Original Article

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

Submitted Oct 07, 2019. Accepted for publication Feb 05, 2020.
doi: 10.21037/tcr.2020.02.44
View this article at: http://dx.doi.org/10.21037/tcr.2020.02.44

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.broadinstitute.org/gsea/msigdb/geneset_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. I^2 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, I^2 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 X-Ray Repair Cross Complementing 1 (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, $P=3.124\times10^{-5}$, *Figure 2A*; MM *vs.* MW + WW: OR 1.926, 95% CI: 1.396–2.656, $P=6.468\times10^{-5}$, *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, $P=7.243\times10^{-5}$, *Figure 2C*; MM *vs.* WW: OR 0.705, 95% CI: 0.598–0.832, $P=3.409\times10^{-5}$; and MM *vs.* MW + WW: OR 0.780, 95% CI: 0.684–0.889, $P=1.927\times10^{-4}$, *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, $P=2.119\times10^{-4}$, *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.

Table 1 Details of enrolled studies for current meta-analysis and systematic review

Gene-polymorphism	First author	Year	Ethnicity	Source of control	Case			Control			
					WW	MW	MM	WW	MW	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
	Cătană *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	468	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*)

Table 1 (*continued*)

Gene-polymorphism	First author	Year	Ethnicity	Source of control	Case			Control			
					WW	MW	MM	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

Table 1 (*continued*)

Table 1 (*continued*)

Gene-polymorphism	First author	Year	Ethnicity	Source of control	Case			Control			
					WW	MW	MM	WW	MW	MM	Y (HWE)
	Singh *et al.*	2016	Caucasian	P-B	93	186	51	79	176	70	Y
XRCC1-rs25489	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	H-B	105	4	0	96	14	0	Y
	Yin *et al.*	2008	Asian	H-B	190	46	2	179	59	4	Y
	Li *et al.*	2008	Asian	H-B	266	79	5	74	72	4	N
	Yin *et al.*	2009	Asian	H-B	41	7	1	52	18	2	Y
	Chang *et al.*	2009	Caucasian	P-B	86	25	1	242	51	5	Y
	Yoo *et al.*	2014	Asian	P-B	506	88	5	448	127	5	Y
	Han *et al.*	2015	Asian	P-B	100	87	23	109	82	19	Y
	Singh *et al.*	2016	Caucasian	P-B	32	250	48	26	268	31	N
XRCC1-rs3213245	Hu *et al.*	2005	Asian	H-B	500	198	12	558	148	4	Y
	Hao *et al.*	2006	Asian	H-B	783	223	18	924	182	12	Y
	De Ruyck *et al.*	2007	Caucasian	H-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
XRCC1-rs3547	Yin *et al.*	2008	Asian	H-B	183	43	1	191	49	2	Y
	Yin *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
XRCC1-rs915927	Matullo *et al.*	2006	Caucasian	Mixed	36	58	22	342	508	243	N
	Yin *et al.*	2008	Asian	H-B	169	68	2	203	43	0	Y
	Yin *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
APEX1-rs1130409	Misra *et al.*	2003	Caucasian	P-B	64	167	79	65	160	77	Y
	Ito *et al.*	2004	Asian	H-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

Table 1 (*continued*)

Table 1 (*continued*)

Gene-polymorphism	First author	Year	Ethnicity	Source of control	Case			Control			
					WW	MW	MM	WW	MW	MM	Y (HWE)
	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-rs1760944	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
APEX1-rs2307486	Zienolddiny *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
OGG1-rs1052133	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
	Zienolddiny *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
	Karahalil *et al.*	2008	Caucasian	H-B	86	65	14	115	106	29	Y
	Miyaishi *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*)

Table 1 (*continued*)

Gene-polymorphism	First author	Year	Ethnicity	Source of control	Case			Control			
					WW	MW	MM	WW	MW	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 al.*	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.

