The Effect of XPD Polymorphisms on Digestive Tract Cancers Risk: A Meta-Analysis

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Abstract

Background: The Xeroderma pigmento-sum group D gene (XPD) plays a key role in nucleotide excision repair. Single nucleotide polymorphisms (SNP) located in its functional region may alter DNA repair capacity phenotype and cancer risk. Many studies have demonstrated that XPD polymorphisms are significantly associated with digestive tract cancers risk, but the results are inconsistent. We conducted a comprehensive meta-analysis to assess the association between XPD Lys751Gln polymorphism and digestive tract cancers risk. The digestive tract cancers that our study referred to, includes oral cancer, esophageal cancer, gastric cancer and colorectal cancer.

Methods: We searched PubMed and EmBase up to December 31, 2012 to identify eligible studies. A total of 37 case-control studies including 9027 cases and 16072 controls were involved in this meta-analysis. Statistical analyses were performed with Stata software (version 11.0, USA). Odds ratios (ORs) with 95% confidence intervals (CIs) were used to assess the strength of the association.

Results: The results showed that XPD Lys751Gln polymorphism was associated with the increased risk of digestive tract cancers (homozygote comparison (GlnGln vs. LysLys): OR = 1.12, 95% CI = 1.01–1.24, P = 0.029, I² heterogeneity = 0.133). We found no statistical evidence for a significantly increased digestive tract cancers risk in the other genetic models. In the subgroup analysis, we also found the homozygote comparison increased the susceptibility of Asian population (OR = 1.28, 95% CI = 1.01–1.63, P = 0.045, I² heterogeneity = 0.287). Stratified by cancer type and source of control, no significantly increased cancer risk was found in these subgroups. Additionally, risk estimates from hospital-based studies and esophageal studies were heterogeneous.

Conclusions: Our meta-analysis suggested that the XPD 751Gln/Gln genotype was a low-penetrant risk factor for developing digestive tract cancers, especially in Asian populations.

Introduction

Digestive tract cancers, especially gastric, esophageal and colorectal cancers, are a major global health problem. Globocan data in 2008 showed [1] that the standardized incidence of colorectal cancer, gastric cancer and esophageal cancer were located in 4th, 6th and 9th in all tumors, respectively. The standardized mortality rate of gastric cancer, coming after lung cancer and breast cancer, ranked the third place. Moreover, colorectal cancer and esophageal cancer also ranked top ten in cancer mortality rankings. The incidence of different cancer varies widely among different racial and ethnic groups which may be partly attributed to lifestyle and genetic background [2]. Exposure to environmental carcinogens can cause different types of DNA damage that subsequently lead to carcinogenesis of different tissues, if left unrepaired [3].

DNA repair mechanisms, such as the nucleotide excision repair (NER), base excision repair pathway (BER) and double-strand break pathway, are essential for maintaining genome integrity and preventing carcinogenesis. NER, the most versatile, well studied DNA repair mechanism in humans, is mainly responsible for repairing bulky DNA damage, such as DNA adducts caused by UV radiation, mutagenic chemicals, or chemotherapeutic drugs [4]. The major component of NER, xeroderma pigmentosum group D (XPD or ERCC2, mapped in chromosome 19q13.3, spans over 20 kb, contains 23 exons and encodes the 761-amino acid
### Table 1. Characteristics of XPD polymorphisms Included in the Meta-analysis.

