Association between the ERCC2 Asp312Asn polymorphism and risk of cancer

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ABSTRACT

Cancer is the leading cause of death in economically developed countries and the second leading cause of death in developing countries. The relationship between genetic polymorphisms and the risk of cancers has been widely researched. Excision repair cross-complementing group 2 (ERCC2) gene plays important roles in the nucleotide excision repair pathway. There is contrasting evidence on the association between the ERCC2 Asp312Asn polymorphism and the risk of cancer. We conducted a comprehensive meta-analysis in order to assess the correlation between these factors. We searched the PubMed, EMBASE, Science Direct, Web of Science, and CNKI databases for studies published from January 1, 2005 to January 1, 2016. Finally, 86 articles with 38,848 cases and 48,928 controls were included in the analysis. The overall analysis suggested a significant association between the ERCC2 Asp312Asn polymorphism and cancer risk. Furthermore, control source, ethnicity, genotyping method, and cancer type were used for subgroup analysis. The result of a trial sequential analysis indicated that the cumulative evidence is adequate; hence, further trials were unnecessary in the overall analysis for homozygote comparison. In summary, our results suggested that ERCC2 Asp312Asn polymorphism is associated with increased cancer risk. A significantly increased cancer risk was observed in Asian populations, but not in Caucasian populations. Furthermore, the ERCC2 Asp312Asn polymorphism is associated with bladder, esophageal, and gastric cancers, but not with breast, head and neck, lung, prostate, and skin cancers, and non-Hodgkin lymphoma. Further multi-center, well-designed studies are required to validate our results.
INTRODUCTION

Cancer describes a group of diseases characterized by the uncontrolled growth and spread of abnormal cells [1]. It is the leading cause of death in economically developed countries and the second leading cause of death in developing countries [2]. According to statistics, a total of 1,658,370 new cancer cases and 589,430 cancer deaths were projected to occur in the United States in 2015 [3]. In general, cancer is the result of multiple environmental and genetic risk factors, as well as gene-environment interactions [4]. Among genetic factors, genetic and epigenetic mutations, such as aberrant DNA methylation, can lead to carcinogenesis [1].

Recently, the relationship between genetic polymorphisms and the risk of cancer has been widely researched. Among the polymorphic genes, excision repair cross-complementing group 2 (ERCC2), also called xeroderma pigmentosum group D (XPD), plays important roles in the nucleotide excision repair (NER) pathway [5]. The ERCC2 gene is located on chromosome 19q13.3, comprises 23 exons, and spans approximately 54,000 base pairs [6]. It encodes an evolutionarily conserved helicase, which has ATP-dependent helicase activity within its multi subunit core transcription factor IIIH (TFIIH). The helicase participates in DNA unwinding as part of the NER pathway, and plays an important role in the recognition and repair of structurally unrelated DNA lesions containing bulky adducts and thymidine dimers [7, 8]. Some studies have shown that ERCC2 polymorphisms may be related to reduced DNA repair due to a possible reduction in its helicase activity [9, 10].

There are two important single nucleotide polymorphisms (SNPs) in the ERCC2 gene. One is the Lys751Gln polymorphism, which has been shown to be involved in genetic susceptibility to some cancer types. Another common ERCC2 polymorphism in the coding region is Asp312Asn (rs1799793) [11], which is characterized by a G to A transition at position 312 in exon 10 causing an aspartic acid (Asp) to asparagine amino acid (Asn) exchange [12]. This polymorphism has been widely studied for its association with susceptibility to cancer including brain [13], esophageal [14–16], head and neck [11], bladder [17–19], and breast cancers [20–22]. However, the results reported by these studies were inconsistent.

To provide a comprehensive assessment of and to clarify associations between the ERCC2 Asp312Asn polymorphisms and the risk of cancer, we performed a meta-analysis of all the eligible case-control studies.

RESULTS

Eligible studies

A total of 449 articles were reviewed, and eventually 86 articles with 38,848 cases and 48,928 controls met the inclusion criteria. Among these publications, there was 1 osteosarcoma [23], 1 hepatocellular cancer (HCC) [24], 3 oral cancer [25–27], 5 skin cancer [28–32], 5 colorectal cancer [23, 33–36], 6 head and neck cancer [37–42], 6 esophageal cancer [43–48], 6 non-Hodgkin lymphoma [49–54], 6 prostate cancer [55–60], 8 gastric cancer [61–67], 12 bladder cancer [68–79], 14 lung cancer [70, 80–92], and 15 breast cancer [23, 32, 93–105]. The detailed study selection process is shown in Figure 1. Table 1 presents the major characteristics of the 86 articles.

Meta-analysis

Overall analysis

In the dominant model, increased cancer risk was found with an odds ratio (OR) of 1.110 (95% confidence interval [CI] 1.078-1.143, P<0.01). In the recessive model, significantly increased risk was determined with an OR of 1.059 (95% CI 1.013-1.108, P<0.01). Furthermore, when the homozygote and heterozygote comparisons were performed, increased risk was identified, with an OR of 1.103 (95% CI 1.052-1.157, P<0.01), and an OR of 1.106 (95% CI 1.072-1.141, P<0.01), respectively. Overall, the results of our meta-analysis showed a significant association between the ERCC2 polymorphism and cancer risk (Table 2).

