Association between the XPG Asp1104His and XPF Arg415Gln Polymorphisms and Risk of Cancer: A Meta-Analysis

Xiao-Feng He1,*, Li-Rong Liu1,*, Wu Wei3,*, Yi Liu4, Jiao Su5, Su-Lan Wang3, Xu-Liang Shen3, Xian-Bin Yang1

1 Department of Research, Peace Hospital of Changzhi Medical College, Changzhi, China, 2 Department of Clinical Biochemistry, Affiliated Hospital of Guiyang Medical University, Guiyang, China, 3 Department of Hematology, Peace Hospital of Changzhi Medical College, Changzhi, China, 4 Department of Neurosurgery, Nanfang Hospital, Southern Medical University, Guangzhou, China, 5 Department of Biological Chemistry, Changzhi Medical College, Changzhi, China

Abstract

Background: The XPG (xeroderma pigmentosum type G) Asp1104His and XPF (xeroderma pigmentosum type F) Arg415Gln polymorphisms had been implicated in cancer susceptibility. The previous published data on the association between XPG Asp1104His and XPF Arg415Gln polymorphisms and cancer risk remained controversial.

Methodology/Principal Findings: To derive a more precise estimation of the association between the XPG Asp1104His and XPF Arg415Gln polymorphisms and overall cancer risk, we performed a meta-analysis to investigate the association between cancer susceptibility and XPG Asp1104His (32,162 cases and 39,858 controls from 66 studies) and XPF Arg415Gln polymorphisms (17,864 cases and 20,578 controls from 32 studies) in different inheritance models. We used odds ratios with 95% confidence intervals to assess the strength of the association. Overall, significantly elevated cancer risk was found when all studies were pooled into the meta-analysis of XPG Asp1104His (dominant model: OR = 1.05, 95% CI = 1.00–1.10; Asp/His vs. Asp/Asp: OR = 1.06, 95% CI = 1.01–1.11). In the further stratified and sensitivity analyses, significantly decreased lung cancer risk was found for XPF Arg415Gln (dominant model: OR = 0.82, 95% CI = 0.71–0.96; Arg/Gln versus Arg/Arg: OR = 0.83, 95% CI = 0.71–0.97; additive model: OR = 0.83, 95% CI = 0.72–0.95) and significantly increased other cancer risk was found among hospital-based studies for XPG Asp1104His (dominant model: OR = 1.23, 95% CI = 1.02–1.49).

Conclusions/Significance: In summary, this meta-analysis suggests that XPF Arg415Gln polymorphism may be associated with decreased lung cancer risk and XPG Asp1104His may be a low-penetrant risk factor in some cancers development. And larger scale primary studies are required to further evaluate the interaction of XPG Asp1104His and XPF Arg415Gln polymorphisms and cancer risk in specific populations.

Introduction

DNA repair systems play critical roles in protecting cells against mutations and are essential for maintaining the genome integrity. Certain common genetic polymorphisms within the genes involved in DNA damage responses may contribute to the development of cancer and be associated with an increased risk of the disease. Because reduced DNA repair capacity may cause genetic instability and carcinogenesis, genes involved in DNA repair have been proposed as candidate cancer susceptibility genes [1]. Nucleotide excision repair (NER) is a crucial DNA repair mechanism, which counteracts the consequences of mutagenic exposure of cells [2].

The NER pathway consists of >30 proteins involved in DNA damage recognition, incision, DNA ligation and resynthesis. Seven XP (xeroderma pigmentosum) complementation groups have been identified, from XPA to XPG, representing the malfunctioning proteins in the NER mechanism [3]. The XPG (xeroderma pigmentosum type G), one important component of the NER pathway, encodes a structure-specific endonuclease catalyzing 3’ incision and involves the subsequent 5’ incision by ERCC1-XPF heterodimer [4, 5]. It has been observed that there is a relationship between the SNP in exon 15 (G3507C, Asp1104His) and cancer susceptibility. ERCC4/XPF (Arg-to-Gln substitution in codon 415 of exon 8, rs1800067) forms a tight complex with ERCC1 and XPF to incise 5’ to the damage site recognized and repaired by NER [6]. The XPF gene encodes a protein which, together with ERCC1, creates the 5’ endonuclease [7].

To date, a number of molecular epidemiological studies have been done to evaluate the association between XPG Asp1104His and XPF Arg415Gln polymorphisms and different types of cancer risk in diverse populations [8–83]. However, the results were
inconsistent or even contradictory, partially because of the possible small effect of the polymorphism on cancer risk and the relatively small sample size in each of published study. In addition, two recent meta-analyses have studied the association between XPG Asp1104His and XPF Arg415Gln and risk of cancer. However, many published studies were not included in the two recent meta-analyses [84,85]. Therefore, we performed a comprehensive meta-analysis by including the most recent and relevant articles to identify statistical evidence of the association between XPG Asp1104His and XPF Arg415Gln polymorphisms and risk of all cancers that have been investigated. Meta-analysis is an outstanding tool for summarizing the different studies. It can not only overcome the problem of small size and inadequate statistical power of genetic studies of complex traits, but also can provide more reliable results than a single case–control study.

Materials and Methods

Identification and eligibility of relevant studies

A comprehensive literature search was performed using the PubMed and Medline database for relevant articles published (the last search update was Sep 5, 2013) with the following key words “XPG”, “ERCC5”, “XPF”, “ERCC4”, “polymorphism”, “Variant” or “Mutation”, and “Cancer” or “Carcinoma.” In addition, studies were identified by a manual search of the reference lists of reviews and retrieved studies. We included all the case–control studies and cohort studies that investigated the association between XPG Asp1104His and XPF Arg415Gln polymorphisms and cancer risk with genotype data. All eligible studies were retrieved, and their bibliographies were checked for other relevant publications. When the same sample was used in several publications, only the most complete study was considered for further analysis.

Inclusion criteria

The included studies needed to have met the following criteria: (1) only the case–control studies or cohort studies were considered, (2) evaluated the XPG Asp1104His and XPF Arg415Gln polymorphisms and the risk of cancer, and (3) the genotype distribution of the polymorphisms in cases and controls were described in details and the results were expressed as odds ratio (OR) and corresponding 95% confidence interval (95% CI). Major reasons for exclusion of studies were as follows: (1) not for cancer research, (2) only case population, and (3) duplicate of previous publication.

Data extraction

Information was carefully extracted from all eligible studies independently by two investigators according to the inclusion criteria listed above. The following data were collected from each study: first author’s name, year of publication, country of origin, ethnicity, source of controls, sample size, and numbers of cases and controls in the XPG Asp1104His and XPF Arg415Gln genotypes whenever possible. Ethnicity was categorized as “Caucasian,” “African,” (including African Americans) and “Asian.” Two studies were carried out with Hispanic ethnic groups. When one study did not state which ethnic groups was included or if it was impossible to separate participants according to phenotype, the sample was termed as “mixed population.” Meanwhile, studies investigating more than one kind of cancer were counted as individual data set only in subgroup analyses by cancer type. We did not define any minimum number of patients to include in this meta-analysis. In case of articles reported different ethnic groups and different countries or locations, we considered them different study samples for each category cited above.

Statistical analysis

Crude odds ratios (ORs) together with their corresponding 95% CIs were used to assess the strength of association between the XPG Asp1104His and XPF Arg415Gln polymorphisms and the risk of cancer. The pooled ORs were performed for co-dominant model (XPG Asp1104His: His/His versus Asp/Asp and Asp/His versus Asp/Asp, XPF Arg415Gln: Gln/Gln versus Arg/Arg and Arg/Gln versus Arg/Arg); dominant model (XPG Asp1104His: Asp/His + His/His versus Asp/Asp, XPF Arg415Gln: Arg/Gln + Gln/Gln versus Arg/Arg); recessive model (XPG Asp1104His:...
His/His versus Asp/Asp, XPF Arg415Gln: Gln/Gln versus Arg/Arg; and additive model (XPG Asp1104His: His versus Asp, XPF Arg415Gln: Gln versus Arg), respectively. Between-study heterogeneity was assessed by calculating Q-statistic (Heterogeneity was considered statistically significant if \( P < 0.10 \)) [66] and quantified using the I² value, a value that describes the percentage of variation across studies that are due to heterogeneity rather than chance, where I² = 0% indicates no observed heterogeneity, with 25% regarded as low, 50% as moderate, and 75% as high [87]. If results were not heterogeneous, the pooled ORs were calculated by the fixed-effect model (we used the Q-statistic, which represents the magnitude of heterogeneity between-studies) [88]. Otherwise, a random-effect model was used (when the heterogeneity between-studies were significant) [89]. In addition to the comparison among all subjects, we also performed stratification analyses by cancer type (if one cancer type contained less than three individual studies, it was combined into the “other cancers” group). Moreover, the extent to which the combined risk estimate might be affected by individual studies was assessed by consecutively omitting every study from the meta-analysis (leave-one-out sensitivity analysis). This approach would also capture the effect of the oldest or first positive study (first study effect). In addition, we also ranked studies according to sample size, and then repeated this meta-analysis. Sample size was classified according to a minimum of 200 participants and those with fewer than 200 participants. The cite criteria were previously described [90]. Last, sensitivity analysis was also performed, excluding studies whose allele frequencies in controls exhibited significant deviation from the Hardy–Weinberg equilibrium (HWE), given that the deviation may denote bias. HWE was calculated by using the goodness-of-fit test, and deviation was considered when \( P < 0.05 \). Begg’s funnel plots [91] and Egger’s linear regression test [92] were used to assess publication bias. If publication bias existed, the Duval and Tweedie nonparametric “trim and fill” method was used to adjust for it [93]. A meta-regression analysis was carried out to identify the major sources of between-studies variation in the results, using the log of the ORs from each study as dependent variables, and cancer type, ethnicity, sample size, HWE, and source of controls as the possible sources of heterogeneity. All of the calculations were performed using STATA version 10.0 (STATA Corporation, College Station, TX).