| Study | Year | Ethnicity | Source of controls | Cases | Controls | Genotypes | Genotypes | P for HWE |
|-------|------|-----------|--------------------|-------|----------|-----------|-----------|-----------|
|       |      |           |                    | N     | N        | Lys/Lys | Lys/Gln | Gln/Gln | Lys/Lys | Lys/Gln | Gln/Gln |
|       |      |           |                    |       |          |          |          |          |          |          |          |
| Oral cancer | | | | | | | | | | | |
| Surya | 2005 | Asian | PB | 110 | 110 | 49 | 71 | 46 | 31 | 8 | 0.09 |
| Da-Tian | 2007 | Asian | HB | 154 | 105 | 134 | 89 | 18 | 15 | 1 | 0.68 |
| Mousumi | 2007 | Asian | HB | 388 | 309 | 190 | 158 | 40 | 125 | 26 | 0.85 |
| Suparp | 2005 | Asian | PB | 105 | 164 | 83 | 126 | 21 | 36 | 2 | 0.74 |
| Esophageal cancer | | | | | | | | | | | |
| Xing | 2002 | Asian | HB | 433 | 524 | 367 | 451 | 63 | 70 | 3 | 0.87 |
| Xing | 2003 | Asian | HB | 325 | 383 | 278 | 331 | 44 | 49 | 3 | 0.43 |
| Yu | 2004 | Asian | HB | 135 | 152 | 108 | 133 | 16 | 17 | 2 | 0.10 |
| Alan | 2005 | European | HB | 56 | 95 | 31 | 34 | 21 | 46 | 4 | 0.93 |
| Ye | 2006 | European | PB | 303 | 472 | 99 | 198 | 156 | 203 | 71 | 0.11 |
| Geoffrey | 2007 | European | HB | 182 | 336 | 61 | 143 | 98 | 161 | 32 | 0.16 |
| Ranbir | 2007 | Asian | HB | 120 | 160 | 52 | 63 | 61 | 77 | 20 | 0.63 |
| Darren | 2008 | European | HB | 312 | 453 | 104 | 193 | 159 | 208 | 52 | 0.72 |
| Heather | 2008 | European | PB | 208 | 247 | 80 | 91 | 94 | 121 | 35 | 0.60 |
| James | 2008 | European | PB | 263 | 1337 | 108 | 575 | 123 | 588 | 32 | 0.22 |
| Jennifer | 2009 | European | HB | 346 | 456 | 137 | 187 | 153 | 216 | 53 | 0.43 |
| Zhai | 2009 | Asian | HB | 200 | 200 | 167 | 148 | 31 | 51 | 2 | 0.12 |
| Huang | 2012 | Asian | HB | 213 | 358 | 150 | 274 | 55 | 79 | 5 | 0.79 |
| Gastric cancer | | | | | | | | | | | |
| Huang | 2005 | European | PB | 279 | 46 | 381 | 145 | 107 | 163 | 73 | 0.03 |
| Lou | 2006 | Asians | HB | 238 | 200 | 205 | 164 | 30 | 33 | 3 | 0.38 |
| Ye | 2006 | European | PB | 126 | 472 | 49 | 198 | 61 | 203 | 16 | 0.11 |
| Ruzzo | 2007 | European | PB | 89 | 94 | 29 | 25 | 44 | 53 | 16 | 0.18 |
| Zhou | 2006 | Asians | PB | 253 | 612 | 224 | 522 | 26 | 86 | 3 | 0.82 |
| Gabriel | 2008 | European | HB | 245 | 1172 | 99 | 447 | 105 | 555 | 41 | 0.91 |
| Doecke | 2008 | European | PB | 303 | 1337 | 127 | 575 | 140 | 588 | 36 | 0.22 |
| Zhang | 2009 | Asians | PB | 207 | 212 | 166 | 172 | 39 | 39 | 2 | 0.43 |
| Domenico | 2010 | European | PB | 295 | 546 | 90 | 177 | 157 | 284 | 48 | 0.09 |
| EMEL | 2010 | European | PB | 40 | 247 | 14 | 102 | 18 | 114 | 8 | 0.92 |
| Long | 2010 | Asians | HB | 361 | 71 | 616 | 400 | 139 | 164 | 52 | 0.00 |
| Ayse | 2011 | European | HB | 106 | 20 | 116 | 40 | 30 | 43 | 56 | 0.01 |
| Colorectal cancer | | | | | | | | | | | |
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protein. It has two functions: nucleotide excision repair and basal transcription as part of the transcription factor complex (TFIIH) [5]. Mutations on different sites in XPD gene can give rise to repair and transcription defects, and altered DNA repair capacity can render a higher risk of developing different types of cancer [5–11]. Several polymorphisms of XPD were identified, like Asp312Asn, Lys751Gln, Arg194Trp and Arg399Gln. The XPD polymorphic loci that has been of particular interest in molecular epidemiology studies is the Lys751Gln polymorphism (rs13181) in exon 23 [12]. The lysine to glutamine transition at position 751 in exon 23 may affect different protein interactions, diminish the activity of TFIIH complexes, and alter the genetic susceptibility to cancer [13].