Subgroup analysis

In order to evaluate the effects of specific study characteristics on the association between the ERCC2 polymorphism and cancer risk, we performed subgroup analysis if there were 6 or more studies. The ORs and 95% CIs were obtained from the subgroups of control source, ethnicity, genotyping method, and type of cancer. For control source subgroup, we found a significant association between the ERCC2 polymorphism and cancer risk when the source of the controls was hospital-based (HB). Meanwhile, when the studies recruited population-based (PB) control, no association was found. For ethnicity, no significant association was detected in Caucasians, but significant associations were observed in Asians. When stratified according to the genotyping method, significant associations were observed when the method was polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP). By comparison, no relationship was found when the methods used were PCR and TaqMan assay. According to the type of cancer, the ERCC2 polymorphism was associated with a significantly higher risk of bladder cancer. In contrast, we observed no association between this polymorphism and breast cancer. Similarly, the results of subgroups of other cancers indicated no association with the ERCC2 polymorphism, including head and neck, lung, prostate, and skin cancers and non-Hodgkin lymphoma. For the esophageal cancer group, a significant association was obtained in the heterozygote comparison, but not in the
homozygote comparison and the recessive model. In the group with gastric cancer, the ERCC2 polymorphism was confirmed to increase the risk of cancer in the homozygote comparison and the recessive model, but not in the heterozygote comparison and the dominant model. The detailed results are shown in Table 2.

Test of heterogeneity

High heterogeneity was observed after the data were pooled (homozygote comparison: $P$ for heterogeneity = 0, $I^2 = 68.3\%$). As shown in Table 2, when the subjects were stratified on the basis of the control source, high heterogeneity remained with PB controls (homozygote comparison: $P$ for heterogeneity = 0, $I^2 = 79.8\%$). Additionally, in analyses of ethnicity, moderate heterogeneity was found in Asian studies (homozygote comparison: $P$ for heterogeneity = 0.003, $I^2 = 48.3\%$), and high heterogeneity was found in Caucasian studies (homozygote comparison: $P$ for heterogeneity = 0, $I^2 = 50.8\%$). Moreover, in analyses of genotyping methods, low heterogeneity was detected in the TaqMan group (homozygote comparison: $P$ for heterogeneity = 0.163, $I^2 = 24.8\%$), but high heterogeneity was found in the PCR (homozygote comparison: $P$ for heterogeneity = 0, $I^2 = 65\%$) and PCR-RFLP groups (homozygote comparison: $P$ for heterogeneity = 0, $I^2 = 62.5\%$). Furthermore, heterogeneity was not detected in esophageal cancer studies (homozygote comparison: $P$ for heterogeneity = 0.62, $I^2 = 0\%$), lung cancer studies (homozygote comparison: $P$ for heterogeneity = 0.533, $I^2 = 0\%$), and non-Hodgkin lymphoma studies (homozygote comparison: $P$ for heterogeneity = 0.782, $I^2 = 0\%$). Nonetheless, high heterogeneity was still present in studies of prostate cancer (homozygote comparison: $P$ for heterogeneity = 0, $I^2 = 93.5\%$), bladder cancer (homozygote comparison: $P$ for heterogeneity = 0.008, $I^2 = 56.4\%$), breast cancer (homozygote comparison: $P$ for heterogeneity = 0, $I^2 = 66.6\%$), gastric cancer (homozygote comparison: $P$ for heterogeneity = 0.005, $I^2 = 65.3\%$), head and neck cancer

Figure 1: Flow chart showing the selection process for the included studies.
Table 1: Characteristics of the case–control studies included in the meta-analyses

| First author   | Year | Ethnicity  | Country | Source of controls | Cancer site            | Genotyping method | cases | controls |
|----------------|------|------------|---------|--------------------|------------------------|-------------------|-------|----------|
|                |      |            |         |                    |                        |                   |       |          |
| Liu G          | 2007 | Caucasian  | USA     | HB                 | esophageal cancer head and neck cancer | PCR-RFLP          | 75    | 92       | 16       | 144      | 160      | 32       |
| An             | 2007 | Caucasian  | USA     | HB                 | head and neck cancer   | PCR-RFLP          | 330   | 395      | 104      | 370      | 386      | 98       |
| Harth          | 2008 | Caucasian  | Germany | HB                 | head and neck cancer   | Real-time PCR     | 113   | 158      | 40       | 101      | 145      | 52       |
| Abbasi         | 2009 | Caucasian  | Germany | PB                 | head and neck cancer   | Real-time PCR     | 93    | 119      | 34       | 258      | 304      | 82       |
| Ji             | 2010 | Asian      | Korea   | HB                 | head and neck cancer   | PCR                | 235   | 29       | 0        | 309      | 30       | 3        |
| Gugatschka     | 2011 | Caucasian  | Austria | PB                 | head and neck cancer   | TaqMan             | 116   | 133      | 42       | 171      | 208      | 83       |
| Smedby         | 2006 | Caucasian  | Sweden  | PB                 | non-Hodgkin lymphoma   | PCR                | 167   | 211      | 50       | 262      | 255      | 85       |
| Shen           | 2006 | Caucasian  | USA     | PB                 | non-Hodgkin lymphoma   | Real-time PCR      | 199   | 189      | 57       | 226      | 238      | 70       |
| Song           | 2008 | Asian      | China   | HB                 | non-Hodgkin lymphoma   | PCR-RFLP           | 256   | 47       | 4        | 265      | 35       | 3        |
| Baris          | 2009 | Caucasian  | Turkey  | HB                 | non-Hodgkin lymphoma   | PCR-RFLP           | 13    | 16       | 4        | 15       | 27       | 10       |
| Worrillow      | 2009 | Caucasian  | England | PB                 | non-Hodgkin lymphoma   | TaqMan             | 270   | 265      | 79       | 316      | 335      | 79       |
| EI-Din         | 2013 | Caucasian  | Egypt   | HB                 | non-Hodgkin lymphoma   | PCR-RFLP           | 30    | 37       | 14       | 38       | 44       | 18       |
| Capella G      | 2008 | Mixed      | Spain   | PB                 | gastric cancer         | PCR-RFLP           | 110   | 96       | 38       | 444      | 532      | 159      |
| Zhou RM        | 2007 | Asians     | China   | PB                 | gastric cancer         | PCR-RFLP           | 221   | 32       | 0        | 528      | 82       | 2        |
| Lou Y          | 2006 | Asians     | China   | HB                 | gastric cancer         | PCR-RFLP           | 189   | 39       | 10       | 176      | 21       | 3        |
| Agalliu        | 2010 | Caucasian  | USA     | PB                 | prostate cancer        | PCR-RFLP           | 545   | 575      | 120      | 527      | 528      | 166      |
| Agalliu        | 2010 | African    | USA     | PB                 | prostate cancer        | PCR-RFLP           | 106   | 31       | 7        | 65       | 15       | 2        |
| Moreno V       | 2006 | Caucasian  | Spain   | HB                 | colorectal cancer      | PCR                | 95    | 91       | 100      | 77       | 72       | 63       |
| Hansen RD      | 2007 | Caucasian  | Denmark | PB                 | colorectal cancer      | TaqMan             | 159   | 191      | 46       | 333      | 354      | 108      |