Results

Eligible studies and meta-analysis databases

Fig. 1 graphically illustrates the trial flow chart. A total of 236 articles regarding XPG Asp1104His and XPF Arg415Gln...
| First author/year | Country | Ethnicity | Cancer type | SC | XPG Asp1104His (Case/control) | XPF Arg415Gln (Case/control) | HWE |
|-------------------|---------|-----------|-------------|----|------------------------------|-------------------------------|-----|
| Smith [8] 2003    | USA     | Caucasian | Breast      | HB | NA                           | NA                           | Yes |
| Kumar [9] 2003    | Finland | Caucasian | Breast      | HB | 108/182                      | 96/107                       | NA  |
| Jeon [10] 2003    | Korea   | Asian     | Lung        | HB | 58/90                        | 164/132                      | 88/89| No  |
| Sanyal [11] 2004 | Sweden  | Caucasian | Bladder     | NA | 182/173                      | 109/91                       | 8/20| Yes |
| Blankenburg [12] 2005 | Germany | Caucasian | Melanoma | HB | 184/232                      | 100/124                      | 9/18| Yes |
| Weiss [13] 2005   | USA     | Mixed     | Endometrial | PB | 215/250                      | 134/148                      | 22/22| Yes |
| Shen [14] 2005    | China   | Asian     | Lung        | PB | 26/25                        | 52/46                        | NA  | No  |
| Bigler [15] 2005  | USA     | Mixed     | Colorectal  | PB | 440/353                      | 243/226                      | 36/37| Yes |
| Sakiyama [16] 2005 | Japan  | Asian     | Lung        | HB | 300/228                      | 500/333                      | 202/124| Yes |
| Cui [17] 2006     | USA     | Mixed     | Lung        | PB | 244/468                      | 212/356                      | 41/78| Yes |
| Cui [17] 2006     | USA     | Mixed     | Multiple    | PB | 214/474                      | 194/357                      | 35/80| Yes |
| Zienoldidiny [18] 2006 | Norway | Caucasian | Lung        | HB | NA                           | NA                           | 195/178| Yes |
| Millikan [19] 2006 | USA    | Caucasian | Melanoma    | PB | 731/1513                     | 389/780                      | 73/115| Yes |
| Mechanic [20] 2006 | USA    | Caucasian | Breast      | PB | 771/661                      | 409/412                      | 69/60| Yes |
| Mechanic [20] 2006 | USA    | African   | Breast      | PB | 231/231                      | 387/320                      | 139/123| Yes |
| Huang [21] 2006   | USA     | Mixed     | Colorectal  | PB | 407/403                      | 243/265                      | 29/29| Yes |
| Garcia-Closas [22] 2006 | Spain | Caucasian | Bladder     | HB | 629/607                      | 434/445                      | 78/84| Yes |
| Moreno [23] 2006  | Spain   | Caucasian | Colorectal  | HB | NA                           | NA                           | 282/257| Yes |
| Shen [24] 2006    | USA     | Mixed     | NHL         | PB | 260/352                      | 170/169                      | 34/29| Yes |
| Shen [25] 2006    | USA     | Mixed     | Breast      | FB | 83/82                        | 63/62                        | 8/7  | Yes |
| Wen [26] 2006     | China   | Asian     | HNC         | PB | 55/129                       | 81/296                       | 39/100| No  |
| Li [27] 2006      | USA     | Caucasian | Melanoma    | HB | 373/370                      | 206/206                      | 23/27| Yes |
| Wu [28] 2006      | USA     | Caucasian | Bladder     | HB | 364/371                      | 225/211                      | 26/18| Yes |
| Sugimura [29] 2006 | Japan  | Asian     | HNC         | HB | 20/52                        | 59/112                       | 43/77| Yes |
| Thirumaran [30] 2006 | Multiple| Caucasian | Skin        | HB | 325/330                      | 172/173                      | 32/30| Yes |
| Hill [31] 2006    | Multiple | Mixed     | NHL         | PB | 599/521                      | 425/331                      | 77/71| Yes |
| Crew [32] 2007    | USA     | Mixed     | Breast      | PB | 562/571                      | 371/409                      | 66/71| Yes |
| Jorgensen [33] 2007 | USA    | Caucasian | Breast      | PB | 159/165                      | 93/95                        | 12/15| Yes |
| Romanowicz [34] 2007 | Poland | Caucasian | Breast      | NA | NA                           | NA                           | 31/21| Yes |
| Povey [35] 2007   | UK      | Caucasian | Melanoma    | PB | 314/252                      | 169/162                      | 24/27| Yes |
| Wang [36] 2007    | USA     | Mixed     | Skin        | HB | 146/200                      | 89/119                       | 11/10| Yes |
| Shen [37] 2007    | Australia| Caucasian | NHL         | PB | 340/294                      | 170/163                      | 30/27| Yes |
| McWilliams [38] 2008 | USA    | Mixed     | Pancreatic  | HB | NA                           | NA                           | 411/481| Yes |
| Hooker [39] 2008  | USA     | African   | Prostate    | HB | 74/100                       | 119/141                      | 61/60| Yes |
| Smith [40] 2008   | USA     | Caucasian | Breast      | HB | 195/256                      | 113/124                      | 12/28| Yes |
Table 1. Cont.

