XPG gene polymorphisms and cancer susceptibility: evidence from 47 studies

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ABSTRACT

Xeroderma pigmentosum group G (XPG) is a single-strand-specific DNA endonuclease that functions in the nucleotide excision repair pathway. Genetic variations in XPG gene can alter the DNA repair capacity of this enzyme. We evaluated the associations between six single nucleotide polymorphisms (SNPs) in XPG (rs1047768 T>C, rs2296147 T>C, rs2227869 G>C, rs2094258 C>T, rs751402 C>T, and rs873601 G>A) and cancer risk. Forty-seven studies were identified in searches of the PubMed, Scopus, Web of Science, China National Knowledge Infrastructure, and WanFang databases. Crude odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using a fixed or random effects model. We found that rs873601 G>A was associated with an increased overall cancer risk (AA vs. GG: OR = 1.14, 95% CI = 1.06–1.24; GA/AA vs. GG: OR = 1.08, 95% CI = 1.02–1.15; A vs. G: OR = 1.06, 95% CI = 1.02–1.10). In a stratified analysis, rs1047768 T>C was associated with an increased risk of lung cancer, rs2227869 G>C was associated with a decreased risk of cancer in population-based studies, and rs751402 C>T and rs873601 G>A were associated with the risk of gastric cancer. Our data indicate that rs873601 G>A is associated with cancer susceptibility.

INTRODUCTION

There were an estimated 14.1 million new cancer cases and 8.2 million cancer-related deaths in 2012 worldwide [1, 2]. Although recent advances in the diagnosis and treatment of various cancers have improved patient prognosis, most malignancies still impose a heavy burden on society. Cancer is a multifactorial, chronic disease caused by both endogenous (genetic, immune, and endocrine disorders) and exogenous factors (environmental carcinogens and unhealthy behaviors) [1]. Among these etiological factors, gene-environment interactions have been shown to play key roles in cancer development.

The maintenance of genomic integrity is essential for human health. However, DNA damage can occur due to exposure to various chemicals, environmental agents, and ultraviolet radiation. DNA damage can also occur naturally. For example, metabolic processes can generate compounds that damage DNA, which include reactive oxygen and reactive nitrogen species. There are five major DNA damage repair pathways in humans: nucleotide excision repair (NER), base excision repair, double-strand break repair, mismatch repair, and homologous
recombination [3]. Failure to properly repair DNA damage can lead to tumorigenesis. The versatile NER pathway is responsible for excising DNA lesions including cross-links, bulky adducts, thymidine dimers, alkylating damage, and oxidative DNA damage [3].

There are at least eight core functional genes in the NER pathway. These include Excision repair cross complementing group 1 (ERCC1) and Xeroderma pigmentosum group (XP) A-G. XPG, also known as ERCC5, is located on chromosome 13q22-q33 [4]. The XPG gene encodes a single-strand specific DNA endonuclease of 1,186 amino acids that cleaves the damaged DNA strand at the 3’ end [5]. Defects in the XPG gene can impair DNA repair resulting in genomic instability and carcinogenesis [6]. Single nucleotide polymorphisms (SNPs) in the XPG gene have been associated with various cancers including colorectal [7], lung [8, 9], gastric [10, 11], and laryngeal [12]. However, different studies have achieved conflicting results. For example, Duan et al. found that rs2296147 T>C in XPG was associated with an increased risk of gastric cancer [13], but this association was not replicated in other studies [10, 11]. The discordances might be attributed to the limited sample sizes of individual studies, different sources of controls, and ethnic variation. In this study, we performed a meta-analysis of the associations between six potentially functional SNPs: rs1047768 T>C, rs2296147 T>C, rs2227869 G>C, rs2094258 C>T, rs751402 C>T, and rs873601 G>A in the XPG gene and the risk of cancer.

RESULTS

Study characteristics

A total of 215 articles were identified using the Web of Science, Scopus, and PubMed. An additional 26 potential relevant articles were identified in the CNKI and WanFang databases. After screening the titles and abstracts, 135 studies remained for further full-text review. We excluded 17 meta-analyses and reviews as well as 69 studies that did not assess the SNPs of interest. A detailed assessment was then performed of 49 studies. Two of these studies were removed, one because there was a lack of detailed genotype data and the other because of study population overlap. The final meta-analysis included 47 articles. There were 22 articles with 12,833 cases and 151,86 controls for rs1047768 T>C [7-9, 12, 14-31], 14 studies with 11,327 cases and 12,684 controls for rs2296147 T>C [9-11, 13, 18, 24, 26-28, 32-37], 11 studies with 5,898 cases and 7,448 controls for rs2227869 G>C [8, 9, 14, 17, 18, 20, 22, 25, 38-40], 17 studies with 9,826 cases and 10,552 controls for rs2094258 C>T [10, 11, 18, 24, 26-28, 34-37, 41-46], 21 studies with 10,369 cases and 11,207 controls for rs751402 C>T [10, 13, 24, 26-29, 31, 32, 36, 37, 42-45, 47-52], and 14 studies with 10,873 cases and 12,535 controls for rs873601 G>A [9-11, 18, 24, 26-28, 32, 34, 36, 52-54]. A flow chart summarizing the process of relevant study identification is shown in Figure 1, and the study characteristics are shown in Table 1.