(Continued)
| First author | Year | Ethnicity | Country | Source of controls | Cancer site | Genotyping method | cases | controls |
|--------------|------|-----------|---------|--------------------|-------------|-------------------|-------|----------|
| De Ruyck     | 2007 | Caucasian | Belgium | HB                 | Lung Cancer | PCR-RFLP          | 44    | 49       |
| Zienolddiny  | 2006 | Caucasian | Norway  | PB                 | Lung Cancer | PCR               | 119   | 120      |
| Matullo      | 2006 | Caucasian | Europe  | PB                 | Lung Cancer | PCR-RFLP          | 49    | 418      |
| Hu           | 2006 | Asian     | China   | HB                 | Lung Cancer | TaqMan            | 850   | 874      |
| Shen         | 2005 | Asian     | China   | PB                 | Lung Cancer | PCR               | 109   | 99       |
| Huang        | 2006 | Mixed     | USA     | NA                 | Lung Cancer | PCR               | 301   | 301      |
| De Ruyck     | 2007 | Caucasian | Belgium | HB                 | Lung Cancer | PCR-RFLP          | 16    | 61       |
| Zienolddiny  | 2006 | Caucasian | Norway  | PB                 | Lung Cancer | PCR               | 153   | 155      |
| Matullo      | 2006 | Caucasian | Europe  | PB                 | Lung Cancer | PCR-RFLP          | 225   | 248      |
| Hu           | 2006 | Asian     | China   | HB                 | Lung Cancer | TaqMan            | 48    | 418      |
| Shen         | 2005 | Asian     | China   | PB                 | Lung Cancer | PCR               | 114   | 205      |
| Huang        | 2006 | Mixed     | USA     | NA                 | Lung Cancer | PCR               | 113   | 205      |
| Schabath     | 2005 | Mixed     | USA     | HB                 | bladder cancer | PCR-RFLP | 92   | 103       |
| Andrew       | 2006 | Mixed     | USA     | PB                 | bladder cancer | PCR-RFLP | 517   | 538       |
| Garcia-Closas| 2006 | Caucasian | Spain   | HB                 | bladder cancer | PCR-RFLP | 473   | 467      |
| Wu           | 2006 | Caucasian | USA     | HB                 | bladder cancer | PCR-RFLP | 264   | 283      |
| Fontana      | 2008 | Caucasian | France  | HB                 | bladder cancer | TaqMan | 25    | 21       |
| Chang        | 2009 | Asian     | China   | HB                 | bladder cancer | PCR-RFLP | 153   | 199      |
| Gangwar      | 2009 | Asian     | India   | HB                 | bladder cancer | PCR-RFLP | 72    | 128      |
| Mittal       | 2012 | Asian     | India   | PB                 | bladder cancer | PCR-RFLP | 78    | 128      |
| Ye           | 2006 | Caucasian | Sweden  | PB                 | esophageal cancer | PCR-RFLP | 61    | 176      |
| Tse          | 2008 | Mixed     | USA     | HB                 | esophageal cancer | TaqMan | 117   | 199      |
| Pan          | 2009 | Caucasian | USA     | HB                 | esophageal cancer | TaqMan | 16    | 201      |
| Pan          | 2009 | Caucasian | USA     | HB                 | esophageal cancer | TaqMan | 137   | 201      |
| Huang        | 2012 | Asian     | China   | HB                 | esophageal cancer | PCR-RFLP | 171   | 298      |
| Li           | 2013 | Asian     | China   | HB                 | esophageal cancer | PCR-RFLP | 342   | 351      |
| Han          | 2005 | Mixed     | USA     | PB                 | Skin Cancer | TaqMan | 88    | 342      |