Genetic variant in XPD Lys751Gln had been demonstrated to be associated with some cancers risk in different meta-analysis, such as esophageal cancer, gastric cancer, colorectal cancer, breast cancer, prostate cancer, lung cancer and bladder cancer [14–23]. However, due to an insufficient number of publications, they did not calculate pooled odds ratios (ORs) of digestive tract cancers comprehensively. In consideration of the extensive role of XPD in digestive tract cancers, we performed a meta-analysis of all 37 eligible case–control studies: oral cancer, esophageal cancer, gastric cancer, colorectal cancer, to derive a more precise association of XPD Lys751Gln polymorphism and different types of digestive tract cancers risk.

Materials and Methods

Identification of eligible studies

Using PubMed, we identified all published case–control studies which investigated the association between the XPD Lys751Gln polymorphism and digestive tract cancers risk using a retrieving query formulation "(XPD or ERCC2) polymorphisms AND (colorectal cancer OR gastric cancer OR esophageal cancer OR oral cancer)". The digestive tract cancers in this article refer to oral cancer, esophageal cancer, gastric cancer and colorectal cancer. We also searched references in published articles and reviews on this topic in PubMed. Eligible studies had to meet the following criteria: (a) only case-control designs were considered, (b) The study explored the correlation between different types of digestive tract cancers and XPD Lys751Gln polymorphism. Major exclusion criteria were (a) no control population, (b) no available genotype frequency. (c) Genotypic distribution of the controls was not in agreement with Hardy-Weinberg equilibrium (HWE). (d) Duplication of the previous publications, the largest or most recent publication was selected.

Data Extraction

Information was carefully extracted from all eligible publications independently by two authors according to the inclusion criteria listed above. If the two pieces of typed data were different, a third investigator would be asked to check and to make sure all data were right. The following information was extracted from each study: first author, year of publication, country of study population, ethnicity, source of controls, number of cases and controls with different genotypes and HWE (Table 1).

Table 1. Cont.

| Study | Year | Ethnicity | Source of controls | Cases | Controls | Genotypes | N | Genotypes | N | P for HWE |
|-------|------|-----------|--------------------|-------|----------|-----------|---|-----------|---|----------|
| Camilla | 2006 | Asians | PB | 105 | 43 | 6 | 47 | 48 | 15 | 0.44 |
| Mariana | 2006 | European | PB | 740 | 387 | 55 | 298 | 22 | 66 | 0.18 |
| Sybella | 2006 | European | PB | 156 | 58 | 76 | 76 | 22 | 75 | 0.48 |
| Victor | 2006 | European | PB | 357 | 138 | 130 | 318 | 49 | 145 | 0.92 |
| Minna | 2007 | European | PB | 305 | 251 | 84 | 112 | 48 | 3 | 0.86 |
| Chih-Ching | 2007 | Asians | HB | 717 | 602 | 3 | 112 | 4 | 3 | 0.05 |
| Rikke | 2007 | European | PB | 396 | 160 | 6 | 117 | 4 | 3 | 0.04 |
| Tomas | 2009 | European | PB | 100 | 56 | 33 | 178 | 11 | 58 | 0.02 |
| Wang | 2010 | Asians | HB | 302 | 138 | 34 | 31 | 112 | 4 | 3 | 0.07 |
| Jelonek | 2010 | European | PB | 123 | 54 | 47 | 47 | 22 | 66 | 0.88 |
| Canbay | 2011 | European | PB | 79 | 31 | 37 | 11 | 287 | 152 | 0.92 |

HB: hospital based. PB: population based.