Meta-analysis results

We observed no significant association between rs1047768 T>C and overall cancer risk (Table 2). However, in stratified analysis, rs1047768 T>C was associated with an increased risk of lung cancer under homozygous [odds ratio (OR) = 1.32, 95% confidence interval (CI) = 1.06–1.64], heterozygous (OR = 1.35, 95% CI = 1.10–1.65), dominant (OR = 1.35, 95% CI = 1.12–1.63), and allele contrast (OR = 1.14, 95% CI = 1.02–1.27) models. No significant association was observed between rs2296147 T>C and overall cancer risk. Similarly, there was no significant association between rs2227869 G>C and overall cancer risk. However, a significant association was identified in population-based studies when the data were stratified based on the source of the controls under heterozygous (OR = 0.80, 95% CI = 0.65–0.99) and allele contrast (OR = 0.84, 95% CI = 0.71–0.99) models. We observed an association between rs2094258 C>T and overall cancer risk under the homozygous model (OR = 1.09, 95% CI = 1.00–1.19), which approached borderline statistical significance. Another borderline significant association was observed between rs751402 C>T and overall cancer risk under the homozygous model (OR = 1.18, 95% CI = 1.00–1.39). In the stratified analysis, a significant association was observed for gastric cancer under homozygous (OR = 1.38, 95% CI = 1.12–1.70), heterozygous (OR = 1.14, 95% CI = 1.05–1.24), recessive (OR = 1.27, 95% CI = 1.06–1.51), dominant (OR = 1.17, 95% CI = 1.08–1.26), and allele contrast (OR = 1.17, 95% CI = 1.07–1.27) models.

A significant association was observed between rs873601 G>A and overall cancer risk under homozygous (OR = 1.14, 95% CI = 1.06–1.24), dominant (OR = 1.08, 95% CI = 1.02–1.15), and allele contrast (OR = 1.06, 95% CI = 1.02-1.10) models (Figure 2). The association with gastric cancer remained statistically significant under homozygous (OR = 1.18, 95% CI = 1.04–1.34), recessive (OR = 1.16, 95% CI = 1.04–1.28), and allele contrast (OR = 1.09, 95% CI = 1.02–1.16) models.

Heterogeneity and sensitivity analysis

Study heterogeneity was observed for the association between rs1047768 T>C and overall cancer risk under homozygous, dominant, and allele contrast models (P = 0.010, P = 0.038, and P = 0.012, respectively); rs2094258 C>T under homozygous and allele contrast models (P = 0.025 and P = 0.015, respectively); rs751402 C>T under homozygous, recessive, dominant, and allele contrast models (P < 0.001, P = 0.006, P < 0.001, P < 0.001, respectively); and rs873601 G>A under a recessive model.
These data indicated that the removal of any individual study from the analysis did not qualitatively change the pooled ORs (data not shown).

Publication bias

The Begg’s funnel plots of the associations between the SNPs in the XPG gene and cancer risk were basically symmetrical (Figure 3). Egger’s tests indicated there was no publication bias for rs1047768 T>C under homozygous ($P = 0.107$), heterozygous ($P = 0.190$), recessive ($P = 0.325$), dominant ($P = 0.137$), and allele contrast ($P = 0.301$) models; rs2296147 T>C under homozygous ($P = 0.789$), heterozygous ($P = 0.925$), recessive ($P = 0.577$), dominant ($P = 0.464$), and allele contrast ($P = 0.129$) models; rs2227869 G>C under homozygous ($P = 0.708$), heterozygous ($P = 0.289$), recessive ($P = 0.042$), dominant ($P = 0.297$), and allele contrast ($P = 0.197$) models; rs2094258 C>T under homozygous ($P = 0.387$), heterozygous ($P = 0.350$), recessive ($P = 0.844$), dominant ($P = 0.276$), and allele contrast ($P = 0.351$) models; rs751402 C>T under homozygous ($P = 0.107$), heterozygous ($P = 0.336$), recessive ($P = 0.137$), dominant ($P = 0.325$), and allele contrast ($P = 0.301$) models; and rs873601 G>A under homozygous ($P = 0.395$), heterozygous ($P = 0.656$), recessive ($P = 0.645$),

- Potential relevant studies from PubMed, Scopus and Web of Science (n=215)
- Potential relevant studies from CNKI and WanFang database (n=26)
- Records excluded after title and abstract review (n=106)
- 135 studies chosen for full text review
- Records excluded (n=86):
  - 17 meta-analyses and reviews
  - 69 without concerned polymorphisms
- 49 studies chosen for detailed assessment
- Records excluded (n=2):
  - 1 without detailed data
  - 1 overlapped with the other
- 47 studies included in the meta-analysis
  - 22 studies for rs1047768 T>C, 14 studies for rs2296147 T>C, 11 studies for rs2227869 G>C, 17 studies for rs2094258 C>T, 21 studies for rs751402 C>T, 14 studies for rs873601 G>A