(Continued)
| First author   | Year | Ethnicity         | Country | Source of controls | Cancer site          | Genotyping method  | cases | controls |
|---------------|------|-------------------|---------|--------------------|----------------------|-------------------|-------|----------|
|               |      |                   |         |                    |                      |                   |       |          |
| Wang LL       | 2009 | Asian             | China   | HB                 | colorectal cancer    | PCR-RFLP           | 132   | 29       | 9        | 176     | 21     | 3       |
| Mahimkar MB   | 2010 | Asian             | India   | NA                 | oral cancer          | PCR-RFLP           | 23    | 13       | 4        | 23      | 21     | 1       |
| Wang Y        | 2007 | Caucasian         | USA     | HB                 | oral cancer          | PCR and Taqman     | 50    | 59       | 16       | 140     | 109    | 29      |
| Majumder M    | 2007 | Asian             | India   | HB                 | oral cancer          | PCR                | 269   | 208      | 52       | 205     | 146    | 36      |
| Crew          | 2007 | NA                | USA     | PB                 | breast cancer        | Taqman             | 415   | 478      | 138      | 490     | 454    | 139     |
| Jorgensen     | 2007 | Caucasian         | USA     | PB                 | breast cancer        | Taqman             | 110   | 128      | 22       | 102     | 142    | 29      |
| Kuschel       | 2005 | Australian        | UK      | PB                 | breast cancer        | TaqMan             | 1529  | 1530     | 497      | 1401    | 1437   | 430     |
| Lee           | 2005 | Asian             | Korea   | HB                 | breast cancer        | PCR                | 475   | 50       | 3        | 401     | 41     | 3       |
| Bernard-Gallon| 2008 | NA                | France  | HB                 | breast cancer        | Taqman             | 403   | 383      | 118      | 458     | 418    | 118     |
| Debniai       | 2006 | Polish            | Poland  | PB                 | breast cancer        | PCR-RFLP           | 672   | 785      | 269      | 180     | 252    | 79      |
| Jakubowska    | 2010 | Polish            | Poland  | HB                 | breast cancer        | PCR                | 118   | 152      | 44       | 106     | 135    | 49      |
| Mechanic      | 2006 | Caucasian         | USA     | PB                 | breast cancer        | PCR-RFLP           | 543   | 589      | 130      | 489     | 516    | 128     |
| Mechanic      | 2006 | African-American  | USA     | PB                 | breast cancer        | PCR-RFLP           | 564   | 181      | 15       | 517     | 145    | 13      |
| Shen          | 2006 | American          | USA     | PB                 | breast cancer        | Taqman             | 60    | 80       | 16       | 59      | 64     | 30      |
| Smith         | 2008 | Caucasian         | USA     | HB                 | breast cancer        | PCR                | 126   | 137      | 41       | 161     | 188    | 42      |
| Smith         | 2008 | African-American  | USA     | HB                 | breast cancer        | PCR                | 33    | 14       | 2        | 57      | 16     | 1       |
| Zhang         | 2005 | Asian             | China   | PB                 | breast cancer        | PCR-RFLP           | 89    | 111      | 20       | 119     | 140    | 51      |
| Hussien       | 2012 | Caucasian         | Egypt   | HB                 | breast cancer        | PCR                | 12    | 45       | 43       | 25      | 50     | 25      |
| Jelonek       | 2010 | Mixed             | Poland  | PB                 | breast cancer        | PCR-RFLP           | 41    | 59       | 21       | 85      | 123    | 23      |
| Wang          | 2010 | Asian             | China   | PB                 | breast cancer        | PCR-RFLP           | 624   | 388      | 220      | 925     | 315    | 193     |
| Zhou          | 2012 | Asian             | Asia    | PB                 | Lung Cancer          | PCR-RFLP           | 85    | 18       | 0        | 85      | 17     | 1       |
| Sakoda        | 2012 | Caucasian         | USA     | PB                 | Lung Cancer          | TaqMan             | 326   | 329      | 89       | 610     | 685    | 182     |
| Qian          | 2011 | Asian             | China   | PB                 | Lung Cancer          | PCR                | 464   | 82       | 4        | 497     | 79     | 3       |
| Yin           | 2009 | Asian             | China   | HB                 | Lung Cancer          | PCR-RFLP           | 246   | 38       | 1        | 255     | 30     | 0       |
| Raaschou-Nielsen | 2008 | Caucasian        | Denmark | PB                 | Lung Cancer          | PCR                | 177   | 188      | 59       | 329     | 351    | 107     |
| Chang         | 2008 | Latino-American   | USA     | PB                 | Lung Cancer          | WGA                | 60    | 40       | 8        | 192     | 93     | 12      |
| Chang         | 2008 | African-American  | USA     | PB                 | Lung Cancer          | WGA                | 186   | 58       | 3        | 212     | 60     | 5       |
| Yin           | 2007 | Asian             | China   | HB                 | Lung Cancer          | PCR-RFLP           | 200   | 1        | 0        | 170     | 0      | 1       |
| Lopez-Cima    | 2007 | Caucasian         | Spain   | HB                 | Lung Cancer          | PCR-RFLP           | 240   | 221      | 55       | 260     | 230    | 43      |

(Continued)
| First author | Year | Ethnicity | Countrya | Source of controls | Cancer site               | Genotyping method | cases | controls |
|--------------|------|-----------|----------|-------------------|--------------------------|------------------|-------|----------|
| Han          | 2005 | Mixed     | USA      | PB                | Skin Cancer              | TaqMan           | 104   | 342      |
| Han          | 2005 | Mixed     | USA      | PB                | Skin Cancer              | TaqMan           | 128   | 342      |
| Lovatt       | 2005 | Caucasian | UK       | PB                | Skin Cancer              | PCR-RFLP         | 224   | 151      |
| Li           | 2006 | Mixed     | USA      | HB                | Skin Cancer              | PCR              | 242   | 273      |
| Millikan     | 2006 | Caucasian | USA      | PB                | Skin Cancer              | PCR              | 1039  | 1039     |
| Debniaik     | 2006 | Polish    | Poland   | mixed             | Skin Cancer              | PCR              | 168   | 492      |
| Bau          | 2007 | Asian     | Taiwan   | HB                | prostate cancer          | PCR              | 62    | 310      |
| Mandal       | 2010 | Asian     | India    | PB                | prostate cancer          | PCR              | 76    | 99       |
| Lavende      | 2010 | African   | America  | HB                | prostate cancer          | PCR and Taqman   | 146   | 510      |
| Dhillon      | 2011 | Caucasian | Australia| NA               | prostate cancer          | PCR-RFLP         | 71    | 80       |
| Yuan T       | 2011 | Asian     | China    | HB                | gastric Cancer           | PCR              | 156   | 220      |
| Chen Z       | 2011 | Asian     | China    | HB                | gastric Cancer           | PCR-RFLP         | 75    | 132      |
| Zhang CZ     | 2009 | Asian     | China    | HB                | gastric Cancer           | PCR-RFLP         | 75    | 41       |
| Ruzzo A      | 2007 | Caucasian | Italy    | HB                | gastric Cancer           | PCR-RFLP         | 23    | 41       |
| Deng Sl      | 2010 | Asian     | China    | HB                | gastric Cancer           | PCR              | 132   | 118      |
| Wu JS        | 2014 | Asian     | China    | HB                | HCC                       | PCR              | 138   | 181      |
| Sambuddha    | 2015 | Asian     | Northeast India | NA | head and neck cancer | PCR              | 32    | 57       |
| Benjamin     | 2015 | Mexican   | Mexico   | HB                | osteosarcoma             | PCR              | 21    | 68       |
| Benjamin     | 2015 | Mexican   | Mexico   | HB                | colorectal cancer        | PCR              | 74    | 81       |
| Benjamin     | 2015 | Mexican   | Mexico   | HB                | breast cancer            | PCR              | 54    | 54       |
| Min Ni       | 2014 | Asian     | China    | HB                | colorectal cancer        | Real-time PCR    | 182   | 210      |
| Volha P. Ramaniku      | 2014 | Belarusians | Belarus | HB                | bladder cancer           | PCR-RFLP         | 99    | 128      |
| Aneta Mirecka   | 2014 | Polish    | Poland   | PB                | prostate cancer          | real-time PCR    | 199   | 377      |