| First author/year | Country   | Ethnicity | Cancer type | SC  | XPG Asp1104His (Case/control) | XPF Arg415Gln (Case/control) | HWE |
|-------------------|-----------|-----------|-------------|-----|-------------------------------|-------------------------------|-----|
| Smith [40] 2008   | USA       | African   | Breast      | HB  | 13/18                         | 32/37                        | 7/20| 51/73                          | 2/2  | 0/0                           | Yes  |
| Chang [41] 2008   | USA       | Hispanic  | Lung        | HB  | 60/138                        | 44/127                       | 9/34| 97/267                        | 16/31| 0/1                           | Yes  |
| Chang [41] 2008   | USA       | African   | Lung        | HB  | 68/93                         | 119/138                      | 68/49| NA                           | NA   | NA                           | Yes  |
| Rajaraman [42] 2008 | USA     | Caucasian | Breast      | PB  | 482/674                      | 288/352                      | 49/53| 714/922                      | 124/147| No for Asp1104His  |
| Freidlin [43] 2008 | Russia   | Caucasian | Multiple    | HB  | 38/92                         | 12/36                        | 2/12| NA                           | NA   | NA                           | Yes  |
| Hung [44] 2008    | Multiple  | Mixed     | Lung        | NA  | 1852/2485                    | 1155/1510                    | 209/286| 220/21208                    | 306/390 | 13/21                      |
| He [45] 2008      | China     | Asian     | Cervical    | HB  | 35/53                        | 94/80                        | 71/67| NA                           | NA   | NA                           | No   |
| Padhani [46] 2008 | Czech     | Caucasian | Colorectal  | HB  | 334/356                      | 177/153                      | 21/23| NA                           | NA   | NA                           | Yes  |
| Joshi [47] 2009   | USA       | Caucasian | Colorectal  | FB  | 183/213                      | 125/148                      | 265/313| 40/47                        | NA   | No                           | Yes  |
| El-Zein [48] 2009 | USA       | Mixed     | NHL         | HB  | 104/127                      | 78/80                        | 16/12| NA                           | NA   | NA                           | Yes  |
| Wen [49] 2009     | China     | Asian     | Bladder     | HB  | 15/45                        | 57/233                       | 3/3 | NA                           | NA   | NA                           | Yes  |
| Narter [50] 2009  | Turkey    | Caucasian | Bladder     | NA  | 25/18                        | 28/19                        | 3/3 | NA                           | NA   | NA                           | Yes  |
| Abbas [51] 2009   | Germany   | Caucasian | HNC         | PB  | 137/380                      | 103/230                      | 8/37| 203/554                      | 44/90 | 1/3                        |
| Hussain [52] 2009 | China     | Asian     | Gastric     | PB  | 38/90                        | 104/180                      | 39/91| NA                           | NA   | NA                           | Yes  |
| McKeen-Cowdin [53] 2009 USA | Caucasian | Glioma     | PB  | 499/989                     | 348/657                      | 157/311| NA                          | NA   | NA                           | No   |
| Pan [54] 2009     | USA       | Caucasian | esophageal  | HB  | 222/287                      | 145/155                      | 15/15| NA                           | NA   | NA                           | Yes  |
| Han [55] 2009     | USA       | Caucasian | Breast      | PB  | 142/285                      | 80/167                       | 17/20| 200/401                      | 38/69 | 0/2                        |
| Liu [56] 2009     | USA       | Caucasian | Glioma      | PB  | 353/351                      | 20/13                        | NA | NA                           | NA   | NA                           | Yes  |
| Abbagnesi [57] 2010 | USA     | Caucasian | Prostate    | PB  | NA                           | NA                          | NA | 1023/1012                    | 183/202 | 13/5                      |
| Abbagnesi [57] 2010 | USA     | African   | Prostate    | PB  | NA                           | NA                          | NA | 136/78                       | 8/3   | 0/0                        |
| Rajaraman [58] 2010 | USA     | Caucasian | Glioma      | HB  | 206/286                      | 123/156                      | 13/26| 280/405                      | 56/62 | 1/4                        |
| Ming-Shiean [59] 2010 | China    | Asian     | Breast      | HB  | 134/159                      | 191/243                      | 76/129| NA                           | NA   | NA                           | Yes  |
| Liu [60] 2010     | China     | Asian     | Liver       | HB  | 174/151                      | 233/265                      | 93/91| NA                           | NA   | NA                           | Yes  |
| Canbay [61] 2010  | Turkey    | Caucasian | Gastric     | NA  | 25/148                       | 12/83                        | 3/16| NA                           | NA   | NA                           | Yes  |
| Figl [62] 2010    | Multiple  | Caucasian | Melanoma    | HB  | 703/725                      | 409/465                      | 74/84| NA                           | NA   | NA                           | Yes  |
| Rouissi [63] 2010 | Tunisia   | African   | Bladder     | HB  | 95/87                        | 70/86                        | 28/20| NA                           | NA   | NA                           | Yes  |
| Liu [64] 2011     | China     | Asian     | Colorectal  | HB  | 233/329                      | 603/537                      | 192/219| NA                          | NA   | NA                           | Yes  |
| Canbay [65] 2011  | Turkey    | Caucasian | Colorectal  | NA  | 43/148                       | 34/83                        | 2/16| NA                           | NA   | NA                           | Yes  |
| Goncalves [66] 2011 | Brazil    | Caucasian | Melanoma    | HB  | 105/109                      | 77/74                        | 10/25| NA                           | NA   | NA                           | Yes  |
| Ibarrola-Villavea [67] 2011 Spain | Caucasian | Melanoma    | HB  | 412/242                      | 222/140                      | 50/24| 560/316                      | 117/87 | 7/3                        |
| Doherty [68] 2011 | USA       | Mixed     | Endometrial | PB  | 418/408                      | 254/248                      | 42/47| 593/620                      | 107/89 | 3/5                        |
| Blason [69] 2011  | Italy     | Caucasian | Osteosarcoma| HB  | 75/141                       | 39/94                        | 16/15| NA                           | NA   | NA                           | Yes  |
| Krupa [70] 2011   | Poland    | Caucasian | HNC         | HB  | NA                           | NA                          | NA | 221/224                      | 26/29 | 6/0                        |
| Yu [71] 2011      | USA       | Caucasian | HNC         | HB  | NA                           | NA                          | NA | 837/829                      | 195/209 | 8/8                        |
| Ma [72] 2012      | USA       | Caucasian | HNC         | HB  | 648/654                      | 359/350                      | 52/62| NA                           | NA   | NA                           | Yes  |
polymorphisms with respect to cancer were identified. After screening the titles and abstracts, 160 articles were excluded because they were review articles, case reports, other polymorphisms of CYP1A1, or irrelevant to the current study. In addition, of these published articles, 4 publications [76–79] were excluded because of their populations overlapped with another 3 included studies [40,44,68]. Five publications [17,20,40,41,57] including different case–control groups should be considered as two separate studies each. As summarized in Table 1, 72 publications with 98 case–control studies were selected among the meta-analysis, including 32,162 cases and 39,858 controls for XPG Asp1104His (66 studies from 62 publications) and 17,864 cases and 20,578 controls for XPF Arg415Gln (32 studies from 29 publications). Among these studies, for XPG Asp1104His, there were 7 bladder cancer studies, 11 breast cancer studies, 7 colorectal cancer studies, 5 head and neck cancer studies, 7 lung cancer studies, 4 non-Hodgkin lymphoma studies, 3 glioma studies, 8 melanoma studies, and 14 studies with the “other cancers”. There were 10 breast cancer studies, 3 lung cancer studies, 4 head and neck cancer studies, 4 colorectal cancer, 3 glioma studies, and 8 studies with the “other cancers” for XPF Arg415Gln. All of the cases were pathologically confirmed.

XPG Asp1104His

The evaluations of the association of XPG Asp1104His polymorphism with cancer risk are shown in Table 2. Overall, significantly increased risk of cancer was observed in dominant model (OR = 1.05, 95% CI = 1.00–1.10), P value of heterogeneity test (P heterogeneous = 0.001, h = 40.4) and in Asp/His versus Asp/Asp (OR = 1.06, 95% CI = 1.01–1.11, P heterogeneous ≤ 0.001, h = 43.3) when all the eligible studies were pooled into the meta-analysis. Then we performed subgroup analysis by cancer type. No significant association was found in any cancer type, such as breast cancer (dominant model: OR = 1.01, 95% CI = 0.94–1.09, P heterogeneous = 0.128, h = 33.8, recessive model: OR = 0.95, 95% CI = 0.83–1.09, P heterogeneous = 0.173, h = 28.6; additive model: OR = 1.00, 95% CI = 0.93–1.09, P heterogeneous = 0.098, h = 28.6; His/His versus Asp/Asp: OR = 0.99, 95% CI = 0.86–1.14, P heterogeneous = 0.183, h = 27.2; Asp/His versus Asp/Asp: OR = 1.02, 95% CI = 0.94–1.10, P heterogeneous = 0.136, h = 32.8), lung cancer (dominant model: OR = 1.13, 95% CI = 0.98–1.31, P heterogeneous = 0.045, h = 53.4, recessive model: OR = 1.04, 95% CI = 0.93–1.17, P heterogeneous = 0.212, h = 28.4; additive model: OR = 1.08, 95% CI = 0.98–1.19, P heterogeneous = 0.073, h = 48.0; His/His versus Asp/Asp: OR = 1.15, 95% CI = 0.94–1.42, P heterogeneous = 0.071, h = 48.3; Asp/His versus Asp/Asp: OR = 1.13, 95% CI = 0.98–1.31, P heterogeneous = 0.077, h = 47.3), and so on.

We further examined the association of the XPG Asp1104His polymorphism and cancer risk according to cancer type and ethnicity (Table 3). For samples of Caucasians, significant association was only found in head and neck cancer (His/His vs. Asp/His+Asp/Asp: OR = 0.71, 95% CI = 0.51–0.97, P heterogeneous = 0.271, h = 23.5%) but not bladder cancer (dominant model: OR = 0.99, 95% CI = 0.88–1.12, P heterogeneous = 0.673, h = 0.0, recessive model: OR = 0.84, 95% CI = 0.50–1.41, P heterogeneous = 0.078, h = 56.0; additive model: OR = 0.96, 95% CI = 0.89–1.08, P heterogeneous = 0.433, h = 0.0; His/His versus Asp/Asp: OR = 0.85, 95% CI = 0.51–1.42, P heterogeneous = 0.090, h = 53.8; Asp/His versus Asp/Asp: OR = 1.01, 95% CI = 0.89–1.15, P heterogeneous = 0.688, h = 0.0), breast cancer (dominant model: OR = 1.07, 95% CI = 0.92–1.24, P heterogeneous = 0.065, h = 51.8, recessive model: OR = 1.07, 95% CI = 0.86–1.32, P heterogeneous = 0.221, h = 28.6; additive model: OR = 1.03, 95% CI = 0.95–1.12, P heterogeneous = 0.113, h = 43.8; His/His versus Asp/Asp: OR = 1.08, 95% CI = 0.87–1.34, P heterogeneous = 0.215, h = 29.3; Asp/His versus Asp/Asp: OR = 1.07, 95% CI = 0.91–1.26, P heterogeneous = 0.048,
### Table 2. Stratified analysis of XPG Asp1104His and XPF Arg415Gln polymorphisms on cancer risk. 1

