Associations between polymorphisms in genes of base excision repair pathway and lung cancer risk

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Background: The correlation between at-risk polymorphisms in genes of base excision repair (BER) pathways and lung cancer (LC) risk was newly considered but still not clear, a systematic review and updated meta-analysis was performed in the current study.

Methods: We identified and recorded the eligible publications from Google Scholar, PubMed, Medicine and Web of Science. For all calculates, odds ratios (ORs) and 95% confidence intervals (CIs) were applied to estimate the potential relationship between these genetic variants and LC risk. Subsequently, Begg’s funnel plot and Egger’s test were used to appraising the publication bias.

Results: A total of 202 case-control studies extracted from 116 publications were enrolled. Firstly, we analyzed six polymorphisms in XRCC1, the overall analysis results of homozygote and recessive models illustrated that rs3213245 polymorphism was remarkably linked to an upgrade LC risk. Then, in the subgroup analysis stratified by ethnicity, we uncovered a meaningfully raised risk of LC in Asian population in homozygote and recessive models for rs3213245 polymorphism, as well as in the allelic contrast, heterozygous and dominant models for rs915927 polymorphism. For APEX1-rs1760944 polymorphism, the overall analysis suggested a significantly decreased risk. Another gene was OGG1, we identified a significantly upregulated risk in recessive model of OGG1-rs1052133 polymorphism for LC.

Conclusions: XRCC1-rs3213245 and OGG1-rs1052133 polymorphisms are risk factors for LC, while APEX1-rs1760944 polymorphism is a protective factor.

Keywords: Lung cancer (LC); risk; base excision repair pathway (BER pathway); polymorphism

Introduction

Lung cancer (LC) is the most prevalent cancer and the main cause of cancer-specific death around the world, with a poor prognosis and a high mortality, there are about 228,150 new cases and 142,670 deaths of LC around the USA in 2019 (1). Non-small cell lung cancer (NSCLC) comprises 85% of all lung cancer, while small cell lung cancer (SCLC) accounts for 15–17% (2). The underlying mechanisms of LC remain unclear, however, a serious of studies indicated that tobacco smoking has been a high-risk factor (3-5). At the first years of this century, most evidence supported the notion that exposure to environmental carcinogens (6-9), including cigarette and electronic cigarette (10,11), result in alterations to the structural integrity of DNA and DNA lesions that may lead to mutations in oncogenes and tumor suppressor genes, thus initiating tumorigenesis (12-17).
The correlation between at-risk polymorphisms in genes of DNA repair pathways and LC risk was newly considered, reported from environmentally exposed workers or smokers (18-21). DNA repair pathway is a complex molecular network, which could continuously monitor and correct incorrect nucleotides after exposure to carcinogens, such as ultraviolet ray and benzene-based pollutants (22-24). There are several DNA repair pathways, which could minimize the mutant and toxic DNA sequence, including nucleotide excision repair (NER) pathway, base excision repair (BER) pathway, homologous recombination (HR) pathway, mismatch repair (MMR) pathway, as well as non-homologous end-joining (NHEJ) pathway. Among them, the BER is an essential pathway involved in genome stability maintaining and thus in human diseases’ prevention, ensuring to correct the abnormal DNA base modifications and base loss [such as apurinic/apyrimidinic (AP) sites] (25-27).

Recently, increasing studies indicated that DNA repair capacity could be influenced by genetic polymorphism in the BER pathway genes, which might also alter protein function that subsequently contributes to the unstable of gene sequence and cancer risk (28,29). Till now, numerous studies have focused on the potential relationship between genetic variants in BER pathway gene and LC risk, however, the results are discordant. In addition, many studies only focused on a few polymorphisms or neglected non-coding region genes, while other studies performed on a small number of cases. After all, we exhaustively extracted all eligible studies reported on genetic variations of BER pathway gene related to LC risk, and performing the current systematic review and meta-analysis to illustrated the overall relationship.

Methods

Obtain BER pathway gene set from KEGG

In order to obtain the whole gene set of BER pathway, we searched it on Kyoto Encyclopedia of Genes and Genomes (KEGG) website. Thirty-five genes in BER pathway were provided from online KEGG signaling database (http://software.broad institute.org/gsea/msigdb/gene set_ page.jsp?geneSet Name=KEGG_BASE_EXCISION_REPAIR&keywords=BASE%20EXCISION%20REPAIR).

Study description

The resent study was conducted to reveal the correlation between genetic variants in BER pathway and LC risk. In current work, PubMed, Google Scholar, Medicine, EMbase and Web of Science databases were used to comprehensively enrolled and recorded all eligible publications. The retrieve formula was: (‘gene name’ OR ‘abbreviation of gene name’) AND (‘cancer’ OR ‘tumor’ OR ‘carcinoma’ OR ‘neoplasms’) AND (‘polymorphism’ OR ‘mutation’ OR ‘variant’ OR ‘SNP’ OR ‘genotype’). We also reviewed each reference of eligible articles, avoiding to missing any additional conform-to-criteria study. The entire retrieval was finished on October 5th, 2019. All enrolled studies were published in primary literature without any replication one. In addition, for these polymorphisms, whose eligible case-control studies are less than three will be excluded.

Enrolled criteria and exclusion criteria

There are several criteria which should be conformed are: (I) assessing whether the gene polymorphisms of BER pathway affect LC risk; (II) studies with specific case group and control group; and (III) genotype frequencies could be obtained directly or after calculating. Meanwhile, some other criteria should not be touched: (I) lacking control group, such as case-only study or review and (II) lacking sufficient genotype data.

Extraction of basic data

The ground on the enrollment standard mentioned above, all the basic data was extracted by two independent reviewers, accompany with an argument, discussion and reach an agreement. In each publication, several items were recorded, including the name of the first author, year of publication, ethnicity, source of control, number of each genotype group, and so on. Finally, we also estimated the quality of each enrolled study with the help of Newcastle-Ottawa Scale (NOS).

Statistical analysis

Hardy-Weinberg equilibrium (HWE) in the control group was tested, and P>0.05 means that the study does not deviate from HWE (30). Strength of the links between polymorphisms in BER pathway gene and LC risk was evaluated through calculating ORs and 95% CIs in five genetic models (W present for wild type allele; M present for mutant allele): allele contrast model (M vs. W), dominant contrast model (MM + MW vs. WW), recessive
contrast model (MM vs. MW + WW), homozygous contrast model (MM vs. WW), and heterozygous contrast model (MW vs. WW). After that, subgroup analysis stratified by different items were also conducted. I² statistics were used to evaluate the heterogeneity assumption between studies in each calculating group, aim to obtain the quantified inconsistency caused by heterogeneity (31). Among these studies, I² value was regarded as a significant heterogeneity if it is higher than 50% (32), and random-effect model was performed the calculated the pooled OR and 95% CI; on the contrast, fixed-effect model will be hireling (33). To confirm the veracity of result, we use sensitivity analysis to assess the stability of results, use Begg’s funnel plot and Egger’s test to appraise any publication bias (34). We use STATA (version 12.0; STATA Corp.) to calculate all the results, and P<0.05 was regarded as statistically significant.