a Country of first author.
Table 2: Results of overall and stratified meta-analyses

| Model (Comparison)               | Subgroup            | No. of trials | I²(%) | P* | Fixed       | Random       | P for bias |
|---------------------------------|---------------------|---------------|-------|----|-------------|--------------|------------|
|                                 |                     |               |       |    | 1.103(1.052,1.157) | 1.170(1.060,1.293) | 0.079     |
| homozygote comparison           |                     |               |       |    |             |              |            |
| (Asn/Asn vs. Asp/Asp)           |                     |               |       |    |             |              |            |
|                                 | Total               | 95            | 68.3  | 0  | 1.103(1.052,1.157) | 1.170(1.060,1.293) | 0.079     |
|                                 | PB                  | 41            | 79.8  | 0  | 1.037(0.977,1.101) | 1.074(0.922,1.250) | 0.53      |
|                                 | HB                  | 49            | 39    | 0.004 | 1.249(1.149,1.358) | 1.283(1.135,1.450) | 0.462     |
|                                 | Asia                | 30            | 48.3  | 0.003 | 1.664(1.461,1.894) | 1.734(1.371,2.192) | 0.961     |
|                                 | Caucasian           | 37            | 50.8  | 0  | 0.964(0.899,1.034) | 1.019(0.913,1.137) | 0.041     |
|                                 | PCR                 | 29            | 65    | 0  | 1.041(0.951,1.140) | 1.175(0.983,1.404) | 0.054     |
|                                 | PCR-RFLP            | 38            | 62.5  | 0  | 1.160(1.068,1.260) | 1.238(1.053,1.455) | 0.054     |
|                                 | Taqman              | 18            | 24.8  | 0.163 | 1.003(0.921,1.093) | 0.983(0.878,1.100) | 0.16      |
|                                 | Bladder cancer      | 12            | 56.4  | 0.008 | 1.370(1.198,1.566) | 1.446(1.160,1.803) | 0.191     |
|                                 | Breast cancer       | 18            | 66.6  | 0  | 1.098(1.009,1.194) | 1.042(0.871,1.246) | 0.543     |
|                                 | Esophageal cancer   | 7             | 0     | 0.62 | 1.219(0.945,1.571) | 1.243(0.962,1.608) | 0.074     |
|                                 | Gastric cancer      | 8             | 65.3  | 0.005 | 1.517(1.167,1.972) | 1.876(1.105,3.186) | 0.258     |
|                                 | Head and neck cancer| 6             | 52.4  | 0.062 | 0.993(0.814,1.212) | 0.989(0.707,1.384) | 0.909     |
|                                 | Lung Cancer         | 16            | 0     | 0.533 | 1.043(0.901,1.207) | 1.042(0.899,1.207) | 0.386     |
|                                 | Prostate cancer     | 7             | 93.5  | 0  | 1.570(1.314,1.874) | 2.038(0.848,4.894) | 0.419     |
|                                 | Skin Cancer         | 7             | 59.9  | 0.021 | 0.784(0.689,0.893) | 0.818(0.657,1.020) | 0.448     |
|                                 | Non- Hodgkin lymphoma| 6             | 0     | 0.782 | 0.998(0.811,1.229) | 1.000(0.812,1.231) | 0.505     |
| heterozygote comparison         |                     |               |       |    |             |              |            |
| (Asp/Asn vs. Asp/Asp)           |                     |               |       |    |             |              |            |
|                                 | Total               | 95            | 61.1  | 0  | 1.106(1.072,1.141) | 1.133(1.072,1.198) | 0.111     |
|                                 | PB                  | 41            | 64.7  | 0  | 1.061(1.020,1.104) | 1.064(0.988,1.146) | 0.889     |
|                                 | HB                  | 49            | 53.9  | 0  | 1.205(1.143,1.270) | 1.229(1.128,1.339) | 0.329     |
|                                 | Asia                | 30            | 71.8  | 0  | 1.373(1.275,1.480) | 1.287(1.105,1.499) | 0.096     |
|                                 | Caucasian           | 37            | 0     | 0.801 | 1.034(0.988,1.083) | 1.034(0.987,1.082) | 0.526     |
|                                 | PCR                 | 29            | 44.2  | 0.006 | 1.057(0.996,1.121) | 1.076(0.982,1.180) | 0.281     |
|                                 | PCR-RFLP            | 38            | 70    | 0  | 1.187(1.126,1.251) | 1.203(1.081,1.338) | 0.745     |
|                                 | Taqman              | 18            | 14.5  | 0.28 | 1.030(0.974,1.090) | 1.039(0.973,1.109) | 0.348     |
|                                 | Bladder cancer      | 12            | 31.2  | 0.142 | 1.235(1.128,1.353) | 1.265(1.125,1.423) | 0.231     |
|                                 | Breast cancer       | 18            | 70.7  | 0  | 1.086(1.025,1.149) | 1.101(0.972,1.248) | 0.42      |
|                                 | Esophageal cancer   | 7             | 0     | 0.994 | 1.213(1.051,1.401) | 1.213(1.051,1.401) | 0.932     |
|                                 | Gastric cancer      | 8             | 91.1  | 0  | 1.209(1.038,1.409) | 1.066(0.614,1.848) | 0.491     |
|                                 | Head and neck cancer| 6             | 27.4  | 0.229 | 1.114(0.977,1.271) | 1.121(0.950,1.323) | 0.334     |
|                                 | Lung Cancer         | 16            | 0     | 0.808 | 1.000(0.918,1.090) | 1.001(0.918,1.091) | 0.294     |
|                                 | Prostate cancer     | 7             | 78.4  | 0  | 1.281(1.140,1.440) | 1.297(0.965,1.743) | 0.879     |
|                                 | Skin Cancer         | 7             | 36.5  | 0.15 | 1.018(0.938,1.105) | 1.023(0.913,1.146) | 0.868     |
|                                 | Non- Hodgkin lymphoma| 6             | 27.7  | 0.227 | 1.038(0.907,1.187) | 1.047(0.881,1.244) | 0.938     |