Overall analysis and subgroup analysis does not include these studies' data.

PLOS ONE | www.plosone.org 3 May 2014 | Volume 9 | Issue 5 | e96301
statistic indicated a lack of heterogeneity across studies, allowing for the use of the fixed-effects model (the Mantel-Haenszel method) [25]. If P value less than 0.05 was considered as having heterogeneity, the results can not be pooled together and discussed. The risks ORs of digestive tract cancers associated with the XPD Lys751Gln polymorphism were estimated for each study. The pooled ORs were evaluated on co-dominant model (Lys/Gln vs. Lys/Lys, Gln/Gln vs. Lys/Lys), dominant model (Gln/Gln + Lys/Gln vs. Lys/Lys), recessive model (Gln/Gln vs. Lys/Gln+Lys/Lys), respectively. Subgroup analyses were performed by cancer types, ethnicity and source of controls. The publication bias was diagnosed by the funnel plot, in which the standard error of log (OR) of each study was plotted against its log (OR). Funnel plot asymmetry was assessed by Egger’s linear regression test. The significance of the intercept was determined by the t test suggested by Egger (P<0.05 was considered representative of statistically significant publication bias) [26]. All the statistical tests were performed with STATA version11.0 (Stata Corporation, College Station, TX, USA).

**Results**

**Study characteristic**

A total of 107 potential relevant studies were retrieved through PubMed (Figure 1). After carefully reviewing, 40 eligible case-control studies (3 studies not consistent with HWE were also...
shown) on the relationship between XPD Lys715Gln polymorphism and digestive cancers risk were involved in this meta-analysis, including 4 oral cancer studies [62–65], 13 esophageal cancer studies [27–39], 12 gastric cancer studies [36,40–50] and 11 colorectal cancer studies [51–61]. As shown in Table 1, 17 studies were conducted in Asians, 20 studies in Europeans. In addition, there were 18 hospital-based studies, 19 population-based studies. Diverse genotyping methods were used, including PCR-RFLP, PCR-SSCP, Taqman, Real-time PCR and SEB PCR. All studies indicated that the genotypic distribution of the controls were consistent with HWE.

Meta-analysis

Table 2 lists the main results of the meta-analysis for XPD Lys715Gln: having the Gln/Gln genotype is a risk factor for digestive tract cancers: GlnGln vs. LysLys: OR = 1.12, 95% CI = 1.01–1.24, \( P = 0.029 \), \( P_{\text{heterogeneity}} = 0.133 \). \( I^2 = 20.9\% \) (Figure 2). We did not find any significant association between the other genetic models and digestive tract cancers. The results of stratified analysis by cancer type, source of controls and ethnicity were shown in Table 2. The Gln/Gln vs. Lys/Lys genotype had an elevated risk in Asian population (OR = 1.28, 95% CI = 1.01–1.63, \( P = 0.045 \), \( P_{\text{heterogeneity}} = 0.287 \), \( I^2 = 14.2\% \); Figure 3). High heterogeneity was found in esophageal cancer and hospital-based studies, so the results can not be pooled together. In addition, the results did not suggest any association between XPD Lys715Gln polymorphism and digestive cancers susceptibility for all genetic models in European individuals or in population-based studies overall.

Sensitivity analysis

In the sensitivity analysis, when each particular study had been removed meta-analyses were conducted repeatedly. The corresponding pooled ORs were not qualitatively altered with or without this study. As shown in Figure 4, the most influencing single study on the overall pooled OR estimates seemed to be the one conducted by Mariana et al, which had a relatively large sample size. However, after the removal of the study, the result of the meta-analysis did not been influenced significantly: Gln/Gln vs. Lys/Lys: OR = 1.17, 95% CI: 1.05–1.30, indicating high stability of our results.