Results

The studies and meta-analysis data pool

After searching in diverse databases, we retrieved 116 publications comprising 202 case-control studies that met inclusion and exclusion criteria (at least three eligible case-control studies should be enrolled for each polymorphism). These publications concerned about five BER pathway gene, including XRCC1, Apurinic/Apyrimidinic Endodeoxyribonuclease 1 (APEX1), DNA Ligase 1 (LIG1), 8-Oxoguanine DNA Glycosylase (OGG1) and MutY DNA Glycosylase (MUTYH) gene. In Table 1, characteristics and genotype frequency distributions of all enrolled studies for BER pathway gene were showed, including XRCC1-rs1799782/rs25487 (35-60), rs25489/rs3213245 (61-85), rs3547/rs915927 (86-90), PARP1-rs1136410 (87, 91-94), APEX1-rs1130409/rs1760944/rs2307486 (42,43,47,74,76,79,80,89,92,95-101), LIG1-rs156641/rs20579/rs20581/rs3730931/rs439132 (64,71,102,103), OGG1-rs1052133 (43,47,49,70,72,74,84,85,89,92,104-126) and MUTYH-rs3219489 (104,115,118,127) polymorphisms, and the selection process of current work was described in Figure 1. For this study, we performed each process along with PRISMA 2009 checklist (Table 2), and with the aid of NOS, we also assessed each enrolled study, most of the enrolled study is higher than 7 star, which represented the good quality (129).

Meta-analysis

XRCC1 polymorphisms and LC risk

We investigated six polymorphisms in XRCC1 gene and LC risk, including rs1799782, rs25487, rs25489, rs3213245, rs3547 and rs915927 polymorphisms (Table 3). Overall, rs3213245 polymorphism was observed associated with a significantly raised susceptibility of LC in homozygote contrast model and recessive contrast model (MM vs. WW: OR 2.023, 95% CI: 1.452–2.819, P=3.124×10⁻⁶, Figure 2A; MM vs. MW + WW: OR 1.926, 95% CI: 1.396–2.656, P=6.468×10⁻⁷, Figure 2B), while for other genetic polymorphisms, overall analyses uncovered no remarkable association. In addition, for rs3213245 polymorphism, in the ethnicity subgroup analysis, a meaningful upward risk of LC for Asian population was also uncovered in homozygote and recessive models. While for the subgroup analysis by source of control subgroup, we uncovered a remarkable upgrade risk of LC for H-B groups in allelic contrast, heterogeneous and dominant models. Furthermore, for rs915927 polymorphism, we also performed the subgroup analysis in different ethnicity and source of control, and identified the raised risk for Asian, H-B group in allelic contrast model, heterozygous model, as well as dominant model. For rs25487 polymorphism, overall analysis suggested a null association. We identified that HWE (N) group was associated with LC risk in allelic, homozygote, and recessive models, suggesting potential bias existed. After removing the HWE (N) studies from the pooled analyses, and the final results also suggested a negative result for XRCC1-rs25487 polymorphism.

APEX1 polymorphism and LC risk

For rs1760944 polymorphism, overall analysis suggested a sharp reduced risk of LC in allelic, homozygote and recessive models (M vs. W: OR 0.851, 95% CI: 0.786–0.922, P=7.243×10⁻⁵, Figure 2C; MM vs. WW: OR 0.705, 95% CI: 0.598–0.832, P=3.409×10⁻⁵; and MM vs. MW + WW: OR 0.780, 95% CI: 0.684–0.889, P=1.927×10⁻⁴, Table 3).

OGG1 polymorphism and LC risk

For OGG1-rs1052133 polymorphism, the recessive model showed an increased risk overall group (MM vs. MW + WW: OR 1.157, 95% CI: 1.071–1.249, P=2.119×10⁻⁵, Figure 2D). In addition, when the stratification analysis of Asian subgroup, we illustrated a significantly increased risk of LC in allelic contrast model and homozygote model (Table 3).