(Continued)
| Model (Comparison) | Subgroup                  | No. of trials | I² (%) | P for bias | Fixed     | Random     | P for bias |
|-------------------|---------------------------|---------------|--------|------------|-----------|------------|------------|
|                   |                           |               |        |            |           |            |            |
|                   | Total                     | 95            | 69.3   | 0          | 1.110(1.078,1.143) | 1.143(1.078,1.1212) | 0.126      |
|                   | PB                        | 41            | 75.9   | 0          | 1.060(1.021,1.101)  | 1.067(0.981,1.160)  | 0.754      |
|                   | HB                        | 49            | 56.6   | 0          | 1.217(1.158,1.278)  | 1.237(1.139,1.343)  | 0.587      |
|                   | Asia                      | 30            | 73.4   | 0          | 1.416(1.321,1.518)  | 1.336(1.153,1.547)  | 0.13       |
|                   | Caucasian                 | 37            | 3.2    | 0.414      | 1.020(0.976,1.065)  | 1.021(0.976,1.068)  | 0.102      |
|                   | PCR                       | 29            | 47.4   | 0.003      | 1.053(0.996,1.113)  | 1.091(0.999,1.191)  | 0.137      |
|                   | PCR-RFLP                  | 38            | 74.5   | 0          | 1.191(1.133,1.251)  | 1.216(1.091,1.356)  | 0.647      |
|                   | Taqman                    | 18            | 11.5   | 0.317      | 1.026(0.972,1.082)  | 1.028(0.968,1.093)  | 0.908      |
|                   | Bladder cancer            | 12            | 50.2   | 0.024      | 1.266(1.162,1.379)  | 1.309(1.148,1.494)  | 0.242      |
|                   | Breast cancer             | 17            | 73.4   | 0          | 1.091(1.034,1.151)  | 1.083(0.958,1.223)  | 0.962      |
|                   | Esophageal cancer         | 7             | 0      | 0.989      | 1.214(1.057,1.394)  | 1.214(1.057,1.394)  | 0.236      |
|                   | Gastric cancer            | 8             | 90.7   | 0          | 1.277(1.106,1.474)  | 1.229(0.745,2.027)  | 0.88       |
|                   | Head and neck cancer      | 6             | 50.7   | 0.071      | 1.091(0.963,1.236)  | 1.104(0.908,1.343)  | 0.493      |
|                   | Lung Cancer               | 15            | 0      | 0.763      | 1.010(0.931,1.097)  | 1.010(0.931,1.097)  | 0.474      |
|                   | Prostate cancer           | 7             | 89.8   | 0          | 1.353(1.213,1.509)  | 1.407(0.951,2.081)  | 0.71       |
|                   | Skin Cancer               | 7             | 37.6   | 0.142      | 0.968(0.895,1.046)  | 0.978(0.877,1.090)  | 0.682      |
|                   | Non-Hodgkin lymphoma      | 6             | 9.4    | 0.356      | 1.033(0.909,1.173)  | 1.035(0.901,1.189)  | 0.932      |
|                   |                           |               |        |            |           |            |            |
| reccessive model  |                           |               |        |            |           |            |            |
|                   | Total                     | 95            | 62.7   | 0          | 1.059(1.013,1.108)  | 1.108(1.016,1.208)  | 0.098      |
|                   | PB                        | 41            | 76.4   | 0          | 1.010(0.954,1.069)  | 1.044(0.914,1.192)  | 0.501      |
|                   | HB                        | 49            | 30.6   | 0.025      | 1.157(1.070,1.252)  | 1.178(1.059,1.310)  | 0.481      |
|                   | Asia                      | 30            | 35.8   | 0.032      | 1.445(1.275,1.637)  | 1.515(1.240,1.852)  | 0.668      |
|                   | Caucasian                 | 37            | 52.2   | 0          | 0.954(0.894,1.019)  | 1.006(0.906,1.115)  | 0.555      |
|                   | PCR                       | 29            | 64.2   | 0          | 1.022(0.939,1.113)  | 1.131(0.959,1.335)  | 0.107      |
|                   | PCR-RFLP                  | 38            | 53     | 0          | 1.087(1.006,1.175)  | 1.147(1.002,1.314)  | 0.152      |
|                   | Taqman                    | 18            | 28.8   | 0.123      | 0.987(0.911,1.069)  | 0.958(0.859,1.069)  | 0.082      |
|                   | Bladder cancer            | 12            | 48.6   | 0.029      | 1.225(1.080,1.389)  | 1.271(1.052,1.536)  | 0.189      |
|                   | Breast cancer             | 17            | 60.1   | 0.001      | 1.062(0.981,1.149)  | 1.018(0.874,1.186)  | 0.421      |
|                   | Esophageal cancer         | 7             | 0      | 0.615      | 1.102(0.869,1.398)  | 1.130(0.888,1.437)  | 0.086      |
|                   | Gastric cancer            | 8             | 39     | 0.119      | 1.563(1.215,2.011)  | 1.739(1.190,2.541)  | 0.341      |
|                   | Head and neck cancer      | 6             | 35.4   | 0.171      | 0.951(0.790,1.144)  | 0.944(0.729,1.223)  | 0.815      |
|                   | Lung Cancer               | 15            | 0      | 0.806      | 1.046(0.910,1.203)  | 1.046(0.910,1.203)  | 0.495      |
|                   | Prostate cancer           | 7             | 92.4   | 0          | 1.406(1.186,1.667)  | 1.851(0.846,4.050)  | 0.357      |
|                   | Skin Cancer               | 7             | 63.4   | 0.012      | 0.781(0.691,0.883)  | 0.810(0.653,1.006)  | 0.557      |
|                   | Non-Hodgkin lymphoma      | 6             | 0      | 0.619      | 0.987(0.813,1.200)  | 0.989(0.814,1.203)  | 0.646      |