Figure 1: Flow diagram showing the process used to identify eligible studies.
Table 1: Characteristics of the studies included in the meta-analysis

| Author          | Year | Country | Ethnicity | Source | Cancer   | Case | Control | MAF HWE Score |
|-----------------|------|---------|-----------|--------|----------|------|---------|---------------|
| Shen M          | 2005 | China   | Asian     | PB     | Lung     | 55   | 49      | 14 118 63 36 13 112 0.28 0.037 10 |
| Zienolddiny S   | 2006 | Norway  | Caucasian | PB     | Lung     | 60   | 119     | 137 316 109 126 138 373 0.54 <0.001 11 |
| Moreno V        | 2006 | Spain   | Caucasian | HB     | Colorectal | 114 | 184     | 53 351 105 164 51 320 0.42 0.325 11 |
| Garcia-Closas M | 2006 | Spain   | Caucasian | HB     | Bladder   | 188 | 530     | 385 1103 222 506 366 1094 0.57 0.052 12 |
| Xie WM          | 2007 | China   | Asian     | PB     | HCC      | 194 | 195     | 38 427 235 196 48 479 0.30 0.451 11 |
| Abbasi R        | 2009 | Germany | Caucasian | PB     | Laryngeal | 43  | 127     | 78 248 115 320 212 647 0.57 0.762 13 |
| Hussain SK      | 2009 | China   | Asian     | PB     | Gastric  | 97   | 61      | 12 170 189 168 29 386 0.29 0.173 13 |
| Ma H            | 2012 | USA     | Caucasian | HB     | SCCHN    | 184 | 506     | 369 1059 179 507 379 1065 0.59 0.669 11 |
| Sakoda LC       | 2012 | USA     | Caucasian | PB     | Lung     | 108 | 378     | 256 742 245 722 507 1474 0.59 0.656 15 |
| He J            | 2013 | China   | Asian     | HB     | Gastric  | 571 | 469     | 85 1125 610 474 112 1196 0.29 0.155 13 |
| Paszkowska-     | 2013 | Poland  | Caucasian | PB     | Melanoma | 128 | 291     | 214 633 242 623 465 1330 0.58 0.189 13 |
| Szczur K        |      |         |           |        |          |     |         |    |        |        |        |        |        |        |        |
| Li X            | 2014 | China   | Asian     | HB     | Laryngeal | 49  | 101     | 60 210 46 97 67 210 0.55 0.333 9  |
| Mirecka A       | 2014 | Poland  | Caucasian | HB     | Prostate | 128 | 272     | 221 621 154 368 259 781 0.57 0.260 9  |
| Li XC           | 2014 | China   | Asian     | HB     | Gastric  | 37  | 95      | 85 217 29 93 95 217 0.65 0.414 8  |
| Na N            | 2015 | China   | Asian     | HB     | Breast   | 161 | 140     | 24 325 171 134 20 325 0.27 0.352 10 |
| Paszkowska-     | 2015 | Poland  | Caucasian | PB     | Colorectal | 104 | 221     | 138 463 242 623 465 1330 0.58 0.189 9  |
| Szczur K        |      |         |           |        |          |     |         |    |        |        |        |        |        |        |        |
| He J            | 2016 | China   | Asian     | HB     | Neuroblastoma | 135 | 93      | 20 248 307 198 26 531 0.24 0.409 10 |
| Hua RX          | 2016 | China   | Asian     | HB     | Colorectal | 970 | 758     | 173 1901 1023 812 142 1977 0.28 0.266 10 |
| Hua RX          | 2016 | China   | Asian     | HB     | Gastric  | 607 | 445     | 90 1142 625 461 87 1173 0.27 0.875 11 |
| Li RJ           | 2016 | China   | Asian     | HB     | Gastric  | 57  | 92      | 67 216 68 87 61 216 0.48 0.004 7  |
| Wang MY         | 2016 | China   | Asian     | HB     | Prostate | 491 | 433     | 80 1004 534 440 81 1055 0.29 0.461 10 |
| Bai Y           | 2016 | China   | Asian     | HB     | Gastric  | 41  | 98      | 55 194 32 106 87 225 0.62 0.975 6  |
| rs2296147 T>C   |      |         |           |        |          |     |         |    |        |        |        |        |        |        |        |
| Shao MH         | 2007 | China   | Asian     | HB     | Lung     | 570 | 304     | 52 926 590 358 31 979 0.21 0.008 10 |
| Doherty JA      | 2011 | USA     | Mixed     | PB     | Endometrial | 194 | 356     | 165 715 199 364 157 720 0.47 0.696 11 |
| Duan Z          | 2012 | China   | Asian     | HB     | Gastric  | 257 | 122     | 24 403 260 132 11 403 0.19 0.232 11 |
| He J            | 2012 | China   | Asian     | HB     | Gastric  | 700 | 371     | 54 1125 742 398 56 1196 0.21 0.779 13 |
| Ma H            | 2012 | USA     | Caucasian | HB     | SCCHN    | 280 | 532     | 244 1056 294 543 228 1065 0.47 0.440 11 |
| Sakoda LC       | 2012 | USA     | Caucasian | PB     | Lung     | 182 | 385     | 174 741 407 723 341 1471 0.48 0.565 15 |
| Zhu ML          | 2012 | China   | Asian     | HB     | ESCC     | 757 | 305     | 53 1115 699 368 50 1117 0.21 0.860 13 |
| Yang WG         | 2012 | China   | Asian     | HB     | Gastric  | 208 | 105     | 24 337 196 110 41 347 0.38 <0.001 9  |
| Yang B          | 2013 | China   | Asian     | HB     | Prostate | 37  | 49      | 143 229 25 46 167 238 0.80 <0.001 8 |
| Na N            | 2015 | China   | Asian     | HB     | Breast   | 188 | 104     | 33 325 199 98 28 325 0.24 0.003 9  |
| Sun Z           | 2015 | China   | Asian     | HB     | NPC      | 119 | 177     | 76 372 111 180 80 371 0.46 0.660 11 |
| Chen YZ         | 2016 | China   | Asian     | HB     | Gastric  | 442 | 217     | 33 692 475 264 32 771 0.21 0.535 11 |
| He J            | 2016 | China   | Asian     | HB     | Neuroblastoma | 160 | 79      | 9 248 343 170 18 531 0.19 0.583 10 |