Heterogeneity analysis

There was moderate heterogeneity among these studies in GlnGln+GlnLys vs. LysLys comparisons and Gln/Gln vs. Lys/Lys. We explored the source of heterogeneity for dominant model by cancer type, ethnicity, source of control, and found that esophageal cancer and hospital-based studies contributed to substantial heterogeneity (Table 3). One reason may be that hospital-based studies had relatively small samples and were more prone to random error and false positive or negative results. Furthermore, it is very likely that
the heterogeneity in esophageal studies and hospital-based studies are related since hospital-based studies predominate among the esophageal studies.

Publication Bias

Begg’s rank correlation method and Egger’s weighted regression method were used to assess publication bias. There was no evidence of publication bias in XPD Lys751Gln (Begg’s test \( P = 0.284 \), Egger’s test \( P = 0.324 \), \( t = 1.00 \), 95% CI = 0.41–1.21). We present funnel plot for ORs of Gln/Gln versus Lys/Lys (Figure 3).

Discussion

XPD plays a crucial role in NER, which is significant in the elimination of certain DNA cross-links, ultraviolet (UV) photolysis, and bulky chemical adducts. The XPD protein possesses both single-strand DNA-dependent ATPase and 5'-3' DNA helicase activities, which is essential for NER pathway and transcription [66]. Genetic variation in XPD may contribute to impaired DNA repair capacity and increased cancer risk. The Lys to Gln change at position 751 of XPD results in complete changes about the charge configuration of the amino acid, which affects the interactions of XPD protein and its helicase activator [67]. To date, a number of epidemiological studies have been conducted to evaluate the role of Lys751Gln polymorphism on several cancer risks, but the results remain controversial. As far as we know, several previous meta-analyses on XPD Lys751Gln polymorphism and cancer risk have been performed, such as gastric cancer, colorectal cancer, esophageal cancer, breast cancer and bladder cancer [14–23]. But to date, there is no meta-analysis on the association between digestive tract cancers risk and XPD Lys751Gln polymorphism. In order to derive a more precise estimation of relationship, we performed this meta-analysis of 37 studies, including 9027 cases and 16072 controls.

Through analyzing genotypes from the 37 eligible studies, we found the Gln/Gln genotype carries might be at potential risk to digestive tract cancers. The Lys to Gln variation on position 751 of XPD resulted in complete changes about the electronic configuration of the amino acid, which affected the interactions of XPD protein and its helicase activator [68]. Digestive tract cancers represent a homogenous group of malignancies in some ways. Different primary sites of digestive tract cancers have some shared risk factors. For example, except for smoking and alcohol consumption, eating rough, spicy, hot and non-digestible food is likely to damage the digestive tract tissue. In addition, H. Pylori infection is a major cause of gastric cancer, while nitrates derived from red meat and processed meat is a key risk factor for esophageal cancer and colorectal cancer. Such risk factors and their tissue specificity raise the possibility that the XPD polymorphism may be associated with digestive tract cancers risk. The functional XPD Lys751Gln polymorphism resulting in decreased activity of XPD protein may increase risk of digestive tract cancers on the basis of damage tissue.
Table 2. Pooled ORs and 95% CIs of stratified meta-analysis.