Other gene polymorphism and LC risk

While for other polymorphisms in genes the BER pathway, such as LIG1-rs156641, MUTYH-rs3219489, we failed to identify any significant association.
| Gene-polymorphism | First author | Year | Ethnicity | Source of control | Case WW | Case MW | Case MM | Control WW | Control MW | Control MM | Y (HWE) |
|------------------|-------------|------|-----------|------------------|--------|--------|--------|-----------|-----------|-----------|--------|
| XRCC1-rs1799782  | David-Beabes et al. | 2001 | African | P-B | 142 | 10 | 2 | 205 | 36 | 2 | Y |
|                  | David-Beabes et al. | 2001 | Caucasian | P-B | 158 | 22 | 0 | 407 | 54 | 0 | Y |
|                  | Chen et al. | 2002 | Asian | P-B | 48 | 44 | 11 | 57 | 40 | 5 | Y |
|                  | Ratnasinghe et al. | 2003 | Asian | P-B | 52 | 47 | 9 | 85 | 104 | 21 | Y |
|                  | Shen et al. | 2005 | Asian | P-B | 65 | 41 | 12 | 64 | 40 | 8 | Y |
|                  | Chan et al. | 2005 | Asian | H-B | 50 | 22 | 3 | 79 | 67 | 16 | Y |
|                  | Schneider et al. | 2005 | Caucasian | H-B | 389 | 53 | 4 | 544 | 75 | 3 | Y |
|                  | Hung et al. | 2005 | Caucasian | H-B | 1878 | 259 | 10 | 1828 | 292 | 12 | Y |
|                  | Hu et al. | 2005 | Asian | H-B | 335 | 311 | 64 | 339 | 308 | 63 | Y |
|                  | Zienolddiny et al. | 2006 | Caucasian | P-B | 309 | 26 | 1 | 368 | 35 | 2 | Y |
|                  | Landi et al. | 2006 | Caucasian | H-B | 263 | 32 | 1 | 262 | 53 | 1 | Y |
|                  | Matullo et al. | 2006 | Caucasian | Mixed | 98 | 16 | 2 | 951 | 141 | 2 | Y |
|                  | Hao et al. | 2006 | Asian | P-B | 524 | 409 | 91 | 572 | 459 | 87 | Y |
|                  | De Ruyck et al. | 2007 | Caucasian | H-B | 101 | 8 | 1 | 93 | 17 | 0 | Y |
|                  | Pachouri et al. | 2007 | Caucasian | P-B | 40 | 39 | 24 | 52 | 47 | 23 | N |
|                  | Improta et al. | 2008 | Caucasian | P-B | 78 | 9 | 7 | 104 | 17 | 0 | Y |
|                  | Yin et al. | 2008 | Asian | H-B | 120 | 98 | 23 | 119 | 109 | 21 | Y |
|                  | Li et al. | 2008 | Asian | H-B | 184 | 136 | 30 | 196 | 133 | 21 | Y |
|                  | Chang et al. | 2009 | African | P-B | 221 | 34 | 0 | 248 | 31 | 1 | Y |
|                  | Yin et al. | 2009 | Asian | H-B | 29 | 21 | 1 | 28 | 38 | 8 | Y |
|                  | Chang et al. | 2009 | Caucasian | P-B | 89 | 23 | 1 | 223 | 66 | 10 | Y |
|                  | Tanaka et al. | 2010 | Asian | H-B | 28 | 15 | 7 | 25 | 23 | 2 | Y |
|                  | Buch et al. | 2011 | Caucasian | H-B | 682 | 36 | 2 | 839 | 83 | 6 | N |
|                  | Mei et al. | 2013 | Asian | P-B | 138 | 90 | 23 | 155 | 119 | 27 | Y |
|                  | Du et al. | 2014 | Asian | P-B | 68 | 33 | 19 | 88 | 21 | 11 | N |
|                  | Yoo et al. | 2014 | Asian | P-B | 281 | 249 | 67 | 268 | 255 | 54 | Y |
|                  | Çatånş et al. | 2015 | Caucasian | P-B | 89 | 3 | 10 | 197 | 22 | 3 | N |
|                  | Han et al. | 2015 | Asian | P-B | 99 | 90 | 21 | 106 | 87 | 17 | Y |
|                  | Zhu et al. | 2015 | Asian | P-B | 180 | 137 | 3 | 111 | 206 | 29 | N |
|                  | Singh et al. | 2016 | Caucasian | P-B | 256 | 72 | 2 | 267 | 55 | 3 | Y |
| XRCC1-rs25487    | Divine et al. | 2001 | Caucasian | H-B | 82 | 61 | 29 | 65 | 64 | 14 | Y |
|                  | David-Beabes et al. | 2001 | African | P-B | 105 | 46 | 3 | 164 | 70 | 9 | Y |
|                  | Ratnasinghe et al. | 2001 | Asian | P-B | 59 | 40 | 8 | 117 | 80 | 11 | Y |
|                  | David-Beabes et al. | 2001 | Caucasian | P-B | 87 | 76 | 17 | 186 | 217 | 58 | Y |
|                  | Chen et al. | 2002 | Asian | P-B | 55 | 43 | 5 | 52 | 40 | 7 | Y |
|                  | Park et al. | 2002 | Asian | P-B | 100 | 75 | 17 | 81 | 48 | 6 | Y |
|                  | Misra et al. | 2003 | Caucasian | P-B | 151 | 140 | 24 | 154 | 130 | 29 | Y |
|                  | Zhou et al. | 2003 | Caucasian | P-B | 467 | 488 | 156 | 551 | 545 | 143 | Y |
|                  | Harms et al. | 2004 | Caucasian | H-B | 59 | 42 | 9 | 56 | 55 | 8 | Y |
|                  | Vogel et al. | 2004 | Caucasian | H-B | 117 | 104 | 35 | 108 | 121 | 40 | Y |
|                  | Ito et al. | 2004 | Asian | H-B | 98 | 66 | 14 | 253 | 169 | 26 | Y |