(Continued)
| Author          | Year | Country | Ethnicity | Source | Cancer | Case BB | Case Bb | Case bb | Control BB | Control Bb | Control bb | MAF HWE Score |
|-----------------|------|---------|-----------|--------|--------|---------|--------|---------|------------|------------|-------------|----------------|
| Hua RX          | 2016 | China   | Asian     | HB     | Colorectal | 1169 644  88 1901 1213 692 72 1977 0.21 0.027 | 9 |
| Hua RX          | 2016 | China   | Asian     | HB     | Gastric    | 725 364  53 1142 746 388 39 1173 0.20 0.182 | 11 |
| rs2227869 G>C   |      |         |           |        |          |         |        |         |            |            |             |                |
| Shen M          | 2005 | China   | Asian     | PB     | Lung      | 103 14 1 118 100 11 0 111 0.05 0.583 | 11 |
| Garcia-Closas M | 2006 | Spain   | Caucasian | HB     | Bladder   | 1050 91 2 1143 1046 90 0 1136 0.04 0.164 | 12 |
| Huang WY        | 2006 | USA     | Caucasian | PB     | Colorectal | 598 52 1 651 601 60 1 662 0.05 0.694 | 14 |
| Hooker S        | 2006 | USA     | African   | HB     | Prostate   | 234 20 0 254 274 27 0 301 0.05 0.415 | 7 |
| Hussain SK      | 2009 | China   | Asian     | PB     | Gastric    | 174 13 0 187 314 56 3 372 0.08 0.773 | 13 |
| Ma H            | 2012 | USA     | Caucasian | HB     | SCCHN      | 987 70 2 1059 974 90 2 1066 0.04 0.958 | 11 |
| Sakoda LC       | 2012 | USA     | Caucasian | PB     | Lung       | 1 63 680 744 2 110 1362 1474 0.96 0.886 | 15 |
| Santos LS       | 2013 | Portugal | Caucasian | HB     | Thyroid    | 99 6 1 106 184 27 1 212 0.02 0.993 | 8 |
| Paszkowska-Szczur K | 2013 | Poland  | Caucasian | PB     | Melanoma   | 567 67 2 636 1168 162 2 1332 0.06 0.137 | 13 |
| Mirecka A       | 2014 | Poland  | Caucasian | HB     | Prostate   | 485 83 3 571 682 99 1 782 0.06 0.181 | 9 |
| Paszkowska-Szczur K | 2015 | Poland  | Caucasian | HB     | Colorectal | 372 55 2 429 1168 162 2 1332 0.06 0.137 | 9 |
| rs2094258 C>T   |      |         |           |        |          |         |        |         |            |            |             |                |
| He J            | 2012 | China   | Asian     | HB     | Gastric    | 457 518 150 1125 457 560 179 1196 0.62 0.728 | 13 |
| Ma H            | 2012 | USA     | Caucasian | HB     | SCCHN      | 706 295 37 1038 721 291 41 1053 0.82 0.092 | 11 |
| Yang WG         | 2012 | China   | Asian     | HB     | Gastric    | 131 149 57 337 145 166 36 347 0.66 0.252 | 10 |
| Zhu ML          | 2012 | China   | Asian     | HB     | ESCC       | 414 524 177 1115 424 525 168 1117 0.61 0.793 | 13 |
| Yang B          | 2013 | China   | Asian     | HB     | Prostate   | 61 75 93 229 58 75 75 105 238 0.40 <0.001 | 9 |
| Na N            | 2015 | China   | Asian     | HB     | Breast     | 102 157 66 325 131 147 47 325 0.63 0.581 | 10 |
| Sun Y           | 2015 | China   | Asian     | HB     | Laryngeal  | 140 106 25 271 152 101 18 271 0.75 0.826 | 11 |
| Sun Z           | 2015 | China   | Asian     | HB     | NPC        | 209 68 95 372 211 66 94 371 0.66 <0.001 | 10 |
| Chen YZ         | 2016 | China   | Asian     | HB     | Gastric    | 287 304 101 692 291 368 112 771 0.62 0.803 | 11 |
| He J            | 2016 | China   | Asian     | HB     | Neuroblastoma | 116 93 39 248 203 254 74 531 0.62 0.701 | 10 |
| Hua RX          | 2016 | China   | Asian     | HB     | Colorectal | 797 856 248 1901 899 881 197 1977 0.68 0.378 | 10 |
| Feng YB         | 2016 | China   | Asian     | HB     | Gastric    | 15 75 87 177 15 96 127 238 0.26 0.577 | 6 |
| Hua RX          | 2016 | China   | Asian     | HB     | Gastric    | 499 508 135 1142 527 524 122 1173 0.67 0.623 | 11 |
| Lu JJ           | 2016 | China   | Asian     | HB     | Gastric    | 17 67 100 184 13 72 121 206 0.24 0.605 | 6 |
| Ma SH           | 2016 | China   | Asian     | HB     | Breast     | 27 136 157 320 15 96 127 238 0.26 0.577 | 7 |
| Yang LQ         | 2016 | China   | Asian     | HB     | Gastric    | 71 74 10 155 121 111 14 246 0.72 0.076 | 6 |
| Ying MF         | 2016 | China   | Asian     | HB     | Pancreatic | 87 92 16 195 117 115 22 254 0.69 0.400 | 7 |
| rs751402 C>T    |      |         |           |        |          |         |        |         |            |            |             |                |
| Shao MH         | 2007 | China   | Asian     | HB     | Lung      | 105 429 433 967 110 425 448 983 0.67 0.544 | 11 |
| Yoon AJ         | 2011 | Taiwan  | Asian     | HB     | HCC       | 11 52 33 96 32 137 167 336 0.70 0.614 | 6 |
| Duan Z          | 2012 | China   | Asian     | HB     | Gastric    | 47 181 172 400 29 165 206 400 0.72 0.605 | 11 |
| He J            | 2012 | China   | Asian     | HB     | Gastric    | 148 491 486 1125 137 499 560 1196 0.68 0.110 | 13 |
| Author     | Year | Country | Ethnicity | Source | Cancer      | Case | Control | MAF  | HWE  | Score |
|------------|------|---------|-----------|--------|-------------|------|---------|------|------|-------|
| Zavras AI  | 2012 | Taiwan  | Mixed     | HB     | OSCC        | BB   | Bb      | bb   | All  | 0.70  |
| Meng X     | 2013 | China   | Asian     | HB     | Salivary gland | BB   | Bb      | bb   | All  | 0.64  |
| Na N       | 2015 | China   | Asian     | HB     | Breast      | BB   | Bb      | bb   | All  | 0.65  |
| Sun Z      | 2015 | China   | Asian     | HB     | NPC         | BB   | Bb      | bb   | All  | 0.21  |
| Wang H     | 2016 | China   | Asian     | HB     | Breast      | BB   | Bb      | bb   | All  | 0.70  |
| Chen YZ    | 2016 | China   | Asian     | HB     | Gastric     | BB   | Bb      | bb   | All  | 0.67  |
| He J       | 2016 | China   | Asian     | HB     | Neuroblastoma | BB   | Bb      | bb   | All  | 0.62  |
| Hua RX     | 2016 | China   | Asian     | HB     | Colorectal  | BB   | Bb      | bb   | All  | 0.61  |
| Guo BW     | 2016 | China   | Asian     | HB     | Gastric     | BB   | Bb      | bb   | All  | 0.68  |
| Feng YB    | 2016 | China   | Asian     | HB     | Gastric     | BB   | Bb      | bb   | All  | 0.65  |
| Hua RX     | 2016 | China   | Asian     | HB     | Gastric     | BB   | Bb      | bb   | All  | 0.67  |
| Li RJ      | 2016 | China   | Asian     | HB     | Gastric     | BB   | Bb      | bb   | All  | 0.68  |
| Lu JJ      | 2016 | China   | Asian     | HB     | Gastric     | BB   | Bb      | bb   | All  | 0.66  |
| Ma SH      | 2016 | China   | Asian     | HB     | Breast      | BB   | Bb      | bb   | All  | 0.67  |
| Yang LQ    | 2016 | China   | Asian     | HB     | Gastric     | BB   | Bb      | bb   | All  | 0.64  |
| Wang MY    | 2016 | China   | Asian     | HB     | Prostate    | BB   | Bb      | bb   | All  | 0.67  |
| Zhou RM    | 2016 | China   | Asian     | HB     | Gastric     | BB   | Bb      | bb   | All  | 0.67  |