| Genetic model | N | Recessive model | Dominant model | Homozygote | Heterozygote | Additive model |
|---------------|---|-----------------|----------------|------------|--------------|---------------|
|               | OR (95%CI) | P* (%) | OR (95%CI) | P* (%) | OR (95%CI) | OR (95%CI) | P* (%) |
| XPG Asp1104His | Overall | 66 (32162/39858) | 1.00 (0.94–1.07)* | 0.073/21.2 | 1.05 (1.00–1.10)* | 0.012/30.9 | 1.06 (1.01–1.11)* | <0.001/43.3 | 1.03 (0.99–1.06)* | 0.008/32.8 |
| Cancer type | | | | | | | | | | |
| Bladder cancer | 7 | 2488/2809 | 1.06 (0.72–1.56)* | 0.041/56.8 | 1.10 (0.85–1.44)* | 0.001/74.9 | 1.11 (0.69–1.80)* | 0.066/60.7 | 1.02 (0.94–1.10) | <0.001/77.5 |
| Breast cancer | 11 | 5474/6157 | 0.95 (0.83–1.09) | 0.173/28.6 | 1.01 (0.94–1.09) | 0.128/33.8 | 0.99 (0.86–1.14) | 0.185/27.2 | 1.02 (0.94–1.10) | <0.001/77.5 |
| Colorectal cancer | 7 | 3471/3638 | 0.91 (0.77–1.08) | 0.696/0.0 | 1.07 (0.88–1.29)* | 0.004/69.1 | 1.08 (0.89–1.30) | 0.411/0.7 | 1.11 (0.86–1.42)* | <0.001/78.0 |
| Glioma | 3 | 1719/2789 | 0.98 (0.81–1.13) | 0.262/25.3 | 1.03 (0.90–1.18) | 0.984/0.0 | 0.97 (0.78–1.19) | 0.322/0.0 | 1.06 (0.92–1.23) | 0.810/0.0 |
| HNC | 5 | 1709/2691 | 0.92 (0.74–1.15) | 0.114/46.4 | 1.01 (0.89–1.16) | 0.244/26.6 | 0.86 (0.67–1.10) | 0.257/24.6 | 1.05 (0.83–1.31)* | 0.087/50.8 |
| NHL | 4 | 2303/2176 | 1.06 (0.84–1.35) | 0.389/0.6 | 1.12 (0.99–1.26) | 0.117/49.2 | 1.11 (0.88–1.42) | 0.279/22.0 | 1.12 (0.99–1.27) | 0.194/36.3 |
| Lung cancer | 7 | 5509/6867 | 1.04 (0.93–1.17) | 0.212/28.4 | 1.13 (0.98–1.31)* | 0.045/53.4 | 1.15 (0.94–1.42)* | 0.071/48.3 | 1.13 (0.98–1.31)* | 0.077/47.3 |
| Melanoma | 8 | 5297/7072 | 0.87 (0.69–1.12) | 0.050/30.3 | 0.97 (0.90–1.04) | 0.762/0.0 | 0.87 (0.68–1.11) | 0.098/48.4 | 0.98 (0.90–1.06) | 0.854/0.0 |
| Other cancer | 14 | 4192/5659 | 1.07 (0.93–1.22) | 0.578/0.0 | 1.06 (0.97–1.15) | 0.406/41 | 1.12 (0.96–1.30) | 0.330/0.7 | 1.05 (0.96–1.15) | 0.290/14.9 |

| XPF Arg415Gln | Overall | 32 (17864/20578) | 1.11 (0.81–1.52)* | 0.068/30.5 | 1.04 (0.93–1.15)* | <0.001/62.6 | 1.10 (0.79–1.54)* | 0.035/53.7 | 1.02 (0.91–1.14)* | <0.001/62.5 |

| Cancer type | | | | | | | | | | |
| Breast cancer | 10 | 5096/5542 | 1.22 (0.82–1.83)* | 0.017/58.9 | 1.03 (0.92–1.15) | 0.167/30.2 | 1.18 (0.76–1.83)* | 0.007/63.8 | 0.99 (0.87–1.12) | 0.277/18.6 |
| Lung cancer | 3 | 2857/3118 | 0.75 (0.40–1.41) | 0.491/0.0 | 0.82 (0.71–0.96) | 0.104/55.7 | 0.73 (0.39–1.37) | 0.466/0.0 | 0.83 (0.71–0.97) | 0.132/50.7 |
| HNC | 4 | 1643/2156 | 1.47 (0.72–2.98) | 0.364/5.8 | 1.04 (0.88–1.23) | 0.359/6.9 | 1.48 (0.73–3.00) | 0.370/4.5 | 1.02 (0.86–1.21) | 0.323/13.9 |
| Colorectal cancer | 4 | 1501/1497 | 0.51 (0.06–4.45)* | 0.069/67.9 | 0.93 (0.76–1.14) | 0.605/0.0 | 0.51 (0.06–4.45)* | 0.067/70.3 | 0.93 (0.74–1.18) | 0.526/0.0 |
| Glioma | 3 | 874/1359 | 1.51 (0.83–2.74) | 0.368/0.0 | 2 | <0.001/87.0 | 1.61 (0.88–2.93) | 0.357/3.0 | 2 | <0.001/88.0 |
| Other cancer | 8 | 5903/6906 | 1.03 (0.69–1.53) | 0.239/24.9 | 0.95 (0.82–1.10)* | 0.048/50.6 | 1.02 (0.68–1.52) | 0.254/23.0 | 0.95 (0.82–1.11)* | 0.040/52.3 |

1All summary ORs were calculated using fixed-effects models. In the case of significant heterogeneity (indicated by *), ORs were calculated using random-effects models.
2The results were excluded due to high heterogeneity. The bold values indicate that the results are statistically significant.

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Table 3. Summary ORs (95% CI) categorized by ethnicity for the XPG Asp1104His and XPF Arg415Gln polymorphisms under different genetic models and cancer type.1