Table 1 (continued)
| Gene-polymorphism | First author | Year | Ethnicity | Source of control | Case WW | MW | MM | Control WW | MW | MM | Y (HWE) |
|-------------------|--------------|------|-----------|------------------|--------|----|----|-----------|----|----|---------|
| Popanda et al.    | 2004         | Caucasian | H-B     | 186 214 63      | 171    | 222 | 67 | Y         |
| Liu et al.        | 2004         | Caucasian | H-B     | 400 397 138     | 551    | 539 | 143 | Y         |
| Li et al.         | 2005         | Asian    | H-B     | 22 20 8         | 27     | 21  | 2  | Y         |
| Shen et al.       | 2005         | Asian    | P-B     | 72 40 4         | 54     | 51  | 4  | Y         |
| Chan et al.       | 2005         | Asian    | H-B     | 40 31 4         | 90     | 61  | 11 | Y         |
| Schneider et al.  | 2005         | Caucasian | H-B     | 199 198 49      | 264    | 280 | 78 | Y         |
| Hu et al.         | 2005         | Asian    | H-B     | 378 284 48      | 370    | 282 | 58 | Y         |
| Zhang et al.      | 2005         | Asian    | H-B     | 535 363 102     | 531    | 380 | 89 | Y         |
| Hung et al.       | 2005         | Caucasian | H-B     | 844 951 254     | 874    | 881 | 260| Y         |
| Zienolddiny et al.| 2006         | Caucasian | P-B     | 129 171 31      | 151    | 186 | 54 | Y         |
| Hao et al.        | 2006         | Asian    | H-B     | 566 376 82      | 585    | 432 | 101| Y         |
| Matullo et al.    | 2006         | Caucasian | Mixed  | 51 58 7         | 484    | 482 | 128| Y         |
| De Ruyck et al.   | 2007         | Caucasian | H-B     | 38 53 18        | 46     | 50  | 13 | Y         |
| Yin et al.        | 2007         | Asian    | H-B     | 138 65 2        | 132    | 52  | 9  | Y         |
| Pachouri et al.   | 2007         | Caucasian | P-B     | 53 38 12        | 35     | 70  | 17 | Y         |
| López-Cima et al. | 2007         | Caucasian | H-B     | 222 219 75      | 217    | 234 | 82 | Y         |
| Improta et al.    | 2008         | Caucasian | P-B     | 42 41 11        | 53     | 61  | 7  | N         |
| Sreeja et al.     | 2008         | Caucasian | P-B     | 78 86 47        | 102    | 80  | 29 | N         |
| Li et al.         | 2008         | Asian    | H-B     | 168 139 43      | 201    | 123 | 26 | Y         |
| Yin et al.        | 2009         | Asian    | H-B     | 31 13 1         | 36     | 15  | 1  | Y         |
| Cote et al.       | 2009         | African  | P-B     | 86 23 6         | 88     | 28  | 5  | Y         |
| Chang et al.      | 2009         | African  | P-B     | 182 69 4        | 209    | 65  | 5  | Y         |
| Chang et al.      | 2009         | Caucasian | P-B     | 54 47 12        | 155    | 127 | 16 | Y         |
| Cote et al.       | 2009         | Caucasian | P-B     | 172 159 56      | 160    | 200 | 46 | Y         |
| Li et al.         | 2011         | Asian    | H-B     | 236 193 26      | 220    | 196 | 27 | Y         |
| Kiyohara et al.   | 2012         | Asian    | H-B     | 243 171 48      | 242    | 121 | 16 | Y         |
| Natukula et al.   | 2013         | Caucasian | P-B     | 40 19 41        | 55     | 10  | 36 | N         |
| Ouyang et al.     | 2013         | Asian    | P-B     | 52 22 8         | 105    | 86  | 10 | Y         |
| Mei et al.        | 2013         | Asian    | P-B     | 142 95 14       | 145    | 126 | 30 | Y         |
| Letkova et al.    | 2013         | Caucasian | P-B     | 138 202 42      | 157    | 185 | 37 | Y         |
| Du et al.         | 2014         | Asian    | P-B     | 81 16 23        | 95     | 15  | 10 | N         |
| Sarlinova et al.  | 2014         | Caucasian | P-B     | 17 24 9         | 23     | 41  | 5  | N         |
| Uppal et al.      | 2014         | Caucasian | P-B     | 18 32 50        | 12     | 65  | 23 | N         |
| Saikia et al.     | 2014         | Caucasian | P-B     | 146 103 23      | 322    | 188 | 34 | Y         |
| Yoo et al.        | 2014         | Asian    | P-B     | 344 207 47      | 313    | 245 | 33 | Y         |
| Han et al.        | 2015         | Asian    | P-B     | 156 34 20       | 164    | 30  | 16 | N         |
| Wang et al.       | 2015         | Asian    | P-B     | 259 24 217      | 273    | 43  | 184| N         |
| Zhu et al.        | 2015         | Asian    | P-B     | 221 80 19       | 269    | 72  | 5  | Y         |
| Cătană et al.     | 2015         | Caucasian | P-B     | 43 43 16        | 112    | 86  | 24 | Y         |
| Liu et al.        | 2016         | Asian    | P-B     | 162 114 32      | 162    | 81  | 10 | Y         |
| Gene-polymorphism | First author | Year | Ethnicity | Source of control | Case WW | Case MW | Case MM | Control WW | Control MW | Control MM | Y (HWE) |
|-------------------|--------------|------|-----------|-------------------|--------|--------|--------|-----------|-----------|-----------|---------|
| XRCC1-rs25489     | Singh et al. | 2016 | Caucasian | P-B               | 93     | 186    | 51     | 79        | 176       | 70        | Y       |
|                   | Ratnasinghe et al. | 2001 | Asian     | P-B               | 83     | 20     | 3      | 177       | 32        | 0         | Y       |
|                   | Misra et al.  | 2003 | Caucasian | P-B               | 260    | 47     | 2      | 260       | 42        | 0         | Y       |
|                   | Vogel et al.  | 2004 | Caucasian | H-B               | 229    | 26     | 1      | 241       | 28        | 0         | Y       |
|                   | Shen et al.   | 2005 | Asian     | P-B               | 76     | 30     | 5      | 81        | 28        | 1         | Y       |
|                   | Schneider et al. | 2005 | Caucasian | H-B               | 404    | 40     | 2      | 562       | 60        | 0         | Y       |
|                   | Hung et al.   | 2005 | Caucasian | H-B               | 1901   | 181    | 6      | 1896      | 190       | 6         | Y       |
|                   | Zienolddiny et al. | 2006 | Caucasian | P-B               | 296    | 31     | 2      | 350       | 24        | 3         | N       |
|                   | Hao et al.    | 2006 | Asian     | H-B               | 848    | 169    | 7      | 904       | 204       | 10        | Y       |
|                   | De Ruyck et al. | 2007 | Caucasian | P-B               | 105    | 4      | 0      | 96        | 14        | 0         | Y       |
|                   | De Ruyck et al. | 2007 | African   | P-B               | 37     | 53     | 19     | 40        | 52        | 18        | Y       |
|                   | Li et al.     | 2008 | Asian     | H-B               | 264    | 75     | 11     | 291       | 55        | 4         | Y       |
|                   | Hsieh et al.  | 2009 | Asian     | P-B               | 251    | 40     | 3      | 250       | 37        | 1         | Y       |
|                   | Tang et al.   | 2014 | Asian     | P-B               | 212    | 163    | 45     | 225       | 181       | 19        | N       |
|                   | Yoo et al.    | 2015 | Asian     | P-B               | 494    | 104    | 4      | 462       | 111       | 4         | Y       |
|                   | Xin et al.    | 2008 | Asian     | H-B               | 183    | 43     | 1      | 191       | 49        | 2         | Y       |
|                   | Xin et al.    | 2009 | Asian     | H-B               | 35     | 12     | 0      | 61        | 9         | 1         | Y       |
|                   | Chang et al.  | 2009 | Caucasian | P-B               | 62     | 45     | 6      | 177       | 99        | 23        | Y       |
|                   | Chang et al.  | 2009 | African   | P-B               | 114    | 104    | 37     | 126       | 122       | 32        | Y       |
|                   | Singh et al.  | 2016 | Caucasian | P-B               | 61     | 142    | 127    | 124       | 127       | 74        | N       |
|                   | Matullo et al. | 2006 | Caucasian | Mixed             | 36     | 58     | 22     | 342       | 508       | 243       | N       |
|                   | Xin et al.    | 2008 | Asian     | H-B               | 169    | 68     | 2      | 203       | 43        | 0         | Y       |
|                   | Xin et al.    | 2009 | Asian     | H-B               | 36     | 14     | 1      | 66        | 7         | 0         | Y       |
|                   | Singh et al.  | 2016 | Caucasian | P-B               | 134    | 164    | 32     | 147       | 139       | 39        | Y       |
|                   | Misra et al.  | 2003 | Caucasian | P-B               | 64     | 167    | 79     | 65        | 160       | 77        | Y       |
|                   | Ito et al.    | 2004 | Asian     | P-B               | 62     | 84     | 32     | 159       | 226       | 64        | Y       |
|                   | Popanda et al.| 2004 | Caucasian | H-B               | 135    | 235    | 89     | 118       | 233       | 106       | Y       |
|                   | Shen et al.   | 2005 | Asian     | P-B               | 30     | 61     | 26     | 37        | 61        | 15        | Y       |
|                   | Zienolddiny et al. | 2006 | Caucasian | P-B               | 117    | 67     | 80     | 138       | 60        | 122       | N       |
|                   | Matullo et al. | 2006 | Caucasian | P-B               | 33     | 56     | 27     | 309       | 526       | 259       | Y       |
|                   | De Ruyck et al. | 2007 | Caucasian | H-B               | 21     | 60     | 29     | 41        | 41        | 28        | N       |
| Gene-polymorphism | First author | Year | Ethnicity | Source of control | Case WW | Case MW | Case MM | Control WW | Control MW | Control MM | Y (HWE) |
|------------------|--------------|------|-----------|-------------------|---------|---------|---------|------------|------------|------------|--------|
| APEX1-rs1760944  | Agachan et al. | 2009 | Caucasian | P-B              | 38      | 40      | 20      | 45         | 17         | 5          | Y      |
|                  | Lu et al.     | 2009 | Asian     | H-B              | 182     | 228     | 90      | 176        | 265        | 76         | Y      |
|                  | Lo et al.     | 2009 | Asian     | H-B              | 261     | 349     | 119     | 272        | 332        | 118        | Y      |
|                  | Deng et al.   | 2010 | Asian     | P-B              | 123     | 143     | 49      | 97         | 159        | 58         | Y      |
|                  | Li et al.     | 2011 | Asian     | H-B              | 179     | 199     | 77      | 172        | 213        | 58         | Y      |
|                  | Xue et al.    | 2013 | Asian     | H-B              | 116     | 183     | 111     | 130        | 190        | 90         | Y      |
|                  | Pan et al.    | 2013 | Asian     | H-B              | 48      | 273     | 498     | 25         | 247        | 531        | Y      |
|                  | Li et al.     | 2014 | Asian     | H-B              | 2       | 11      | 3       | 50         | 46         | 14         | Y      |
|                  | Sevilya et al.| 2015 | Caucasian | H-B              | 34      | 50      | 15      | 42         | 46         | 11         | Y      |
| APEX1-rs2307486  | Lu et al.     | 2009 | Asian     | H-B              | 184     | 241     | 75      | 170        | 238        | 109        | Y      |
|                  | Lo et al.     | 2009 | Asian     | H-B              | 271     | 332     | 122     | 234        | 341        | 153        | Y      |
|                  | Li et al.     | 2011 | Asian     | H-B              | 162     | 227     | 66      | 143        | 206        | 94         | Y      |
|                  | Pan et al.    | 2013 | Asian     | H-B              | 114     | 384     | 321     | 98         | 369        | 336        | Y      |
|                  | Li et al.     | 2014 | Asian     | H-B              | 3       | 10      | 3       | 36         | 56         | 18         | Y      |
| OGG1-rs1052133   | Zienoldiny et al. | 2006 | Caucasian | P-B              | 263     | 76      | 1       | 276        | 124        | 10         | Y      |
|                  | Lo et al.     | 2009 | Asian     | H-B              | 669     | 59      | 0       | 659        | 64         | 2          | Y      |
|                  | Li et al.     | 2014 | Asian     | H-B              | 11      | 2       | 0       | 103        | 7          | 0          | Y      |
|                  | Kohno et al.  | 1998 | Asian     | Mixed            | 16      | 19      | 10      | 15         | 20         | 7          | Y      |
|                  | Sugimura et al.| 1999 | Mixed     | H-B              | 85      | 115     | 41      | 63         | 107        | 27         | Y      |
|                  | Wikman et al. | 2000 | Caucasian | P-B              | 68      | 32      | 5       | 60         | 43         | 2          | Y      |
|                  | Marchand et al.| 2002 | Mixed     | P-B              | 15      | 31      | 29      | 29         | 48         | 19         | Y      |
|                  | Marchand et al.| 2002 | Caucasian | P-B              | 78      | 39      | 9       | 98         | 53         | 8          | Y      |
|                  | Sunaga et al. | 2002 | Asian     | H-B              | 54      | 106     | 38      | 50         | 66         | 36         | Y      |
|                  | Marchand et al.| 2002 | Asian     | P-B              | 30      | 40      | 27      | 50         | 74         | 26         | Y      |
|                  | Ito et al.    | 2002 | Asian     | H-B              | 40      | 71      | 27      | 68         | 118        | 54         | Y      |
|                  | Lan et al.    | 2004 | Asian     | P-B              | 37      | 61      | 20      | 51         | 43         | 15         | Y      |
|                  | Park et al.   | 2004 | Caucasian | P-B              | 88      | 60      | 12      | 255        | 87         | 8          | Y      |
|                  | Vogel et al.  | 2004 | Caucasian | P-B              | 149     | 93      | 14      | 159        | 91         | 19         | Y      |
|                  | Liang et al.  | 2005 | Asian     | H-B              | 27      | 132     | 68      | 28         | 123        | 76         | N      |
|                  | Hung et al.   | 2005 | Caucasian | H-B              | 1401    | 661     | 93      | 1368       | 716        | 79         | Y      |
|                  | Loft et al.   | 2006 | Caucasian | P-B              | 144     | 93      | 14      | 154        | 88         | 19         | Y      |
| Zienoldiny et al.| 2006 | Caucasian | P-B              | 182     | 100     | 44      | 194        | 117        | 75         | N      |
| Kohno et al.     | 2006 | Asian     | H-B              | 285     | 544     | 268     | 123        | 190        | 81         | Y      |
| Sorensen et al.  | 2006 | Caucasian | P-B              | 254     | 155     | 22      | 479        | 284        | 33         | Y      |
| Matullo et al.   | 2006 | Caucasian | P-B              | 66      | 46      | 4       | 673        | 371        | 50         | Y      |
| De Ruyck et al.  | 2007 | Caucasian | H-B              | 74      | 33      | 3       | 60         | 46         | 4          | Y      |
| Hatt et al.      | 2008 | Caucasian | P-B              | 92      | 58      | 8       | 93         | 59         | 12         | Y      |
| Karahall et al.  | 2008 | Caucasian | H-B              | 86      | 65      | 14      | 115        | 106        | 29         | Y      |
| Miyashiki et al. | 2009 | Asian     | H-B              | 27      | 55      | 26      | 39         | 54         | 28         | Y      |
| Chang et al.     | 2009 | African   | P-B              | 170     | 78      | 6       | 202        | 70         | 8          | Y      |
## Table 1 (continued)

