust. And no evidence indicated that obvious asymmetry for the 2 models existed. The false-positive report probability analysis and trial sequential analysis of the results of rs751402 suggested that the sample size was sufficient and most of these results are reliable. Therefore, no

### Table 6

| Genetic comparison | Begg test | Egger test | 95% CI |
|--------------------|-----------|------------|--------|
| rs873601 G>A       |           |            |        |
| G vs A             | 0.221     | –1.28      | .290   | –3.59 |
| GG + AG vs AA      | 0.221     | –2.10      | .127   | –1.77 |
| GG vs AG + AA      | 0.806     | –0.39      | .719   | 5.19  |
| GG vs AA           | 0.462     | –1.41      | .252   | 3.33  |
| GG vs AG           | 0.806     | 0.24       | .828   | 5.83  |
| rs2094258 C>T      |           |            |        |
| C vs T             | 1.000     | 0.00       | .996   | 3.59  |
| CC + CT vs TT      | 0.548     | 0.63       | .559   | 3.12  |
| CC vs CT + TT      | 0.368     | –0.46      | .664   | 2.68  |
| CC vs TT           | 1.000     | 0.00       | .999   | 3.43  |
| CC vs CT           | 0.368     | –0.55      | .604   | 2.10  |
| rs2296147 T>C      |           |            |        |
| T vs C             | 0.734     | 0.68       | .568   | 7.00  |
| TT + CT vs CC      | 0.308     | 2.06       | .176   | –1.16 |
| TT vs CT + CC      | 0.734     | –0.04      | .975   | 6.58  |
| TT vs CC           | 0.308     | 1.86       | .203   | 4.70  |
| TT vs CT           | 0.308     | –0.98      | .430   | 6.18  |
| rs751402 C>T       |           |            |        |
| C vs T             | 0.536     | 2.38       | .055   | 0.08 |
| CC + CT vs TT      | 0.711     | 2.75       | .033   | 0.28 |
| CC vs CT + TT      | 0.308     | 2.06       | .085   | 0.36 |
| CC vs TT           | 0.711     | 2.63       | .039   | 0.19 |
| CC vs CT           | 0.386     | 1.83       | .117   | 0.39 |

CI = confidence interval.

### Table 7

| Genotype | Crude OR (95% CI) | Power † | P † | .25 | .1 | .01 | .001 | .0001 |
|----------|-------------------|---------|-----|-----|----|-----|------|-------|
| rs751402 C>T |          |         |     |     |    |     |      |       |
| C vs T    | 1.16 (1.04–1.29)  | 1.000   | .006| .018| .053| .379| .860 | .984  |
| CC + CT vs TT | 1.23 (1.00–1.52) | .967 | .055| .146| .340| .650| .983 | .998  |
| CC vs TT + CT | 1.15 (1.05–1.27) | 1.000 | .006| .017| .049| .364| .852 | .983  |
| CC vs TT  | 1.35 (1.06–1.72)  | 0.803 | .015| .054| .145| .652| .950 | .995  |
| CC vs CT  | 1.13 (1.02–1.25)  | 1.000 | .018| .050| .137| .636| .946 | .994  |

CI = confidence interval. OR = odds ratio.

† Statistical power was calculated using the number of observations in the subgroup and the OR and P values in this table.

† Chi-square test was adopted to calculate the genotype frequency distributions.
further analysis was required to confirm the results of rs751402 with the exception of the results in recessive genetic model.

The data in our study showed that the rs751402 C>T was associated with high risk of gastric cancer in Chinese populations. On the one hand, it suggests the clinicians that the individuals with T allele of rs751402 may have a high susceptibility to gastric cancer in Chinese populations. Therefore, the screening for gastric cancer in these individuals may be more important. And it is good for the early detection and treatment of gastric cancer. On the other hand, it suggests researchers that the cells with T allele of rs751402 may be more likely to lead to cancer. The underlying mechanism needs further research and the relevant study may provide a clue for gastric cancer prevention.

All of the studies included in this meta-analysis met our inclusion criteria. In spite of these, several limitations that exist in the current meta-analysis have to be acknowledged. First, some valuable information, involved in gastric carcinogenesis, from individual participants was missing in our study, such as occupation, physical activity, local environmental factor, and Helicobacter pylori infection. Second, our analysis was performed with only Chinese populations. Therefore, it is unknown whether the results will extend to other populations. Third, we carried out meta-regression considering only publication year without other factors. Last, certain obvious publication bias was detected.

Despite these limitations, the meta-analysis still provides new insights into the relationship of XPG gene and the occurrence of gastric cancer. A part of the research results from the previous studies included in the current meta-analysis were in accordance with our results. However, the numbers of studies and subjects

Figure 6. Trial sequential analysis of rs751402 polymorphism and the risk of gastric cancer in Chinese populations. (A) Allelic model (C vs T). (B) Recessive genetic model (CC + CT vs TT). (C) Dominant genetic model (CC vs CT + TT). (D) Additive genetic model (CC vs TT). (E) Heterozygous comparison model (CC vs CT).
were relatively small in this meta-analysis, which might reduce the statistical power for identifying the potential association between these XPG gene polymorphisms and gastric cancer susceptibility. A larger study should be performed to confirm the present negative results.

In conclusion, our meta-analysis demonstrates that rs751402, but not rs873601, rs2094258, or rs2296147, was associated with gastric cancer risk. These results suggest that the SNP has the potential to be the biomarker for susceptibility to gastric cancer. However, large-scale studies among different ethnic groups with more detailed individual information are needed to validate our conclusion.

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