*a P for heterogeneity.
(homozygote comparison: $P$ for heterogeneity = 0.062, $I^2 = 52.4\%$), and skin cancer (homozygote comparison: $P$ for heterogeneity = 0.021, $I^2 = 59.9\%$).

**Publication bias and sensitivity analysis**

We used the Begg's funnel plot to estimate publication bias. There was no statistical evidence of publication bias in the overall analysis under each model (Figure 2). Table 2 shows the P details for bias. We also removed studies one by one to determine their effect on the test of heterogeneity, and evaluated the stability of the overall results; the results did not change in the overall analysis (Supplementary Table 1) neither in other analysis.

**Trial sequential analysis (TSA)**

In the overall analysis for homozygote comparison, the required information size was 72,622 patients to demonstrate the issue (Figure 3), and the result showed that the Z-curve had crossed the trial monitoring boundary before reaching the required information size, indicating that the cumulative evidence is adequate and further trials are unnecessary.

**DISCUSSION**

Nowadays, cancer is one of the most important global public health problems [106]. Personalized analysis and improved methods of cancer diagnoses can be provided, based on an understanding of the association between genetic polymorphisms and cancer risk [107]. In the relationship between gene polymorphisms and cancer risk, the $ERCC2$ Asp312Asn polymorphism is an important risk factor. Impaired DNA repair capacity is a risk factor for the development of cancer. The $ERCC2$ Asp312Asn polymorphism influences DNA repair through the NER pathway. To date, many publications have shown an association between the $ERCC2$ Asp312Asn polymorphism and risk of cancer. However, the results remain controversial. In order to resolve this conflict, we performed a meta-analysis that evaluates the relationship between the $ERCC2$ Asp312Asn polymorphism and risk of cancer.

In our meta-analysis, the association of the $ERCC2$ Asp312Asn polymorphism with the risk of cancer was evaluated in 38,848 cases and 48,928 controls. A significant association was observed between the $ERCC2$ Asp312Asn polymorphism and overall cancer risk in all genetic models. To the best of our knowledge, this is the most comprehensive meta-analysis on this topic until now. Moreover, the result of the TSA indicated that the cumulative evidence is adequate and further trials are unnecessary in the overall analysis for homozygote comparison.

In the subgroup analysis based on ethnicity, a significantly increased cancer risk was observed in Asian populations, but not in Caucasian populations. One possible reason for these discrepancies is that different ethnicities may have distinct genetic backgrounds, and

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**Figure 2:** (A) Begg’s funnel plot for the publication bias test in the overall analysis under homozygote comparison. (B) Begg’s funnel plot for the publication bias test in the overall analysis under heterozygote comparison. (C) Begg’s funnel plot for the publication bias test in the overall analysis under dominant model. (D) Begg’s funnel plot for the publication bias test in the overall analysis under recessive model.
therefore, tumor susceptibility can be influenced by ethnicity [108]. Moreover, this may indicate that these groups have distinct environmental or genetic cancer co-etiologies [109]. In subgroup analysis based on the control source, we found that a significantly increased cancer risk was observed in HB studies, but not in PB studies. The former may have certain biases for such controls and may only represent a sample of an ill-defined reference population. Furthermore, HB controls may not be representative of the general population or it may be that numerous subjects in the PB controls were individuals susceptible to cancer [110]. In the subgroup analysis based on the genotyping method, a significantly increased cancer risk was found in the PCR-RFLP studies, but not in the PCR or TaqMan studies. A possible reason for this may be that the different genotyping methods are specialized for different aspects, and the results would be more accurate and reliable if the same genotyping method was applied in different studies [111].