| Gene-polymorphism | First author | Year | Ethnicity | Source of control | Case WW | Case MW | Case MM | Control WW | Control MW | Control MM | Y (HWE) |
|-------------------|--------------|------|-----------|-------------------|--------|--------|--------|----------|----------|-----------|---------|
|                   | Chang et al. | 2009 | Caucasian | P-B               | 53     | 47     | 12     | 135      | 132      | 29        | Y       |
|                   | Chang et al. | 2009 | Asian     | P-B               | 142    | 518    | 436    | 154      | 482      | 361       | Y       |
|                   | Okasaka et al.| 2009 | Asian     | H-B               | 117    | 257    | 141    | 250      | 544      | 236       | Y       |
|                   | Liu et al.   | 2010 | Asian     | H-B               | 68     | 158    | 132    | 110      | 294      | 312       | N       |
|                   | Janik et al. | 2011 | Caucasian | H-B               | 48     | 24     | 16     | 57       | 21       | 1         | Y       |
|                   | Li et al.    | 2011 | Asian     | H-B               | 83     | 208    | 164    | 60       | 219      | 164       | Y       |
|                   | Qian et al.  | 2011 | Asian     | H-B               | 100    | 288    | 193    | 125      | 291      | 185       | Y       |
|                   | Cheng et al. | 2012 | Asian     | P-B               | 26     | 9      | 15     | 17       | 3        | 10        | N       |
|                   | Ouyan et al. | 2013 | Asian     | P-B               | 14     | 42     | 26     | 40       | 94       | 67        | Y       |
|                   | Letkova et al.| 2013 | Caucasian | P-B               | 244    | 119    | 19     | 250      | 110      | 18        | Y       |
|                   | Xue et al.   | 2013 | Asian     | H-B               | 55     | 178    | 177    | 68       | 200      | 142       | Y       |
|                   | Doherty et al.| 2013 | Caucasian | P-B               | 440    | 265    | 39     | 873      | 519      | 85        | Y       |
|                   | Wang et al.  | 2015 | Asian     | P-B               | 77     | 182    | 241    | 80       | 165      | 25        | N       |
|                   | Qin et al.   | 2016 | Asian     | P-B               | 59     | 121    | 37     | 72       | 124      | 30        | N       |
| LIG1-rs20579      | Landi et al. | 2006 | Caucasian | Mixed             | 206    | 73     | 6      | 245      | 61       | 0         | Y       |
|                   | Chang et al. | 2008 | Caucasian | P-B               | 72     | 36     | 5      | 217      | 75       | 7         | Y       |
|                   | Chang et al. | 2008 | African   | P-B               | 150    | 92     | 13     | 137      | 117      | 26        | Y       |
|                   | Lee et al.   | 2008 | Caucasian | P-B               | 294    | 118    | 11     | 586      | 187      | 7         | Y       |
|                   | Sakoda et al.| 2012 | Caucasian | P-B               | 583    | 141    | 18     | 1126     | 312      | 36        | N       |
| LIG1-rs3730931    | Landi et al. | 2006 | Caucasian | Mixed             | 220    | 64     | 5      | 255      | 52       | 2         | Y       |
|                   | Chang et al. | 2008 | Caucasian | P-B               | 79     | 30     | 4      | 226      | 67       | 6         | Y       |
|                   | Chang et al. | 2008 | African   | P-B               | 151    | 92     | 11     | 158      | 103      | 19        | Y       |
|                   | Sakoda et al.| 2012 | Caucasian | P-B               | 595    | 137    | 11     | 1137     | 313      | 26        | Y       |
| LIG1-rs156641     | Chang et al. | 2008 | African   | P-B               | 189    | 62     | 4      | 215      | 60       | 5         | Y       |
|                   | Chang et al. | 2008 | Caucasian | P-B               | 59     | 43     | 11     | 143      | 126      | 30        | Y       |
|                   | Sakoda et al.| 2012 | Caucasian | P-B               | 271    | 352    | 121    | 596      | 709      | 164       | N       |
| LIG1-rs20581      | Chang et al. | 2008 | African   | P-B               | 176    | 73     | 6      | 199      | 68       | 13        | N       |
|                   | Chang et al. | 2008 | Caucasian | P-B               | 38     | 48     | 27     | 89       | 151      | 59        | Y       |
|                   | Lee et al.   | 2008 | Caucasian | P-B               | 78     | 148    | 86     | 142      | 346      | 155       | Y       |
| LIG1-rs439132     | Chang et al. | 2008 | Caucasian | P-B               | 108    | 5      | 0      | 269      | 29       | 1         | Y       |
|                   | Lee et al.   | 2008 | Caucasian | P-B               | 326    | 39     | 6      | 585      | 54       | 2         | Y       |
|                   | Chang et al. | 2008 | African   | P-B               | 129    | 112    | 14     | 117      | 91       | 12        | Y       |
| MUTYH-rs3219489   | Al-tassan et.| 2003 | Caucasian | P-B               | 142    | 109    | 14     | 58       | 36       | 7         | Y       |
|                   | Miyaishi et al.| 2009 | Asian     | P-B               | 22     | 57     | 29     | 37       | 69       | 15        | N       |
|                   | Qian et al.  | 2011 | Asian     | P-B               | 230    | 261    | 90     | 243      | 283      | 77        | Y       |
|                   | Doherty et al.| 2013 | Caucasian | P-B               | 417    | 279    | 42     | 825      | 562      | 79        | Y       |
| PARP1-rs1136410   | Zhang et al. | 2005 | Asian     | H-B               | 307    | 509    | 184    | 359      | 504      | 137       | Y       |
|                   | Yin et al.   | 2011 | Mixed     | H-B               | 117    | 35     | 7      | 50       | 12       | 2         | Y       |
|                   | Xue et al.   | 2013 | Asian     | H-B               | 129    | 202    | 79     | 138      | 205      | 67        | Y       |
|                   | Yu et al.    | 2014 | Asian     | H-B               | 46     | 164    | 163    | 34       | 164      | 162       | Y       |
|                   | Wang et al.  | 2015 | Asian     | P-B               | 151    | 97     | 252    | 14       | 109      | 251       | Y       |