| Stratification           | No. case/control | GlnGln vs LysLys | OR (95%CI) | P  | GlnLys vs LysLys | OR (95%CI) | P  | GlnGln+GlnLys vs LysLys | OR (95%CI) | P  | GlnGln vs GlnLys+LysLys | OR (95%CI) | P  |
|--------------------------|------------------|------------------|------------|----|------------------|------------|----|------------------------|------------|----|------------------------|------------|----|
| Total                    | 40(9773/17185)   | 1.12(1.01,1.24)  | 0.029      | 1.04(0.98-1.11) | 0.194 | 1.06(1.00,1.12)  | 0.064 | 1.09(0.99,1.20)  | 0.072     |
| Cancer type              |                  |                  |            |    |                  |            |    |                        |            |    |                        |            |    |
| Colorectal cancer        | 11(3378/5319)    | 0.99(0.3,1.17)   | 0.870      | 0.99(0.89,1.09) | 0.776 | 0.99(0.90,1.09)  | 0.790 | 1.00(0.85,1.17) | 0.954     |
| Gastric cancer           | 12(2542/5905)    | 1.05(0.85,1.29)  | 0.639      | 0.97(0.85,1.10) | 0.612 | 0.98(0.86,1.11)  | 0.744 | 1.05(0.87,1.28) | 0.630     |
| Esophageal cancer        | 13(3096/5173)    | 1.29(1.08,1.54)  | 0.005      | 0.90(0.81,1.00) | 0.056 | 0.91(0.77,1.07)  | 0.235 | 0.84(0.66,1.07) | 0.159     |
| Oral cancer              | 4(757/688)       | 1.50(0.96,2.35)  | 0.078      | 0.88(0.60,1.30) | 0.518 | 0.85(0.56,1.28)  | 0.430 | 0.72(0.47,1.12) | 0.147     |
| Ethnicity                |                  |                  |            |    |                  |            |    |                        |            |    |                        |            |    |
| Asian                    | 18(4669/6521)    | 1.28(1.01,1.63)  | 0.045      | 1.05(0.95,1.17) | 0.340 | 1.08(0.98,1.19)  | 0.133 | 1.21(0.96,1.53) | 0.110     |
| European                 | 22(5104/10564)   | 1.09(0.97,1.22)  | 0.144      | 1.04(0.96,1.12) | 0.363 | 1.05(0.97,1.13)  | 0.232 | 1.07(0.96,1.19) | 0.210     |
| Source of control        |                  |                  |            |    |                  |            |    |                        |            |    |                        |            |    |
| HB                       | 20(5290/7075)    | 1.19(1.01,1.40)  | 0.038      | 1.02(0.93,1.12) | 0.703 | 1.02(0.89,1.16)  | 0.787 | 1.16(0.95,1.41) | 0.140     |
| PB                       | 20(4483/10010)   | 1.08(0.94,1.23)  | 0.267      | 1.06(0.98,1.16) | 0.157 | 1.07(0.98,1.15)  | 0.122 | 1.04(0.92,1.18) | 0.715     |

NO: involved studies' number; Gln Lys vs LysLys: Heterozygote comparison; GlnGln vs LysLys: Homozygote comparison; GlnGln+GlnLys vs LysLys: Dominant model; GlnGln vs GlnLys+LysLys: Recessive model; Random model was chosen for data pooling when P>0.10 and/or I²>50%; otherwise fixed model was used.

*the results were excluded due to potential heterogeneity.

doi:10.1371/journal.pone.0096301.t002
In stratified analysis by cancer type, we found that all genetic models did not appear to have an effect on the risks of esophageal, gastric, colorectal and oral cancers. This was different from Ling Yuan's and Wu XB's studies [69,70]. However Bo Chen et al. [71] detected that Gln/Gln genotype carriers might have an increased risk of gastric cancer in the Helico-bacter pylori (H.pylori)-positive population, but not in the Helico-bacter pylori (H. pylori)-negative population. One possible explanation is that the modulation of digestive tract cancers risk may depend not only on a single gene/single nucleotide polymorphism, but also on a joint effect of multiple polymorphisms within different genes or pathways, or on close interaction between polymorphisms and environmental factor. The other is that Helicobacter pylori infection is one of the clear etiologies of gastric cancer and maybe there is some relationship between helicobacter pylori and the polymorphic loci. In the subgroup of ethnicity, we found significant association

![Figure 4. Influence analysis of the summary odds ratio coefficients on the association between XPD Lys751Gln homozygote comparison with digestive tract cancers risk.](image)

In stratified analysis by cancer type, we found that all genetic models did not appear to have an effect on the risks of esophageal, gastric, colorectal and oral cancers. This was different from Ling Yuan's and Wu XB's studies [69,70]. However Bo Chen et al. [71] detected that Gln/Gln genotype carriers might have an increased risk of gastric cancer in the Helico-bacter pylori (H.pylori)-positive population, but not in the Helico-bacter pylori (H. pylori)-negative population. One possible explanation is that the modulation of digestive tract cancers risk may depend not only on a single gene/single nucleotide polymorphism, but also on a joint effect of multiple polymorphisms within different genes or pathways, or on close interaction between polymorphisms and environmental factor. The other is that Helicobacter pylori infection is one of the clear etiologies of gastric cancer and maybe there is some relationship between helicobacter pylori and the polymorphic loci. In the subgroup of ethnicity, we found significant association