In the subgroup analysis according to the cancer site, a significant association with the ERCC2 Asp312Asn polymorphism was observed for bladder, esophageal, and gastric cancers; however, no significant association was observed for breast, head and neck, lung, prostate, and skin cancers, and non-Hodgkin lymphoma. Some previous meta-analyses assessed the effect of the ERCC2 Asp312Asn polymorphism on the risk of these cancers and reached conclusions consistent with those of our study. For example, Li et al. [19] and Wen et al. [14] suggested that the ERCC2 Asp312Asn polymorphism might be associated with an increased risk of bladder cancer and esophageal cancer, respectively. Yin et al. [48] showed that this polymorphism might be a potential biomarker of gastric cancer susceptibility in the overall population. In contrast, Yan et al. [21], Hu et al. [11], and Zhu et al. [112] suggested that the ERCC2 Asp312Asn polymorphism was not associated with breast cancer, head and neck cancer, and skin cancer, respectively. Moreover, Chen et al. [113], Feng et al. [12], and Ma et al. [114] suggested that the ERCC2 Asp312Asn polymorphism contributed to the risk of non-Hodgkin lymphoma, lung cancer, and prostate cancer, respectively. Because we only included studies published from 2005 to 2016, we drew different conclusions in lung cancer and prostate cancer studies. Therefore, more research should be undertaken in the future. Moreover, the exact mechanism for the associations between different cancer sites and the ERCC2 Asp312Asn polymorphism is not clear; the mechanism of carcinogenesis may differ between different cancer sites and the ERCC2 genetic variants may exert varying effects in different cancers [115].

Notably, HCC, osteosarcoma, oral cancer, and colorectal cancer were not included for further analysis as there were fewer than 6 studies available for analysis for such cancers. Wu et al. indicated that the ERCC2 Asp312Asn polymorphism was not associated with the development of HCC [24]. Gomez-Diaz et al. demonstrated no relationship between ERCC2 Asp312Asn polymorphism and osteosarcoma [23]. Interestingly, based on a study by Mahimkar et al. this polymorphism was associated with an overall increase in chromosomal damage in oral cancer [25]. Wang et al. [35] observed a slightly lower statistical significance between the ERCC2 Asp312Asn polymorphism and colorectal cancer. In fact,
this polymorphism has also been shown to be related to other diseases; previous studies have indicated that it may have a role in the development of ultraviolet-related diseases, such as maturity onset cataract [116]. However, no significant association of this polymorphism was found with either idiopathic azoospermia [117] or arsenic-related skin lesions [118]. Therefore, the equivocal association between the ERCC2 Asp312Asn polymorphism and some diseases remains to be confirmed.

Heterogeneity is a major concern for meta-analysis [119]. In our overall analysis, high heterogeneity was observed for all genetic models. However, when data were pooled in to subgroups according the control source, ethnicity, genotyping method, and cancer type, the heterogeneity decreased. Sensitivity analysis showed that the results have sufficient statistical power. There are some limitations of our meta-analysis that should be addressed. First, subgroup analysis cannot be conducted based on sex, age, lifestyle, and other factors owing to insufficient data. Second, some cancers, such as oral cancer and colorectal cancer, were not suitable for further analysis because of the small sample sizes. Thus, more studies on these cancers should be conducted in the future. Third, a single gene has only a moderate effect on cancer development; hence, the ERCC2 gene may influence susceptibility of cancer along with other genes. However, enough data for further analysis is not available. Finally, only published articles were included in the analysis; therefore, unpublished data may modify our conclusions.

In summary, our meta-analysis suggested that the ERCC2 Asp312Asn polymorphism is associated with increased cancer risk. A significantly increased cancer risk was observed in Asian populations, but not in Caucasian populations. Moreover, our results indicated that this polymorphism is associated with bladder, esophageal, and gastric cancers, but not with breast, head and neck, lung, prostate, and skin cancers, and non-Hodgkin lymphoma. In addition, stratification analyses based on the control source also indicated that this polymorphism was associated with cancer risk in the HB populations, but not in the PB populations. In subgroup analysis according to the genotyping method, a significantly increased cancer risk was found in the PCR-RFLP studies, but not in the PCR and TaqMan studies. Considering the limitations of this study, further multi-center, well-designed research should be undertaken in the future.

MATERIALS AND METHODS

Literature search

A systematic search of articles relating to the ERCC2 Asp312Asn polymorphism and cancer was conducted by 2 researchers, using the PubMed, EMBASE, Science Direct, Web of Science and the China National Knowledge Infrastructure (CNKI) databases. The search included studies published between January 1, 2005 and January 1, 2016. The search strategy was based on various combinations of the following terms: “xeroderma pigmentosum group d protein” [MeSH Terms] OR “xeroderma pigmentosum group d protein” [All Fields] OR “ercc2” [All Fields] AND Asp312Asn [All Fields] AND (“neoplasms” [MeSH Terms] OR “neoplasms” [All Fields] OR “cancer” [All Fields]). In addition, the reference lists of the publications identified were searched for further relevant studies. The PRISMA Checklist was used for this meta-analysis (Supplementary Table 2).

Selection criteria

The following inclusion criteria were set and reviewed by two independent investigators: (I) case-control study; (II) evaluation of the ERCC2 Asp312Asn polymorphism and cancer; and (III) detailed data available for calculating ORs and the corresponding 95% CIs. Studies were excluded if they: (I) had no control population; (II) were review articles or previous meta-analyses; (III) contained insufficient or duplicate data; or (IV) had no full text available.

Data extraction

Two authors performed data extraction independently. For all publications, the following data were extracted: first author, year of publication, ethnicity of the population, country, source of cases and controls, cancer site, genotyping method, and number of cases and controls.

Trial sequential analysis

To evaluate whether our meta-analysis had sufficient sample size to reach firm conclusions about the effect of interventions [120], TSA was used in this meta-analysis. If the cumulative Z curve in results exceeds the TSA boundary, a sufficient level of evidence for the anticipated intervention effect may have been reached and no further trials are needed. However, when the Z curve does not exceed the TSA boundaries and the required information size has not been reached, evidence to draw a conclusion is insufficient [121]. We used two-sided tests, type I error set at 5%, and power set at 80%. The required information size was calculated based on a relative risk reduction of 10%. Trials ignored in interim appear to be due to too low use of information (<1.0%) by the software. TSA was performed using the TSA software (version 0.9.5.5).

Statistical analysis

The primary objective of our meta-analysis was to calculate ORs and their 95% CIs to evaluate the
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**CONFLICTS OF INTEREST**

The authors declare no conflicts of interest.

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