| Ethnicity | Cancer type | N  | Recessive model |  | Dominant model |  | Homozygote |  | Heterozygote |  | Additive model |
|-----------|-------------|----|----------------|---|----------------|---|-------------|---|--------------|---|----------------|
| XPG Asp1104His |  |  | OR (95%CI) | P/ I2 (%) | OR (95%CI) | P/ I2 (%) | OR (95%CI) | P/ I2 (%) | OR (95%CI) | P/ I2 (%) | OR (95%CI) | P/ I2 (%) |
| Caucasian | Bladder cancer | 4 (2111/2060) | 0.84 (0.50–1.41)* | 0.078/56.0 | 0.99 (0.88–1.12) | 0.673/0.0 | 0.85 (0.51–1.42)* | 0.090/53.8 | 1.01 (0.89–1.15) | 0.688/0.0 | 0.98 (0.89–1.08) | 0.433/0.0 |
| | Breast cancer | 6 (3111/3675) | 1.07 (0.86–1.32) | 0.221/28.6 | 1.18 (0.92–1.44) | 0.965/51.8 | 1.08 (0.87–1.34) | 0.215/29.3 | 1.07 (0.89–1.26) | 0.048/50.2 | 1.03 (0.95–1.12) | 0.113/43.8 |
| | Colorectal cancer | 4 (1051/1240) | 0.92 (0.57–1.48) | 0.262/25.2 | 1.05 (0.88–1.24) | 0.372/0.0 | 0.97 (0.79–1.21) | 0.870/0.0 | 1.02 (0.88–1.17) | 0.123/5.8 | 1.00 (0.89–1.11) | 0.774/0.0 |
| | Glioma | 3 (1719/2789) | 0.98 (0.81–1.19) | 0.262/25.3 | 1.07 (0.90–1.18) | 0.322/0.0 | 0.97 (0.78–1.19) | 0.810/0.0 | 1.07 (0.90–1.23) | 0.113/43.8 | 1.02 (0.91–1.12) | 0.774/0.0 |
| | HNC | 3 (1412/1925) | 0.71 (0.51–0.97) | 0.262/25.5 | 1.07 (0.90–1.20) | 0.739/0.0 | 0.73 (0.53–1.02) | 0.378/0.0 | 1.07 (0.95–1.28) | 0.543/0.0 | 0.98 (0.87–1.10) | 0.419/0.0 |
| | Melanoma | 8 (5297/7072) | 0.87 (0.69–1.12)* | 0.050/50.3 | 0.97 (0.89–1.04) | 0.762/0.0 | 0.87 (0.73–1.03) | 0.599/48.4 | 1.00 (0.90–1.06) | 0.854/0.0 | 0.97 (0.91–1.03) | 0.326/12.1 |
| | Other cancer | 5 (1133/1627) | 1.21 (0.86–1.70) | 0.345/10.7 | 1.04 (0.89–1.22) | 0.395/0.0 | 1.14 (0.94–1.36) | 0.142/58.0 | 1.02 (0.86–1.20) | 0.522/0.0 | 1.06 (0.89–1.24) | 0.131/5.0 |
| Asian | Lung cancer | 3 (1428/1105) | 1.07 (0.88–1.29) | 0.673/0.0 | 1.14 (0.90–1.20) | 0.739/0.0 | 1.14 (0.90–1.20) | 0.739/0.0 | 1.14 (0.90–1.20) | 0.739/0.0 | 1.14 (0.90–1.20) | 0.739/0.0 |
| | Other cancer | 4 (1031/1368) | 1.04 (0.85–1.28) | 0.350/8.6 | 1.14 (0.82–1.60)* | 0.029/66.9 | 1.12 (0.88–1.43) | 0.176/39.3 | 1.15 (0.79–1.67)* | 0.077/70.7 | 1.03 (0.92–1.16) | 0.187/37.5 |
| XPF Arg415Gln |  |  | OR (95%CI) | P/ I2 (%) | OR (95%CI) | P/ I2 (%) | OR (95%CI) | P/ I2 (%) | OR (95%CI) | P/ I2 (%) | OR (95%CI) | P/ I2 (%) |
| Caucasian | Breast cancer | 7 (3258/3729) | 2.17 (0.68–6.88)* | 0.022/61.9 | 1.10 (0.96–1.25) | 0.369/3.9 | 2.07 (0.56–7.62)* | 0.008/61.9 | 1.05 (0.89–1.23) | 0.522/0.0 | 1.10 (0.89–1.35)* | 0.094/6.8 |
| | HNC | 4 (1643/2156) | 1.47 (0.72–2.98) | 0.364/5.8 | 1.04 (0.88–1.23) | 0.359/6.9 | 1.48 (0.73–3.00) | 0.370/4.5 | 1.02 (0.86–1.21) | 0.323/13.9 | 1.05 (0.90–1.23) | 0.302/17.7 |
| | Colorectal cancer | 3 (798/781) | 1.26 (0.40–4.01) | – | 0.99 (0.76–1.30) | 0.519/0.0 | 1.28 (0.40–4.01) | – | 0.97 (0.69–1.36) | 0.271/17.6 | 1.00 (0.74–1.36) | 0.253/23.5 |
| | Other cancer | 4 (4215/5095) | 1.20 (0.77–1.87) | 0.168/40.6 | 0.95 (0.85–1.06) | 0.549/0.0 | 1.19 (0.77–1.86) | 0.184/38.0 | 0.94 (0.84–1.05) | 0.406/0.0 | 0.96 (0.87–1.07) | 0.666/0.0 |

1All summary ORs were calculated using fixed-effects models. In the case of significant heterogeneity (indicated by *), ORs were calculated using random-effects models. The bold values indicate that the results are statistically significant.

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Table 4. Summary ORs (95% CI) and value of the heterogeneity of XPG Asp1104His and XPF Arg415Gln polymorphisms for studies according to source of controls and cancer type.

| Source of control | Cancer type | N     | Recessive model | OR (95% CI) | \( P_{\text{ph}} \)/\( I^2 \) (%) | Dominant model | OR (95% CI) | \( P_{\text{ph}} \)/\( I^2 \) (%) | Homozygote | OR (95% CI) | \( P_{\text{ph}} \)/\( I^2 \) (%) | Heterozygote | OR (95% CI) | \( P_{\text{ph}} \)/\( I^2 \) (%) | Additive model | OR (95% CI) | \( P_{\text{ph}} \)/\( I^2 \) (%) |
|-------------------|-------------|-------|-----------------|-------------|-------------------------------|----------------|-------------|-------------------------------|------------|-------------|-------------------------------|------------|-------------|-------------------------------|----------------|-------------|-------------------------------|
| XPG Asp1104His    | PB          | Breast cancer | 6 (4327/4684) | 1.06 (0.91–1.24) | 0.642/0.0 | 1.00 (0.92–1.09) | 0.130/41.4 | 1.09 (0.92–1.29) | 0.579/0.0 | 0.99 (0.91–1.08) | 0.130/41.3 | 1.01 (0.95–1.08) | 0.130/41.3 |
|                   | Melanoma    | 3 (2340/4207) | 0.91 (0.58–1.42)* | 0.366/0.0 | 1.00 (0.90–1.11) | 0.362/0.0 | 0.90 (0.56–1.43) | 0.372/0.0 | 1.00 (0.89–1.12) | 0.372/0.0 | 0.97 (0.83–1.13)* | 0.073/61.7 |
|                   | NHL         | 3 (2105/1957) | 1.03 (0.80–1.31) | 0.345/0.0 | 1.11 (0.89–1.38)* | 0.082/64.0 | 1.07 (0.83–1.38) | 0.238/30.4 | 1.11 (0.90–1.37) | 0.100/56.7 | 1.08 (0.90–1.30)* | 0.053/66.0 |
|                   | Other cancer | 4 (1709/2395) | 0.89 (0.71–1.12) | 0.367/0.0 | 1.08 (0.95–1.23) | 0.062/0.0 | 0.97 (0.76–1.24) | 0.900/0.0 | 1.11 (0.96–1.26) | 0.522/0.0 | 1.02 (0.93–1.13) | 0.840/0.0 |
|                   | HB          | Bladder cancer | 5 (2133/2485) | 1.16 (0.92–1.46) | 0.219/32.3 | 1.39 (0.86–2.23)* | 0.022/68.8 | 1.16 (0.96–1.39) | 0.247/27.4 | 0.97 (0.77–1.22)* | 0.039/64.2 |
|                   | Breast cancer | 4 (993/1322) | 0.71 (0.55–0.92) | 0.262/24.9 | 1.06 (0.89–1.26)* | 0.100/51.9 | 0.74 (0.55–0.98) | 0.213/33.3 | 1.16 (0.96–1.39) | 0.247/27.4 | 0.97 (0.77–1.22)* | 0.039/64.2 |
|                   | Colorectal cancer | 3 (1692/1717) | 0.93 (0.76–1.13) | 0.525/0.0 | 1.33 (1.15–1.55) | 0.188/0.0 | 1.21 (0.96–1.55) | 0.668/0.0 | 1.29 (0.97–1.72)* | 0.072/62.1 | 1.13 (1.02–1.25) | 0.971/0.0 |
|                   | HNC         | 3 (1286/1519) | 0.88 (0.66–1.16) | 0.135/50.1 | 1.04 (0.89–1.22) | 0.548/0.0 | 0.90 (0.66–1.22) | 0.115 | 1.08 (0.91–1.27) | 0.591/0.0 | 1.00 (0.88–1.13) | 0.441/0.0 |
|                   | Lung cancer | 4 (1680/1575) | 1.15 (0.96–1.37) | 0.105/51.1 | 1.22 (0.91–1.63) | 0.030/66.4 | 1.32 (0.93–1.85)* | 0.092/33.5 | 1.21 (0.89–1.63)* | 0.053/65.2 | 1.13 (0.95–1.35)* | 0.057/60.1 |
|                   | Melanoma    | 5 (2957/2865) | 0.88 (0.70–1.09) | 0.145/41.5 | 0.94 (0.85–1.04) | 0.981/0.0 | 0.86 (0.69–1.08) | 0.213/31.3 | 0.95 (0.85–1.06) | 0.915/0.0 | 0.94 (0.86–1.02) | 0.766/0.0 |
|                   | Other cancer | 9 (2443/3017) | 1.18 (0.99–1.41) | 0.576/0.0 | 1.05 (0.94–1.18) | 0.171/310 | 1.22 (1.01–1.47) | 0.322/13.5 | 1.02 (0.90–1.15) | 0.155/32.9 | 1.07 (0.98–1.16) | 0.361/8.9 |
| XPF Arg415Gln     | PB          | Breast cancer | 6 (4356/4687) | 1.05 (0.29–3.77) | 0.098/49.0 | 1.02 (0.90–1.16) | 0.158/37.3 | 1.05 (0.29–3.81)* | 0.093/49.7 | 1.00 (0.87–1.15) | 0.133/42.1 | 0.96 (0.77–1.20)* | 0.069/54.0 |
|                   | Other cancer | 5 (3647/4879) | 1.48 (0.84–2.60) | 0.354/3.9 | 1.03 (0.91–1.17) | 0.477/0.0 | 1.48 (0.84–2.60) | 0.386/12.2 | 1.02 (0.90–1.15) | 0.286/20.2 | 1.05 (0.93–1.17) | 0.731/0.0 |
|                   | HB          | Breast cancer | 4 (730/855) | 3.66 (0.38–34.9)* | 0.009/78.7 | 1.04 (0.78–1.39) | 0.178/38.9 | 3.39 (0.26–41.9)* | 0.003/82.8 | 0.92 (0.68–1.25) | 0.463/0.0 | 1.13 (0.73–1.73)* | 0.054/60.7 |
|                   | Other cancer | 3 (2256/2027) | 0.70 (0.39–1.25) | 0.341/0.9 | 0.79 (0.59–1.07)* | 0.035/70.1 | 0.69 (0.38–1.24) | 0.347/56.0 | 0.81 (0.59–1.09)* | 0.037/70.8 | 0.80 (0.61–1.05)* | 0.045/67.7 |

1 All summary ORs were calculated using fixed-effects models. In the case of significant heterogeneity (indicated by *), ORs were calculated using random-effects models.