**Table 3. Heterogeneity test.**

| Stratification       | Gln Gln vs.LysLys | Gln Lys vs.LysLys | GlnGln+GlnLys vs.LysLys | GlnGln vs. GlnLys+LysLys |
|----------------------|-------------------|-------------------|--------------------------|--------------------------|
|                      | Ph, I² (%)        | Ph, I² (%)        | Ph, I² (%)                | Ph, I² (%)                |
| Digestive cancers    | 0.133, 20.9       | 0.064, 27.6       | 0.011, 38.3               | 0.385, 4.9                |
| Cancer type          |                   |                   |                          |                          |
| Esophageal cancer    | 0.033, 46.6       | 0.022, 49.3       | 0.004, 58.2               | 0.084, 37.4               |
| Gastric cancer       | 0.930,0           | 0.554,0           | 0.698,0                   | 0.864,0                   |
| Colorectal cancer    | 0.310,13          | 0.470,0           | 0.328,12.2                | 0.387,5.9                 |
| Oral cancer          | 0.529, 0          | 0.095, 52.5       | 0.052,61.1                | 0.795, 0                  |
| Source of control    |                   |                   |                          |                          |
| Hospital-based       | 0.043,39.6        | 0.051,38.2        | 0.006,51.6                | 0.180,23.2                |
| Population-based     | 0.550,0           | 0.243,17.3        | 0.184,22.3                | 0.715,0                   |
| Ethnicity            |                   |                   |                          |                          |
| Asian                | 0.287,14.2        | 0.174,24.2        | 0.057,38.0                | 0.353,8.6                 |
| European             | 0.137, 26.3       | 0.074,334         | 0.029,41.2                | 0.414,3.4                 |

*Ph: P-value of Q-test for heterogeneity identification; I² index: a quantitative measurement which indicates the proportion of total variation in study estimates that is due to between-study heterogeneity.*

doi:10.1371/journal.pone.0096301.t003
between XPD Gln/Gln polymorphism and increased risks of digestive tract cancers in Asians but not in European. We think ethnic differences and diverse live environment may partly explain the phenomenon. Furthermore, we believed differences in diet, such as food structure and cooking way, were the main cause of this result. In addition, it was also likely that the observed ethnic differences may be due to chance because studies with small sample size may have insufficient statistical power to detect a slight effect or may have generated a fluctuated risk estimate [72].

In summary, this meta-analysis indicated that XPD Lys751Gln polymorphism, individuals carrying the variant homozygote Gln/Gln may increase the susceptibility of digestive tract cancers. And, significant associations were detected among Asians population. It should be noted explicitly; first, the effective sample size is much smaller for the Gln/Gln vs. Lys/Lys analyses than the other genetic models and therefore it is more prone to random error and false positive results; second, the results for GlnGln vs. GlyLys + LysLys, while not statistically significant (OR 1.09, 95% CI = 0.99–1.20, \( P = 0.072, P_{\text{heterogeneity}} = 0.385 \)), strengthen our conclusion about which genetic model is most appropriate. Large-scale case-control and population-based association studies are warranted to validate the risk identified in the current meta-analysis and investigate the potential gene-gene and gene-environment interactions on digestive tract cancers risk.

Supporting Information

Checklist S1
(DOC)

Author Contributions

Conceived and designed the experiments: HND NNG YQS TC LJZ. Performed the experiments: HND BS QZ ZPC KL TC LJZ. Analyzed the data: HND ZPC LJZ QZ. Contributed reagents/materials/analysis tools: HND ZPC LJZ QZ. Wrote the paper: HND ZPC NNG. Designed the software used in analysis: HND NNG ZPC QZ.

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