**rs873601 G>A**

| Author     | Year | Country | Ethnicity | Source | Cancer      | Case | Control | MAF  | HWE  | Score |
|------------|------|---------|-----------|--------|-------------|------|---------|------|------|-------|
| Shao MH    | 2007 | China   | Asian     | HB     | Lung        | BB   | Bb      | bb   | All  | 0.47  |
| He J       | 2012 | China   | Asian     | HB     | Gastric     | BB   | Bb      | bb   | All  | 0.47  |
| Ma H       | 2012 | USA     | Caucasian | HB     | SCCCHN      | BB   | Bb      | bb   | All  | 0.73  |
| Sakoda LC  | 2012 | USA     | Caucasian | PB     | Lung        | BB   | Bb      | bb   | All  | 0.73  |
| Yang WG    | 2012 | China   | Asian     | HB     | Gastric     | BB   | Bb      | bb   | All  | 0.50  |
| Zhu ML     | 2012 | China   | Asian     | HB     | ESCC        | BB   | Bb      | bb   | All  | 0.47  |
| Na N       | 2015 | China   | Asian     | HB     | Breast      | BB   | Bb      | bb   | All  | 0.43  |
| Zhao F     | 2015 | China   | Asian     | HB     | Pancreatic  | BB   | Bb      | bb   | All  | 0.30  |
| Chen YZ    | 2016 | China   | Asian     | HB     | Gastric     | BB   | Bb      | bb   | All  | 0.48  |
| He J       | 2016 | China   | Asian     | HB     | Neuroblastoma | BB   | Bb      | bb   | All  | 0.49  |
| Wang B     | 2016 | China   | Asian     | HB     | HCC         | BB   | Bb      | bb   | All  | 0.47  |
| Hua RX     | 2016 | China   | Asian     | HB     | Colorectal  | BB   | Bb      | bb   | All  | 0.46  |
| Hua RX     | 2016 | China   | Asian     | HB     | Gastric     | BB   | Bb      | bb   | All  | 0.47  |
| Zhou RM    | 2016 | China   | Asian     | HB     | Gastric     | BB   | Bb      | bb   | All  | 0.46  |