M, mutant allele; W, wild type allele; P-B, population-based; H-B, hospital-based; Mixed, more than one ethnicity; N.A., not mentioned; Y, studies that conforms to HWE; N, study that deviates from HWE.
Figure 1 Flow chart showing the study selection process.
Table 2 PRISMA 2009 checklist

| Section/topic | # | Checklist item                                                                                                                                                                                                                                                                                                                                 | Reported on page # |
|---------------|---|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|
| Title         | 1 | Identify the report as a systematic review, meta-analysis, or both.                                                                                                                                                                                                                                                                           | Page 1            |
| Abstract      |   |                                                                                                                                                                                                                                                                                                                                             |                   |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.                                                   | Page 2–3          |
| Introduction  |   |                                                                                                                                                                                                                                                                                                                                             |                   |
| Rationale     | 3 | Describe the rationale for the review in the context of what is already known.                                                                                                                                                                                                     | Page 4–5          |
| Objectives    | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).                                                                                                                                         | Page 5            |
| Methods       |   |                                                                                                                                                                                                                                                                                                                                             |                   |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.                                                                                                                   | N/A               |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.                                                                                           | Study selection: page 6–7 |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.                                                                                                                  | Search strategy: page 5–6, |
| Search        | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.                                                                                                                                                           | Search strategy: page 5 |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).                                                                                                                                 | Figure 1          |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.                                                                                                                 | Data extraction and quality assessment: page 7 |
| Data items    | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.                                                                                                                                               | Data extraction and quality assessment: page 7 |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.                                                      | Statistical analysis: page 8 |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means).                                                                                                                                                                                                      | Statistical analysis: page 8 |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I²) for each meta-analysis.                                                                                                                                   | Statistical analysis: page 8 |
| Section/topic |   |                                                                                                                                                                                                                                                                                                                                             |                   |
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).                                                                                                                                      | Statistical analysis: page 8 |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.                                                                                                                                 | Statistical analysis: page 8 |

Table 2 (continued)
Table 2 (continued)

| Section/topic               | #  | Checklist item                                                                 | Reported on page # |
|-----------------------------|----|---------------------------------------------------------------------------------|--------------------|
| Results                     |    |                                                                                  |                    |
| Study selection             | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | Description of studies: page 8–9 |
| Study characteristics       | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | Table 1–3          |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | Page 10–12         |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | Page 10–12         |
| Synthesis of results        | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | Page 10–12         |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | Page 10–12         |
| Additional analysis         | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | page 10            |
| Discussion                  |    |                                                                                  |                    |
| Summary of evidence         | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | Page 13–15         |
| Limitations                 | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | Page 15            |
| Conclusions                 | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | Page 17            |
| Funding                     | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | Page 17            |

Adapted from ref. (128).