2 The results were excluded due to high heterogeneity. The bold values indicate that the results are statistically significant. PB Population-based studies, HB Hospital-based studies, the bold values indicate that the results are statistically significant.

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| Genetic model | No. comparisons (SZ case/control) | Recessive model | Dominant model | Homozygote | Heterozygote | Additive model |
|---------------|----------------------------------|----------------|----------------|-------------|-------------|---------------|
|               |                                  | OR (95%CI)     | OR (95%CI)     | OR (95%CI)  | OR (95%CI)  | OR (95%CI)    |
|               |                                  | $P_{het}$ (%)  | $P_{I^2}$ (%)  | $P_{het}$ (%) | $P_{I^2}$ (%) | $P_{het}$ (%)  |
| XPG Asp1104His| Overall                          | 0.99 (0.92–1.07)* | 0.068/22.9 | 1.03 (0.99–1.08)* | 0.092/20.6 | 1.02 (0.94–1.11)* | 0.066/23.4 | 1.04 (1.00–1.09)* | 0.055/24.5 | 1.02 (0.99–1.05) | 0.139/17.3 |
| Cancer type   | Bladder cancer                   | 0.95 (0.62–1.47)* | 0.065/54.9 | 0.97 (0.87–1.09) | 0.724/0.0 | 0.94 (0.73–1.20) | 0.112/46.6 | 0.98 (0.87–1.11) | 0.517/0.0 | 0.98 (0.89–1.08) | 0.599/0.0 |
|               | Glioma                           | 0.99 (0.61–1.60) | 0.102/62.6 | 1.04 (0.78–1.38) | – | 0.69 (0.35–1.38) | – | 1.09 (0.81–1.47) | – | 0.97 (0.77–1.24) | – |
|               | HNC                              | 0.88 (0.67–1.16) | 0.240/29.9 | 1.06 (0.92–1.23) | 0.454/0.0 | 0.90 (0.67–1.22) | 0.194/39.0 | 1.10 (0.95–1.28) | 0.462/0.0 | 1.02 (0.91–1.14) | 0.537/0.0 |
|               | Lung cancer                      | 1.12 (0.95–1.34) | 0.139/42.4 | 1.12 (0.98–1.28) | 0.348/10.2 | 1.19 (0.98–1.44) | 0.171/45.8 | 1.11 (0.96–1.27) | 0.694/0.0 | 1.08 (0.94–1.24)* | 0.098/48.9 |
|               | Other cancer                     | 1.08 (0.93–1.24) | 0.532/0.0 | 1.05 (0.96–1.14) | 0.665/0.0 | 1.10 (0.94–1.29) | 0.667/0.0 | 1.04 (0.95–1.14) | 0.459/0.0 | 1.05 (0.98–1.12) | 0.835/0.0 |
| Ethnicity and cancer type | Lung cancer/Asian | 1.10 (0.88–1.38) | 0.463/0.0 | 1.15 (0.95–1.41) | 0.710/0.0 | 1.20 (0.92–1.55) | 0.517/0.0 | 1.14 (0.92–1.40) | 0.694/0.0 | 1.10 (0.96–1.25) | 0.484/0.0 |
|               | Other cancer/Caucasian           | 1.30 (0.92–1.85) | 0.473/0.0 | 1.07 (0.90–1.26) | 0.679/0.0 | 1.29 (0.91–1.85) | 0.618/0.0 | 1.03 (0.87–1.23) | 0.418/0.0 | 1.09 (0.95–1.25) | 0.811/0.0 |
|               | Other cancer/Asian               | 1.03 (0.81–1.30) | 0.199/38.1 | 0.96 (0.70–1.17) | 0.109/54.8 | 1.02 (0.78–1.34) | 0.240/30.0 | 1.01 (0.71–1.44)* | 0.071/62.1 | 0.99 (0.87–1.13) | 0.269/23.8 |
| Source of controls and cancer type | Bladder cancer/HB | 1.08 (0.84–1.40) | 0.254/27.1 | 0.97 (0.85–1.10) | 0.425/0.0 | 1.04 (0.80–1.36) | 0.299/17.2 | 0.96 (0.84–1.10) | 0.296/17.9 | 1.00 (0.90–1.10) | 0.352/4.1 |
|               | Lung cancer/HB                   | 1.20 (0.80–1.79) | 0.077/61.0 | 1.13 (0.96–1.34) | 0.112/54.3 | 1.23 (0.76–2.00)* | 0.050/66.5 | 1.09 (0.91–1.30) | 0.347/5.5 | 1.09 (0.85–1.40)* | 0.029/71.8 |
|               | Other cancer/HB                  | 1.23 (1.02–1.49) | 0.595/0.0 | 1.03 (0.92–1.16) | 0.375/7.0 | 1.20 (0.97–1.48) | 0.394/4.3 | 0.99 (0.87–1.12) | 0.324/13.9 | 1.07 (0.97–1.17) | 0.515/0.0 |
| XPF Arg415Gln  | Overall                          | 0.98 (0.92–1.05) | 0.047/34.6 | 0.99 (0.91–1.07)* | 0.026/36.4 | 1.07 (0.74–1.53)* | 0.027/38.6 | 0.97 (0.89–1.05)* | 0.059/31.4 | 1.00 (0.91–1.08) | 0.003/47.8 |
| Cancer type   | Glioma                           | 1.44 (0.71–2.93) | 0.161/49.2 | 1.28 (0.96–1.70) | 0.868/0.0 | 1.49 (0.73–3.03) | 0.163/48.5 | 1.25 (0.92–1.69) | 0.716/0.0 | 1.28 (0.99–1.65) | 0.525/0.0 |
|               | HNC                              | 1.58 (0.72–3.46) | 0.204/37.1 | 1.02 (0.85–1.21) | 0.277/22.1 | 1.57 (0.72–3.45) | 0.206/36.6 | 0.99 (0.83–1.19) | 0.264/25.0 | 1.04 (0.88–1.22) | 0.201/37.7 |

*All summary ORs were calculated using fixed-effects models. In the case of significant heterogeneity (indicated by *), ORs were calculated using random-effects models. The bold values indicate that the results are statistically significant.

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Table 6. Summary ORs (95% CI) and value of the heterogeneity of XPG Asp1104His and XPF Arg415Gln polymorphisms under different genetic models according to studies with a minimum of 200 participants on cancer risk. 1

| Genetic model       | No. comparisons (SZ case/control) | Recessive model | Dominant model | Homozygote | Heterozygote | Additive model |
|---------------------|-----------------------------------|----------------|---------------|------------|--------------|---------------|
|                     |                                   | OR (95%CI)     | P_v2 (%)      | OR (95%CI) | P_v2 (%)     | OR (95%CI)     | P_v2 (%)     |
| XPG Asp1104His      | Overall 63 (32002/39603)          | 1.01 (0.94–1.07)* | 0.085/20.6   | 1.04 (0.97–1.13)* | 0.012/31.6  | 1.06 (1.01–1.11)* | <0.001/45.8 |
|                     | Cancer type                       |                |               |            |              |               |              |
|                     | Breast cancer                     | 10 (5422/6082) | 0.97 (0.85–1.11) | 0.089/40.3 | 1.00 (0.87–1.15) | 0.250/25.9  | 1.04 (0.93–1.16)* | <0.001/45.8 |
|                     | Bladder cancer                    | 6 (2432/2769)  | 1.08 (0.71–1.63) | 0.023/64.7 | 1.14 (0.68–1.91)* | 0.003/75.4  | 2              | <0.001/82.0   |
|                     | Other cancer                      | 13 (4140/5519) | 1.08 (0.94–1.24) | 0.618/0.0 | 1.07 (0.98–1.16) | 0.425/21.2  | 1.13 (0.97–1.32) | 0.596/0.0    |
| XPF Arg415Gln       | Overall 31 (17811/20503)          | 1.11 (0.81–1.52)* | 0.068/30.5   | 1.04 (0.93–1.15)* | <0.001/63.7 | 1.10 (0.79–1.54)* | 0.035/35.7   |
|                     | Cancer type                       |                |               |            |              |               |              |
|                     | Breast cancer                     | 9 (5033/5467)  | 1.54 (0.59–3.99)* | 0.017/58.9 | 1.02 (0.91–1.15) | 0.119/37.5  | 1.49 (0.52–4.25) | 0.007/63.8   |

1All summary ORs were calculated using fixed-effects models. In the case of significant heterogeneity (indicated by *), ORs were calculated using random-effects models.
2The results were excluded due to high heterogeneity. The bold values indicate that the results are statistically significant.