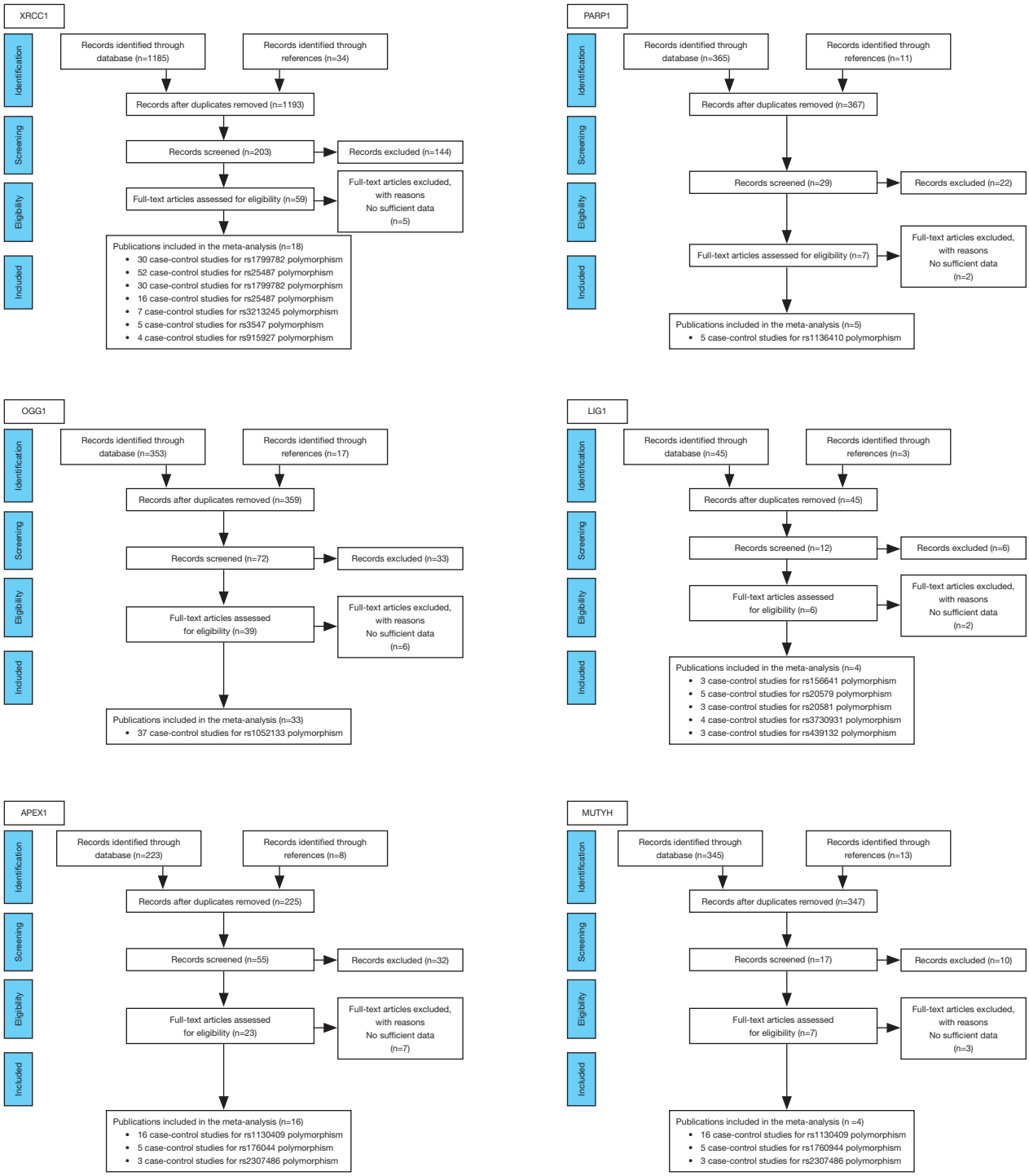

Figure 1 Flow chart showing the study selection process.

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., I^2) 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 form 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	$3.124*10^{-5}$	1.992 (1.422–2.791)	2.023 (1.452–2.819)
	MM *vs.* MW + WW	Overall	7	0.434	$6.468*10^{-5}$	1.894 (1.365–2.627)	1.926 (1.396–2.656)
	MM *vs.* WW	Asian	6	0.720	$1.169*10^{-5}$	2.260 (1.556–3.284)	2.285 (1.579–3.306)
	MM *vs.* MW + WW	Asian	6	0.730	$1.660*10^{-5}$	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	$9.975*10^{-5}$	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	$9.341*10^{-5}$	2.395 (1.287–4.455)	2.191 (1.478–3.247)
	M *vs.* W	H-B	2	0.180	$9.975*10^{-5}$	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	$9.341*10^{-5}$	2.395 (1.287–4.455)	2.191 (1.478–3.247)
XRCC1-rs25487	M *vs.* W	N	8	0.414	$2.741*10^{-7}$	1.345 (1.199–1.508)	1.343 (1.200–1.502)
	MM *vs.* WW	N	8	0.471	$4.463*10^{-5}$	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	$7.243*10^{-5}$	0.851 (0.786–0.922)	0.851 (0.786–0.921)
	MM *vs.* WW	Overall	5	0.534	$3.409*10^{-5}$	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 (1.032–1.265)	1.157 (1.071–1.249)
	M *vs.* W	Asian	13	0.355	$9.988*10^{-5}$	1.123 (1.054–1.196)	1.123 (1.059–1.191)
	MM *vs.* WW	Asian	13	0.353	$3.585*10^{-4}$	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; Pz, adjusted P value of Z test [P<0.05/(17 polymorphisms * 5 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 *XRCC1* rs3213245 polymorphism, the affinity of *XRCC1* 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