*Abbreviations: HB, hospital-based; PB, population-based; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; MAF, minor allele frequency; HWE, Hardy-Weinberg equilibrium; HCC, hepatocellular carcinoma; SCCCHN, squamous cell carcinoma of the head and neck; ESCC, esophageal squamous cell carcinoma; OSCC, oral squamous cell carcinoma; NPC, nasopharyngeal carcinoma.*
Table 2: Associations between the six SNPs in the XPG gene and cancer risk

| Variables | No. of studies | No. of cases | No. of controls | Homozygous | Heterozygous | Recessive | Dominant | Allele |
|-----------|----------------|--------------|-----------------|------------|-------------|-----------|----------|--------|
|           |                | All          | Caucasian       | Asian      | Others      | Lung      | Colorectal | Gastric | Others |
| rs1047768 T>C |                |              |                 |            |             |           |           |        |        |
| CC vs. TT | 1.03 (0.95–1.11) | 1.03 (0.97–1.09) | 1.00 (0.93–1.07) | 1.00 (0.98–1.09) | 1.01 (0.98–1.05) |
| CT vs. TT | 0.010           | 0.192        | 0.171           | 0.038      | 0.012       |
| rs2296147 T>C |                |              |                 |            |             |           |           |        |        |
| CC vs. TT | 1.32 (1.06–1.64) | 1.35 (1.10–1.65) | 1.08 (0.92–1.26) | 1.35 (1.12–1.63) | 1.14 (1.02–1.27) |
| CT vs. TT | 0.175           | 0.278        | 0.360           | 0.172      | 0.059       |
| rs2227869 G>C |                |              |                 |            |             |           |           |        |        |
| CC vs. GG | 1.10 (1.00–1.12) | 1.10 (0.90–1.01) | 1.08 (0.99–1.18) | 0.97 (0.92–1.03) | 1.00 (0.96–1.04) |
| GC vs. GG | 0.068           | 0.480        | 0.057           | 0.297      | 1.18         |
| CC vs. GC/ GG |              |              |                 |            |             |           |           |        |        |
| GC vs. GG | 0.95 (0.86–1.04) | 0.945 (0.78–1.63) | 0.94 (0.86–1.06) | 0.96 (0.88–1.06) | 0.99 (0.91–1.07) |
| rs2094258 C>T |                |              |                 |            |             |           |           |        |        |
| TT vs. CC | 1.08 (0.91–1.11) | 0.96 (0.82–1.11) | 0.98 (0.91–1.74) | 0.98 (0.84–1.13) | 1.00 (0.87–1.15) |
| CT vs. CC | 0.025           | 0.198        | 0.696           | 0.190      | 0.202       |
| TT vs. CT/ CC |              |              |                 |            |             |           |           |        |        |
| CT vs. CC | 1.00 (0.94–1.07) | 0.314 (0.94–1.16) | 0.089 (0.97–1.09) | 0.081 (0.99–1.08) |
| rs751402 C>T |                |              |                 |            |             |           |           |        |        |
| TT vs. CC | 0.020           | 0.936        | 0.053           | 0.437      | 1.17         |
| CT vs. CC | 1.44 (1.05–1.74) | 0.14 (1.05–1.84) | 1.07 (1.27–1.84) | 1.17 (0.76–1.71) | 1.17 (0.76–1.71) |
| TT vs. CT/ CC |              |              |                 |            |             |           |           |        |        |
| CT vs. CC | 1.10 (0.94–1.23) | 0.098 (0.94–1.25) | 0.11 (0.98–1.25) | 1.08 (0.98–1.18) |

(Continued)
False-positive report probability (FPRP) analysis and trial sequential analysis (TSA)

All significant findings remained significant at a prior probability of 0.1, with all the FPRP values less than 0.20 with the exception of the population-designed studies of rs2227869 G>C (Table 4). TSA indicated that the cumulative z-curve crossed the trial sequential monitoring boundary, suggesting that the sample size was sufficient and that no further analysis was required to confirm the results (Figure 4).

DISCUSSION

The NER pathway is critical for the repair of bulky DNA lesions resulting from exposure to chemical carcinogens as well as ionizing radiation in order to maintain genomic integrity and prevent carcinogenesis [55]. Because the XPG gene is an indispensable component of the NER pathway, SNPs in XPG may alter the expression or function of XPG thereby modifying the risk of cancer. Most previous meta-analyses of the association between SNPs in XPG and cancer risk have focused on rs17655 G>C [56-59]. However, recent studies have shown that other SNPs in XPG may also be associated with cancer risk. For example, Chen et al. found that rs873601 G>A was associated with an increased risk of gastric cancer in a Chinese Han population [36]. Wang et al. found that rs751402 C>T was protective against breast cancer in Chinese Han women [47]. Additionally, the T allele of rs2296147 was associated with an increased risk of prostate cancer [35]. However, the results of previous studies have been inconsistent, possibly due to variations in the study populations and limited sample sizes. We therefore performed a meta-analysis of 47 studies to comprehensively evaluate the associations between six SNPs in the XPG gene: rs1047768 T>C, rs2296147 T>C, rs2227869 G>C, rs2094258 C>T, rs751402 C>T, and rs873601 G>A and cancer risk.