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We also examined the association of the XPG Asp1104His polymorphism and cancer risk according to cancer type and source of controls (Table 4). For the population-based studies, no significant association was found between XPG Asp1104His polymorphism and cancer risk according to cancer type and source of controls. For the hospital-based studies, significant association was observed among breast cancer (recessive model: OR = 1.22, 95% CI = 1.01–1.47, \(P = 0.030\), additive model: OR = 1.13, 95% CI = 1.01–1.25, \(P = 0.022\), \(I^2 = 13.5\%\)) but not lung cancer (dominant model: OR = 1.27, 95% CI = 1.02–1.55, \(P = 0.035\), source of controls (dominant model: OR = 1.20, 95% CI = 0.92–1.55; His/His versus Asp/Asp: \(P = 0.213\), additive model: OR = 1.10, 95% CI = 0.92–1.55; His/His versus Asp/Asp: \(P = 0.971\), \(I^2 = 65.2\%\)). In the pooled ORs, the results were changed among overall cancer (dominant model: OR = 1.03, 95% CI = 0.99–1.08), Asians of lung cancer (dominant model: OR = 1.15, 95% CI = 0.95–1.41; His/His versus Asp/Asp: \(P = 0.241\), source of controls (dominant model: OR = 1.20, 95% CI = 0.92–1.55; His/His versus Asp/Asp: \(P = 0.262\), \(I^2 = 66.4\%\)). When these studies were excluded, the results were changed among overall cancer (dominant model: OR = 1.08, 95% CI = 0.99–1.17; His/His versus Asp/Asp: \(P = 0.441\), additive model: OR = 1.00, 95% CI = 0.88–1.16, \(P = 0.90\), \(I^2 = 83.3\%\)) but not lung cancer (dominant model: OR = 1.20, 95% CI = 1.02–1.55; His/His versus Asp/Asp: \(P = 0.272\), \(I^2 = 66.4\%\)).

Examining genotype frequencies in the controls, significant deviation from HWE was detected in the eight studies [10,26,43,44,45,53,80,81]. When these studies were excluded, the results were changed among overall cancer (dominant model: OR = 1.03, 95% CI = 0.99–1.08), Asians of lung cancer (dominant model: OR = 1.15, 95% CI = 0.95–1.41; His/His versus Asp/Asp: \(P = 0.241\), source of controls (dominant model: OR = 1.20, 95% CI = 0.92–1.55; His/His versus Asp/Asp: \(P = 0.262\), \(I^2 = 66.4\%\)). In addition, when the meta-analysis was performed excluding studies with small sample sizes, the results did not change among overall cancer studies and any subgroup analysis, as shown in Table 5. In addition, when the meta-analysis was performed excluding studies with small sample sizes, the results did not change among overall cancer studies and any subgroup analysis, as shown in Table 5.

Last, a single study involved in the meta–analysis was deleted each time to reflect the influence of individual data set to the pooled ORs, the results were changed among Caucasians of head and neck cancer (recessive model: OR = 0.79, 95% CI = 0.51–1.24), hospital-based studies of breast cancer (recessive model: OR = 1.22, 95% CI = 0.98–1.52; His/His versus Asp/Asp: \(P = 0.98–1.52\), Gln/Gln versus Arg/Arg: \(P = 0.19\), 95% CI = 0.51–1.24), hospital-based studies of colorectal cancer (dominant model: OR = 1.15, 95% CI = 0.92–1.43; additive model: OR = 1.12, 95% CI = 0.92–1.35).
XPF Arg415Gln

The evaluations of the association of XPF Arg415Gln polymorphism with cancer risk are shown in Table 2. No significant association was observed between XPF Arg415Gln polymorphism and cancer risk when all the eligible studies were pooled into the meta-analysis (dominant model: OR = 1.04, 95% CI = 0.93–1.15, \( P = 0.178 \), \( I^2 = 39.9 \); recessive model: OR = 5.66, 95% CI = 3.93–9.49, \( P = 0.009 \), \( I^2 = 70.7 \); additive model: OR = 1.13, 95% CI = 0.73–1.73, \( P = 0.354 \), \( I^2 = 66.7 \); Gln/Gln versus Arg/Arg: OR = 3.39, 95% CI = 0.26–43.9, \( P = 0.003 \), \( I^2 = 0.8 \); Arg/Gln versus Arg/Arg: OR = 0.92, 95% CI = 0.68–1.25, \( P = 0.463 \), \( I^2 = 0.0 \) and other cancer (dominant model: OR = 0.79, 95% CI = 0.59–1.07, \( P = 0.354 \), \( I^2 = 52.0 \); Gln/Gln versus Arg/Arg: OR = 0.69, 95% CI = 0.38–1.24, \( P = 0.347 \), \( I^2 = 5.6 \); Arg/Gln versus Arg/Arg: OR = 0.81, 95% CI = 0.59–1.19, \( P = 0.333 \), \( I^2 = 70.9 \)).

There was significant heterogeneity among these studies for dominant model comparison (\( P < 0.001 \), recessive model comparison (\( P = 0.068 \), additive model comparison (\( P < 0.001 \), homozygote model comparison (\( P = 0.035 \), and heterozygote model comparison (\( P < 0.001 \). Then, we assessed the source of heterogeneity by ethnicity, cancer type, source of controls, HWE, and sample size. Meta-regression analysis indicated that HWE (Arg/Gln versus Arg/Arg: \( P = 0.001 \); additive model: \( P = 0.001 \); dominant model: \( P < 0.001 \), and ethnicity (Gln/Gln versus Arg/Arg: \( P = 0.001 \); recessive model: \( P = 0.001 \) but not cancer type (dominant model: \( P = 0.446 \); recessive model: \( P = 0.344 \); Gln/Gln versus Arg/Arg: \( P = 0.314 \); Arg/Gln versus Arg/Arg: \( P = 0.694 \); additive model: \( P = 0.456 \), source of controls (dominant model: \( P = 0.710 \); recessive model: \( P = 0.218 \); Gln/Gln versus Arg/Arg: \( P = 0.221 \); Arg/Gln versus Arg/Arg: \( P = 0.558 \); additive model: \( P = 0.962 \), and sample size (dominant model: \( P = 0.125 \); recessive model: \( P = 0.255 \); Gln/Gln versus Arg/Arg: \( P = 0.076 \); Arg/Gln versus Arg/Arg: \( P = 0.252 \); additive model: \( P = 0.153 \)) contributed to substantial heterogeneity among the meta-analysis. Examining genotype frequencies in the controls, significant deviation from HWE was detected in the two studies [81,82]. When these two studies were excluded, the results were not changed among overall cancer and any subgroup analysis, as shown in Table 5. In addition, when the meta-analysis was performed excluding studies with small sample sizes, the results did not also change among overall cancer and any subgroup analysis, as shown in Table 6. Last, a single study involved in the meta-analysis was deleted each time to reflect the influence of individual data set to the pooled ORs, the results did not also change among this meta-analysis, indicating that our results did not influenced statistically robust.

Both Begg's funnel plot and Egger's test were performed to assess the publication bias of literatures. The Egger's test results \( P = 0.171 \); recessive model: \( P = 0.437 \); additive model: \( P = 0.114 \); Homozygote model: \( P = 0.425 \); Heterozygote model: \( P = 0.229 \) and Begg's funnel plot (Fig. 3) suggested no evidence of publication bias in the meta-analysis.

**Discussion**

NER is a crucial DNA repair mechanism, which counteracts the consequences of mutagenic exposure of cell. XPF and XPG are both central players in the NER pathway, and involved in incision 5'- and 3'-ends, respectively, of the DNA lesion. A number of epidemiological studies have evaluated the association between XPG Asp1104His and XPF Arg415Gln polymorphisms and cancer risk, but the results remain inconclusive.