**Evaluation of stability and publication bias**

The test of the stability of results was assessed by sensitivity analysis, each time we separated one study from data pool, and reviewed whether it affects the ORs and 95% CIs. The results displayed that no substantial change for XRCC1-rs1799782/rs25487/rs25489/rs3213245/rs3547/rs915927, LIG1-rs156641/rs20579/rs20581/rs3730931/rs439132, APEX1-rs1130409/rs1760944/rs2307486, PARP1-rs1136410, OGG1-rs1052133 and MUTYH-rs3219489 polymorphisms.

For behalf of evaluating potential publication bias, we use Begg’s funnel plot and Egger’s test. Significant publication bias may reflect differences in control options, age distributions and other lifestyles. Finally, the shape of Begg’s funnel plot in each polymorphism is symmetrical, while the P value of Egger’s test in each polymorphism and subgroup is higher than 0.05, indicating no evidence of publication bias was found (Table 4).

**Discussion**

The stability of the general genomic sequence is sustained by a pivotal gene family, BER signaling pathway. In human cells, the inability of remove endogenous DNA damage would link with single nucleotide polymorphisms (130–132). On the other hand, the abnormal process occurs on BER pathway or the enzymes mediate it would finally lead to the instable cell chromosomal (133). Recently, increasing evidence suggested that genetic variants in the BER pathway were associated with LC risk. However, these results were
Table 3 Significant results of the association between polymorphisms in BER pathway gene and LC risk

| SNP            | Comparison      | Subgroup | N   | \( P_{H} \)       | \( P_{Z} \)       | Random OR (95% CI) | Fixed OR (95% CI) |
|----------------|-----------------|----------|-----|-------------------|-------------------|--------------------|-------------------|
| XRCC1-rs3213245| MM vs. WW       | Overall  | 7   | 0.512             | 3.124*10⁻⁸       | 1.992 (1.422–2.791)| 2.023 (1.452–2.819)|
|                | MM vs. MW + WW  | Overall  | 7   | 0.434             | 6.468*10⁻⁸       | 1.894 (1.365–2.627)| 1.926 (1.396–2.656)|
|                | MM vs. WW       | Asian    | 6   | 0.720             | 1.169*10⁻⁶       | 2.260 (1.556–3.284)| 2.285 (1.579–3.306)|
|                | MM vs. MW + WW  | Asian    | 6   | 0.730             | 1.660*10⁻⁶       | 2.208 (1.526–3.193)| 2.231 (1.549–3.215)|
|                | M vs. W         | H-B      | 4   | 0.406             | 1.970*10⁻⁸       | 1.433 (1.263–1.625)| 1.433 (1.264–1.625)|
|                | MW vs. WW       | H-B      | 4   | 0.820             | 6.322*10⁻⁷       | 1.446 (1.251–1.672)| 1.446 (1.251–1.672)|
|                | MW + MM vs. WW  | H-B      | 4   | 0.723             | 4.140*10⁻⁸       | 1.485 (1.289–1.710)| 1.485 (1.289–1.710)|
| XRCC1-rs915927 | M vs. W         | Asian    | 2   | 0.180             | 9.975*10⁻⁹       | 2.292 (1.226–4.284)| 2.071 (1.435–2.988)|
|                | MW vs. WW       | Asian    | 2   | 0.234             | 2.147*10⁻⁴       | 2.252 (1.280–3.962)| 2.111 (1.421–3.136)|
|                | MW + MM vs. WW  | Asian    | 2   | 0.203             | 9.341*10⁻⁶       | 2.395 (1.287–4.455)| 2.191 (1.478–3.247)|
|                | M vs. W         | H-B      | 2   | 0.180             | 9.975*10⁻⁹       | 2.292 (1.226–4.284)| 2.071 (1.435–2.988)|
|                | MW vs. WW       | H-B      | 2   | 0.234             | 2.147*10⁻⁴       | 2.252 (1.280–3.962)| 2.111 (1.421–3.136)|
|                | MW + MM vs. WW  | H-B      | 2   | 0.203             | 9.341*10⁻⁶       | 2.395 (1.287–4.455)| 2.191 (1.478–3.247)|
| XRCC1-rs25487  | M vs. W         | N        | 8   | 0.414             | 2.741*10⁻¹⁷      | 1.345 (1.199–1.508)| 1.343 (1.200–1.502)|
|                | MM vs. WW       | N        | 8   | 0.471             | 4.463*10⁻⁸       | 1.481 (1.223–1.793)| 1.486 (1.229–1.797)|
|                | MM vs. MW + WW  | N        | 8   | 0.102             | 3.663*10⁻⁷       | 1.758 (1.332–2.321)| 1.592 (1.331–1.904)|
| APEX1-rs1760944| M vs. W         | Overall  | 5   | 0.530             | 7.243*10⁻⁶       | 0.851 (0.786–0.922)| 0.851 (0.786–0.921)|
|                | MM vs. WW       | Overall  | 5   | 0.534             | 3.409*10⁻⁶       | 0.705 (0.598–0.832)| 0.705 (0.598–0.832)|
|                | MM vs. MW + WW  | Overall  | 5   | 0.315             | 1.927*10⁻⁴       | 0.770 (0.663–0.895)| 0.780 (0.684–0.889)|
| OGG1-rs1052133 | MM vs. MW + WW  | Overall  | 31  | 0.106             | 2.119*10⁻⁴       | 1.143 (1.032–1.285)| 1.157 (1.071–1.249)|
|                | M vs. W         | Asian    | 13  | 0.355             | 9.988*10⁻⁶       | 1.123 (1.054–1.196)| 1.123 (1.059–1.191)|
|                | MM vs. WW       | Asian    | 13  | 0.353             | 3.585*10⁻⁸       | 1.242 (1.090–1.414)| 1.244 (1.103–1.403)|

M, mutant allele; W, wild type allele; P-B, population-based; H-B, hospital-based; Y, studies that conforms to HWE; N, study that deviates from HWE; \( P_{H} \), \( P \) value of heterogeneity test; \( P_{Z} \), adjusted \( P \) value of Z test [\( P<0.05/(17 \text{polymorphisms} \times 5 \text{genetic models}) \)].

inclusive or even controversial. Therefore, we presented the comprehensively updated meta-analysis, aiming to systematically screen out the LC risk or protective factors within genes of the BER pathway.