The rs873601 G>A polymorphism is located in a miRNA binding site in the XPG gene. Thus, it may alter XPG expression by modulating the miRNA-mRNA interaction, which could play a role in carcinogenesis [10]. We demonstrated that rs873601 G>A was significantly associated with overall cancer risk. Individuals with the AA genotype of rs873601 had a dominant (P = 0.811), and allele contrast (P = 0.346) models (Table 3).

Table 3: Publication bias among studies that evaluated the associations between the six SNPs in the XPG gene and cancer susceptibility

| Polymorphism | No. of studies | Egger’s test P values |
|--------------|----------------|----------------------|
|              |                | Homozygous | Heterozygous | Recessive | Dominant | Allele contrast |
| rs1047768    | 22             | 0.107      | 0.190      | 0.325     | 0.137    | 0.301          |
| rs2296147    | 15             | 0.789      | 0.925      | 0.577     | 0.464    | 0.129          |
| rs2227869    | 11             | 0.708      | 0.289      | 0.042     | 0.297    | 0.197          |
| rs2094258    | 17             | 0.387      | 0.350      | 0.844     | 0.276    | 0.351          |
| rs751402     | 21             | 0.107      | 0.336      | 0.137     | 0.325    | 0.301          |
| rs873601     | 14             | 0.395      | 0.656      | 0.645     | 0.811    | 0.346          |
Figure 2: Forest plot of the association between rs873601 G>A in the XPG gene and overall cancer risk under an allele contrast model. For each study, estimated ORs and 95% CIs are plotted with a box and horizontal line, respectively. (◇, pooled ORs and associated 95% CIs).

Figure 3: Funnel plot of the association between rs873601 G>A in the XPG gene and overall cancer risk under an allele contrast model. Each point represents an individual study that reported the indicated association.
| Genotype | Crude OR (95% CI) | P       | Statistical power | Prior probability |
|----------|-------------------|---------|-------------------|-------------------|
|          |                   |         |                   | 0.25  | 0.1   | 0.01  | 0.001 | 0.0001 |
| rs1047768 T>C (lung cancer) |                   |         |                   |       |       |       |       |       |
| CC vs. TT | 1.32 (1.06–1.64)  | 0.012   | 0.998             | 0.035 | 0.097 | 0.542 | 0.923 | 0.992  |
| CT vs. TT | 1.35 (1.10–1.65)  | 0.004   | 0.995             | 0.011 | 0.033 | 0.273 | 0.791 | 0.974  |
| CC/CT vs. TT | 1.35 (1.12–1.63) | 0.002   | 0.859             | 0.006 | 0.019 | 0.177 | 0.685 | 0.956  |
| C vs. T  | 1.14 (1.02–1.27)  | 0.017   | 1.000             | 0.048 | 0.130 | 0.622 | 0.943 | 0.994  |
| rs2227869 G>C (population-based studies) |                   |         |                   |       |       |       |       |       |
| GC vs. GG | 0.80 (0.65–0.99)  | 0.041   | 0.987             | 0.111 | 0.272 | 0.805 | 0.976 | 0.998  |
| C vs. G  | 0.84 (0.71–0.99)  | 0.041   | 1.000             | 0.110 | 0.271 | 0.803 | 0.976 | 0.998  |
| rs751402 C>T (gastric cancer) |                   |         |                   |       |       |       |       |       |
| TT vs. CC | 1.38 (1.12–1.70)  | 0.002   | 1.000             | 0.007 | 0.019 | 0.179 | 0.687 | 0.956  |
| CT vs. CC | 1.14 (1.05–1.24)  | 0.003   | 1.000             | 0.008 | 0.024 | 0.213 | 0.732 | 0.965  |
| TT vs. CT/CC | 1.27 (1.06–1.51) | 0.010   | 1.000             | 0.030 | 0.085 | 0.506 | 0.912 | 0.990  |
| CT/TT vs. CC | 1.17 (1.08–1.26) | <0.001  | 1.000             | 0.001 | 0.002 | 0.019 | 0.161 | 0.658  |
| T vs. C  | 1.17 (1.07–1.27)  | 0.001   | 1.000             | 0.002 | 0.006 | 0.063 | 0.404 | 0.871  |
| rs873601 G>A (overall) |                   |         |                   |       |       |       |       |       |
| AA vs. GG | 1.14 (1.06–1.24)  | 0.001   | 1.000             | 0.002 | 0.006 | 0.061 | 0.394 | 0.867  |
| GA-AA vs. GG | 1.08 (1.02–1.15) | 0.012   | 1.000             | 0.036 | 0.101 | 0.552 | 0.926 | 0.992  |
| A vs. G  | 1.06 (1.02–1.10)  | 0.002   | 1.000             | 0.006 | 0.016 | 0.155 | 0.650 | 0.949  |
| rs873601 G>A (gastric cancer) |                   |         |                   |       |       |       |       |       |
| AA vs. GG | 1.18 (1.04–1.34)  | 0.009   | 1.000             | 0.027 | 0.078 | 0.482 | 0.904 | 0.989  |
| AA vs. GA/GG | 1.16 (1.04–1.28) | 0.008   | 1.000             | 0.022 | 0.064 | 0.431 | 0.884 | 0.987  |
| A vs. G  | 1.09 (1.02–1.16)  | 0.011   | 1.000             | 0.031 | 0.089 | 0.517 | 0.915 | 0.991  |

Chi-square tests were used to assess the genotype frequency distributions.
Statistical power was calculated using the number of observations in the subgroup and the P values in this table.
1.14-fold higher risk of cancer compared to individuals with the GG genotype. Similar results were obtained for gastric cancer. The A allele of rs873601 was previously shown to result in reduced mRNA expression of XPG in both adjacent normal gastric cancer tissue and normal cell lines in a recessive manner [10]. These findings provide insight into the molecular mechanisms by which the AA genotype of rs873601 may increase the risk of gastric cancer.