For instance, McWilliams et al. [38] reported a significantly decreased pancreatic cancer risk with XPF Arg115Gln polymorphism (\( P = 0.003 \). But Liu et al. [64] reported a significantly increased colorectal cancer risk associated with the variant allele of XPG Asp1104His. Goncalves et al. [66] found that significantly...
decreased melanoma cancer risk with the XPG 1104 His/His genotype (OR = 0.32, 95% CI = 0.13–0.75). However, Berhane et al. [74] found that statistically significant increased risk of prostate cancer was observed on individuals that posses His/His genotype of XPG (OR = 2.53, 95% CI = 0.99–6.56, P = 0.031). Ming-Shiuan et al. [59] reported a significantly increased breast cancer risk with the variant allele of XPG Asp1104His (OR = 1.42, 95% CI = 1.00–1.97). He et al. [45] found that Women carrying homozygous Asp1104His genotypes had a significantly decreased risk of cervical or cervical squamous cell carcinoma compared to His1104Asp or His1104His genotypes. Smith et al. [8] reported a statistically significant difference in the XPF Arg415Gln genotype distributions between breast cancer cases and controls (P = 0.02). Furthermore, Kumar et al. [9] reported a marginally significantly increase in breast cancer risk associated with the variant allele of XPG Asp1104His. What’s more, more studies did not find obvious association among them. In order to resolve this conflict, a meta-analysis of 98 eligible studies including 32,162 cases and 39,858 controls for XPG Asp1104His and 17,804 cases and 20,578 controls for XPG Arg15Gln was performed to derive a more precise estimation of the association.

Overall, significantly elevated cancer risk was found when all studies were pooled into the meta-analysis of XPG Asp1104His (dominant model: OR = 1.05, 95% CI = 1.00–1.10; Asp/His versus Asp/Asp: OR = 1.06, 95% CI = 1.01–1.11). Based on biochemical properties described for XPG Asp1104His and XPF Arg15Gln polymorphisms, we would expect that the His or Gln alleles would be associated for all types of cancer. However, our results showed that such association was observed just among lung cancer (dominant model: OR = 0.82, 95% CI = 0.71–0.96; Asp/His versus Asp/Asp: OR = 0.83, 95% CI = 0.71–0.97; additive model: OR = 0.83, 95% CI = 0.72–0.95) for XPF Arg15Gln and hospital-based studies of other cancer (dominant model: OR = 1.23, 95% CI = 1.02–1.49) for XPG Asp1104His, suggesting that other factors may be modulating the XPG Asp1104His and XPF Arg15Gln polymorphisms functionality. However, the exact mechanism for association between different tumor sites and XPG Asp1104His and XPF Arg15Gln polymorphisms was not clear, carcinogenetic mechanism may differ by different tumor sites and the XPG Asp1104His and XPF Arg15Gln genetic variants may exert varying effects in different cancers. Hung et al. [14] reported a marginally significantly decreased lung cancer risk with the variant allele of XPF Arg15Gln (dominant model: OR = 0.70, 95% CI = 0.67–0.91). Our results seem to confirm and establish the trend in the meta-analysis of XPF Arg15Gln polymorphism and lung cancer risk that the data by Hung et al. [40] had indicated. However, at any case, the association between XPF Arg15Gln and lung cancer risk remain an open field, as the number of studies (n = 3 for Arg15Gln) is considerably smaller than that needed for the achievement of robust conclusions [94].

In the subgroup analysis by source of control and cancer type, significantly increased other cancer association was found among the hospital-based studies for the XPG Asp1104His polymorphism, but not the population-based studies. However, the hospital-based studies may have certain biases for such controls and may only represent a sample of an ill-defined reference population, and may not be representative of the general population or it may be that numerous subjects in the population-based controls were susceptible individuals. The results only indicate that participation of XPG Asp1104His may be a genetic susceptibility for other cancer. Therefore, the use of proper and representative population-based controls control subjects is important to reduce biases and in such generic studies.

We noticed with great interest that 2 previous meta-analysis had been reported on the cancer risk with XPG Asp1104His and XPF Arg15Gln polymorphisms [84,85]. Zhu et al. [84] had 49 case-control studies, in which a total of 23,490 cases and 27,168 controls were included. Their meta-analysis suggested that it was unlikely that the XPG Asp1104His polymorphism may contribute to individual susceptibility to cancer risk. Shi et al. [95] had 23 case-control studies, in which a total of 14,632 cancer cases and 15,545 controls. Their meta-analysis suggested that it was unlikely that the XPF Arg15Gln polymorphism may contribute to individual susceptibility to cancer risk. However, several published studies were not included in that meta-analysis [84,85]. By analyzing a larger number of studies than the previous meta-analysis [84,85], our meta-analysis included 32,162 cases and 39,858 controls (from 66 studies) for XPG Asp1104His and 17,804 cases and 20,578 controls (from 32 studies) for XPF Arg15Gln to perform the two gene polymorphisms and cancer risk. Our meta-analysis suggests that XPF Arg15Gln polymorphism may be associated with decreased lung cancer risk and XPG Asp1104His may be a low-penetrant risk factor in some cancer development. Our results seem to confirm and establish the trend in the meta-analysis of the XPG Asp1104His and XPF Arg15Gln polymorphisms according to the previous meta-analysis [84,85].

In the present meta-analysis, between-studies heterogeneity was observed between XPG Asp1104His and XPF Arg15Gln polymorphisms and cancer of risk. Meta-regression analysis indicated that HWE contributed to substantial heterogeneity among the meta-analysis for XPF Arg15Gln polymorphism and sample size contributed to substantial heterogeneity among the meta-analysis for XPG Asp1104His. Deviation of HWE may reflect methodological problems such as genotyping errors, population stratification or selection bias. When these studies were excluded, the results were changed among overall cancer and some subgroup analyses for XPG Asp1104His, indicating that our meta-analysis was not statistically robust. Hence, significant association may be not existed in some cancer types when the results were changed. When the meta-analysis was performed excluding studies with small sample sizes, the results did not change among overall cancer studies and any subgroup analysis, indicating that small sample sizes did not influenced statistically robust.

Our meta-analysis has several strengths. First, a systematic review of the association of XPG Asp1104His and XPF Arg15Gln polymorphisms with cancer risk is statistically more powerful than any single study. Second, the quality of eligible studies included in current meta-analysis was satisfactory and met our inclusion criterion. Third, we did not detect any publication bias indicating that the whole pooled results should be unbiased. However, although we have put considerable efforts and resources into testing possible association between XPG Asp1104His and XPF Arg15Gln polymorphisms and cancer risk, there are still some limitations inherited from the published studies. First, our results were based on single-factor estimations without adjustment for other risk factors including alcohol usage, environmental factors and other lifestyles. At lower levels of alcohol consumption, the difference in cancer risk between the various gene carriers was less striking. And higher levels of alcohol consumption result in production of more acetaldehyde which then can exert its carcinogenic effect [95]. Second, in the subgroup analysis may have had insufficient statistical power to check an association. Third, the controls were not uniformly defined. Some studies used a healthy population as the reference group, whereas others selected hospital patients without organic cancer as the reference group. Therefore, non-differential misclassification bias is possible.
because these studies may have included the control groups who have different risks of developing cancer of various organs.

In conclusion, this meta-analysis suggests that XPF Arg415Gln polymorphism may be associated with decreased lung cancer risk and XPG Asp1104His may be a low-penetrant risk factor in some cancer development. However, it is necessary to conduct large sample studies using standardized unbiased genotyping methods, homogeneous cancer patients and well-matched controls. Moreover, further studies estimating the effect of gene–gene and gene–environment interactions may eventually lead to our better, comprehensive understanding of the association between the XPF Arg415Gln and XPG Asp1104His polymorphisms and cancer risk.

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Supporting Information

Checklist S1 PRISMA Checklist. (DOC)

Author Contributions

Conceived and designed the experiments: XFH WW. Performed the experiments: XFH LRL. Analyzed the data: XFH LRL. Contributed reagents/materials/analysis tools: XFH LRL YL JS SLW XLS XBY.

Wrote the paper: XFH.

Checked the paper: XFH LRL YL JS SLW XLS XBY.

Contributed resources: XFH LRL YL JS SLW XLS XBY.

Performed the experiments: XFH LRL.

Analyzed the data: XFH LRL.

Contributed resources: XFH LRL YL JS SLW XLS XBY.

Wrote the paper: XFH.

Contributed resources: XFH LRL YL JS SLW XLS XBY.

Analyzed the data: XFH LRL.

Contributed resources: XFH LRL YL JS SLW XLS XBY.

Wrote the paper: XFH.

Contributed resources: XFH LRL YL JS SLW XLS XBY.

Designed the experiments: XFH WW.

Conceived and designed the experiments: XFH WW. Performed the experiments: XFH LRL. Analyzed the data: XFH LRL. Contributed reagents/materials/analysis tools: XFH LRL YL JS SLW XLS XBY. Wrote the paper: XFH.
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