Firstly, we investigated the XRCC1, a crucial element of the BER system, it has multiple key roles in the repair process of DNA single nucleotide polymorphism (134,135). We analyzed six commonly studied polymorphisms in XRCC1, and overall analyses suggested that MM genotype of rs3213245 (−77T > C) polymorphism was linked to a sharply enhanced risk of LC compared with WW and MW/WW genotypes, and not the rs25487 and rs1799782 polymorphisms, which were proved associated with LC risk in Chen et al.’s meta-analysis work (136). In addition, rs3213245-MM genotype was also combined with an increased hazard of LC for Asian population. For XRCCI rs3213245 polymorphism, the affinity of XRCCI promoter region to nuclear protein Sp1 would be enhanced by T to C mutation, caused the inhibition of its transcription (40). In our study, seven studies were focused on the correlation of rs3213245 polymorphism and LC risk, and the overall results suggested that the risk in MM genotype group was 2.023 and 1.926-fold raised than WW group and MW + WW group, respectively, almost consistent with Vineis et al.‘s (137) findings.

In addition, the overall calculate illustrated a negative association between XRCC1-rs915927 and LC, but we also identified that M allele, MW and MW + MM genotypes
led to an enhanced risk of LC for the Asian population. For the mechanism part, rs915927 leads to a synonymous mutation, which is a kind of mutation which may not influence the translation of amino acid product, however, this kind of mutation might change the translational efficiency of mRNA, therefore, non-synonymous mutations like XRCC1 rs1799782 (Arg194Trp) and XRCC1 rs25489 (Arg280His) might regulate LC susceptibility, affecting complex assembly or repair efficiency (138). Furthermore, for another XRCC1-rs25487 polymorphism, we observed an enhanced risk of LC in allelic, homozygote, and recessive models for HWE (N) group, which tell us that there might be some potential bias caused by HWE status. Therefore, we decided to remove these HWE (N) studies from pooled analysis, and finally negative results were obtained.

Secondly, APEX1 gene was also analyzed, which specifically activates DNA repair through the identification and cleavage of phosphodiester bonds on the 5’ side of the basic site (139). APEX1 can also participate in oxidative stress, control of cell cycle, and apoptosis (140,141). Recent days, several researchers reported that APEX1 gene polymorphisms would influence the cancer risks (142-144),

Figure 2 The forest plot of the meta-analysis for rs3213245 polymorphism. (A) Homozygous model and (B) recessive model, for rs1760944 polymorphism. (C) Homozygous model, and for rs1052133 polymorphism (D) recessive model.
as well as some meta-analyses (most of them only focus on a few variants) (145). In current work, we analyzed three most commonly polymorphisms reported in APEX1 (rs1130409, rs1760944 and rs2307486) and LC risk, and we found that M allele, MM genotype at rs1760944 were associated with a reduced risk of LC relative to W allele, WW and MW + WW genotypes, respectively. While for the other two polymorphisms, we failed to identify any significant correlations.

In the progression of different types of cancers, APEX1 is another key role. For APEX1-rs1130409, Zhang et al. (146) reported that the G allele and GG/TG genotype associated with the decreased risk of ovarian carcinoma. However, Yuan et al. (147) revealed that rs1130409 do not play any role in head and neck neoplasms in Chinese, another study conducted in gastric cancer reported the same conclusion (148). In our work, we obtained the result that rs1130409 is not associated with LC risks. For another role polymorphism in APEX1, Lu et al. (99) first reported the potential risk of rs1760944 in LC. In a study about Korean, rs1760944 was reported associated with the risk of gastric cancer, but another study conducted in Chinese indicated that GT or GG genotypes might have a higher survival rate (148,149). Dai et al. managed a meta-analysis, the result supported the conclusion that rs1760944 acts as a protector in cancer of Asian (150). Consistent with these data, we demonstrated that M allele and MM genotype were associated with a decreased risk of LC than W allele, WW and MW + WW genotypes.

Another BER gene we analyzed here is OGG1, which plays a key role during the repair process of oxidative DNA damage. rs1052133 polymorphism had been reported could substitution Serene to Cysteine at codon 326, and influence the function of OGG1 protein (151). As reported by Wikman et al. (122), LC susceptibility might not be impacted by the OGG1 polymorphisms in Caucasians. Hung et al. (70) and Vogel et al. (84) also observed no link between OGG1 polymorphisms and LC risk. Ito et al. (107) found that OGG1-rs1052133 polymorphism had no effect on the development of adenocarcinoma or small cell carcinoma. Whereas in our work, overall results suggested a null correlation for this polymorphism and LC risk.

In this meta-analysis, we comprehensively searched all available eligible studies to obtain the precise result. Some advantages of this study should be focused on. Firstly, a wide search was conducted to identify more qualified studies for each genetic variant in BER genes, therefore these analyses were persuasive and substantive. For example, several previous meta-analyses have been published concerning XRCC1 polymorphisms and LC risk, while they only focus limited polymorphisms on LC risk, and their results were not adjusted, increasing the false-positive results rate. Secondly, we evaluated the quality of each registered research by NOS scale before calculating, and eliminated low-quality studies. and adjusted all the results according to Bonferroni corrections, making the conclusions more convincing. Thirdly, according to the subgroup, we also conducted the stratification analyses by ethnicity, source of controls, tumor type or race, in order to eliminate the influence of heterogeneity. Fourthly, the sensitivity analysis was performed to confirm the stability of the obtained results, and Egger’s test and Begg’s funnel plot were performed to draw out the potential publication bias.

Several disadvantages should also be displayed to avoid any incorrect understanding of the results. First of all, there were no sufficient samples for the analyses of some variants, and it might prove an undependable association between polymorphisms and LC. For example, there are only 3 or 4 studies in APEX1-rs2307486, LIG1-rs156641 and PARP1-rs1136410, more studies conducted in these polymorphisms are needed to reveal a more convincible result in the future.

Table 4 Egger’s regression test for polymorphisms in BER pathway gene

| Gene | Polymorphism | Egger’s test (P > |t|) |
|------|--------------|------------------|
| XRCC1| rs1799782    | 0.896            |
|      | rs25487      | 0.248            |
|      | rs25489      | 0.99             |
|      | rs3213245    | 0.497            |
|      | rs3547       | 0.565            |
|      | rs915927     | 0.115            |
| LIG1 | rs156641     | 0.377            |
|      | rs20579      | 0.401            |
|      | rs20581      | 0.388            |
|      | rs3730931    | 0.127            |
|      | rs439132     | 0.589            |
| APEX1| rs1130409    | 0.006            |
|      | rs1760944    | 0.312            |
|      | rs2307486    | 0.38             |
| PARP1| rs1136410    | 0.603            |
| OGG1 | rs1052133    | 0.337            |
Moreover, only the articles in English were enrolled, which might miss the important result in other languages and countries. Finally, the detail information about the histological result of each LC patient was missed, so the stratification analyses based on histological type and the clinical stage could not be conducted.

Conclusions

To conclude, this meta-analysis shows that XRCC1-rs3213245 and OGG1-rs1052133 polymorphisms are risk factors for LC, while APEX1-rs1760944 polymorphism is a protective factor. Future studies with larger sample size are warranted to verify these findings.

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Footnote

Conflicts of Interest: The authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2020.02.44). The authors have no conflicts of interests to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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