The rs751402 C>T polymorphism is located in the E2F1/YY1 binding and response site in the proximal promoter region of XPG [60]. This variant might reduce the DNA repair capacity of XPG by disrupting the DNA binding motifs and altering transcription factor affinities [47]. In our study, rs751402 C>T was significantly associated with overall cancer risk. The TT genotype of rs751402 was associated with an 18% increase in cancer risk compared to the CC genotype. Moreover, a significant association was observed between rs751402 C>T and gastric cancer risk under all genetic models. The rs751402 C>T polymorphism is likely to influence cancer risk by regulating XPG expression, but its effect on XPG function is not yet clear [47].

The rs2094258 C>T polymorphism is located in a transcription factor binding site in the 5’ region of the XPG gene. We found that the association between rs2094258 C>T and overall cancer risk was borderline significant. Individuals with the TT genotype of rs2094258 had a 9% higher risk of cancer compared to those with the CC genotype. However, the association was not significant in gastric cancer, indicating that it may not impact gastric cancer risk. Significant associations were observed among some subgroups for all other selected SNPs. We found that the C allele of rs1047768 may increase the risk of lung cancer. Moreover, the C allele of rs2227869 significantly reduced cancer risk in population-based studies. No statistically significant association was observed between rs2296147 T>C and overall cancer risk.

Although we found significant associations between SNPs in the XPG gene and cancer risk, our study had several limitations. First, although Egger’s tests showed no obvious publication bias, some bias was unavoidable since only studies published in English and Chinese were included in our meta-analysis. Second, we observed significant heterogeneity in some of our analyses, which is a common drawback of a meta-analysis. Third, due to a lack of sufficient individual data, we were unable to perform multivariate analysis with adjustment for potential confounding factors such as tobacco use, alcohol consumption, and other carcinogenic factors.

Our study is the first meta-analysis of the association between the six selected SNPs in XPG gene and cancer risk. The results indicate that the AA genotype of rs873601 increases overall cancer risk. Additionally, rs751402 C>T and rs873601 G>A were associated with gastric cancer risk. Finally, rs1047768 T>C was found to confer susceptibility to lung cancer. Further epidemiological investigations with larger sample sizes are warranted to validate our findings. Functional studies are also required to elucidate the mechanisms by which these SNPs modify cancer risk.

Figure 4: TSA of rs873601 G>A in the XPG gene and overall cancer risk under an allele contrast model.
MATERIALS AND METHODS

Study identification

We searched multiple databases including PubMed, Scopus, Web of Science, CNKI, and the WanFang database using combinations of keywords such as “XPG”, “polymorphism”, and “cancer” as well as synonyms “Xeroderma pigmentosum group G, ERCC5 or Excision repair cross complementing group 5”, “variant or variation”, and “tumor, neoplasm, or carcinoma”. Human studies published before December 20, 2016 in either English or Chinese were included. The reference lists in eligible studies and review articles were examined in order to identify additional relevant studies. In cases of study population overlap, the study with the largest sample size was selected.

Inclusion and exclusion criteria

All studies included in this analysis were required to meet the following criteria: (1) study of the associations between any of the six potentially functional SNPs: rs1047768 T>C, rs2296147 T>C, rs2227869 G>C, rs2094258 C>T, rs751402 C>T, and rs873601 G>A in the XPG gene and cancer risk; (2) case-control study; and (3) sufficient genotype data available to calculate ORs and 95% CIs. The exclusion criteria were: (1) studies conducted in the same or overlapping population and (2) review article or conference report.

Data extraction

Key information was independently extracted from eligible studies by two investigators and included the following items: the first author, year of publication, type of cancer, country, ethnicity, control source, number of cases and controls, the quantity of each genotype in cases and controls, minor allele frequency (MAF), and the Hardy-Weinberg equilibrium (HWE) test P value for the control subjects. Disagreements regarding these items were resolved through discussion.

Statistical analysis

Chi-square tests were used to test deviation from HWE in the study control groups. Genetic associations between the six selected SNPs in the XPG gene and cancer risk were assessed using the crude ORs and corresponding 95% CIs under homozygous, heterozygous, recessive, dominant, and allele contrast models. Heterogeneity between studies was assessed using the Q and I² values. A random effects model was adopted to calculate the pooled OR and 95% CI in the case of Phet < 0.1 or F > 50%. Otherwise, a fixed effects model was applied. Stratified analyses were conducted by ethnicity (Asians and Caucasians), source of control [population-based (PB) or hospital-based (HB)], and cancer type.

Sensitivity analyses were performed to assess the influence of the individual studies on the pooled OR by sequentially removing one study at a time and recalculating the pooled OR. Egger’s tests were used to evaluate publication bias. FPRP analysis [61, 62] and TSA were performed as described previously [63]. All statistical analyses were performed using the STATA 12.0 software (Stata Corporation, College Station, TX, USA). All statistics were two-sided. P values < 0.05 were considered statistically significant.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

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