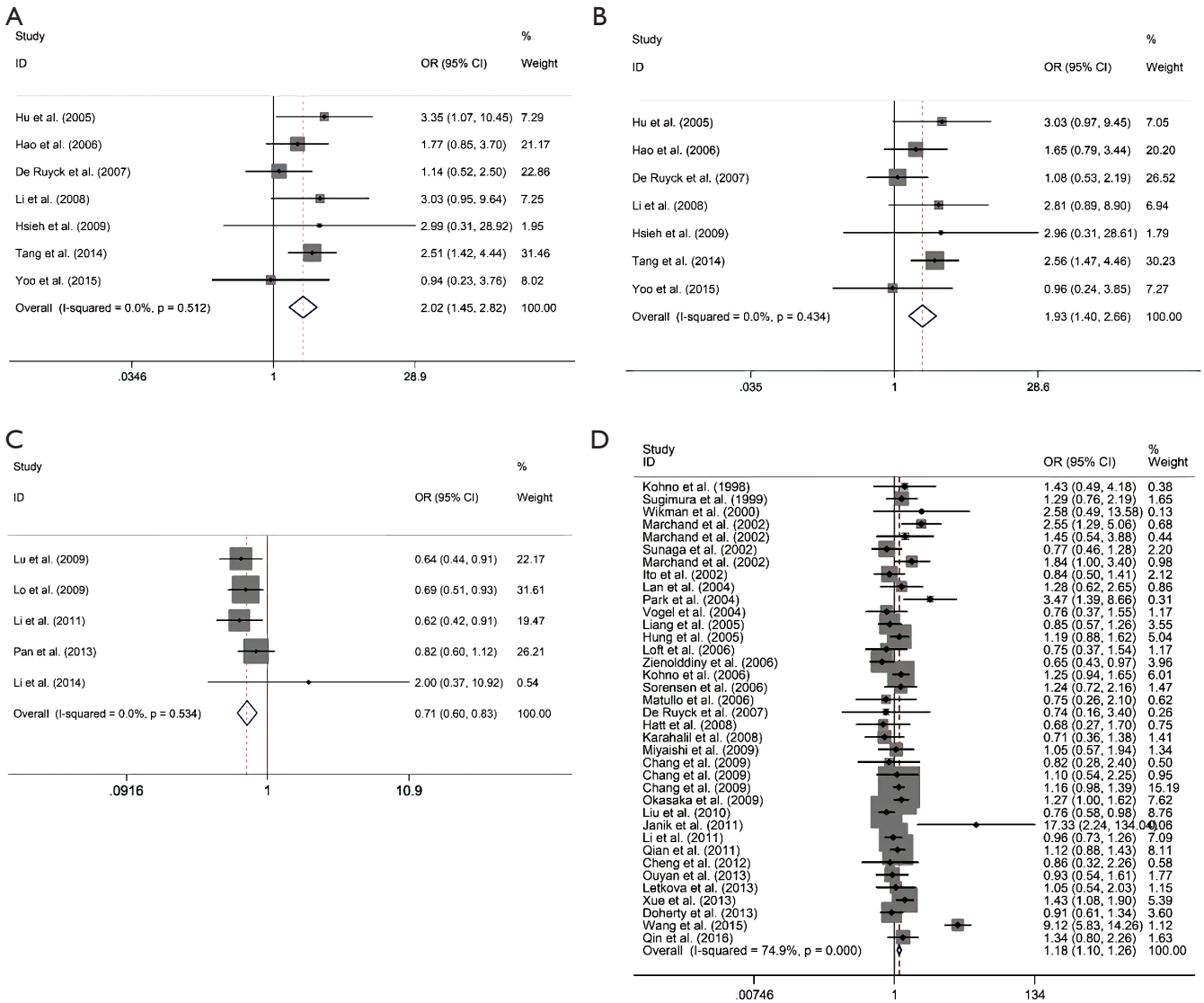

Figure 2 The forest plot of the meta-analysis for rs3213245 polymorphism. (A) Homozygous model and (B) recessive model, for rs1760944 polymorphism. (C) Homozygous model, and for rs1052133 polymorphism (D) recessive model.

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),

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

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 re1130409 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 susceptibility. 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.

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.

Acknowledgments

Funding: The study was supported by Natural Science Foundation of China (81903020), China Postdoctoral Science Foundation (2019M652812), National Multidisciplinary Cooperative Diagnosis and Treatment Capacity Building Project for Major Diseases (Lung Cancer)

Footnote

Conflicts of Interest: The authors have completed the ICMJE uniform disclosure from (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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Cite this article as: Liu S, Xiao Y, Hu C, Li M. Associations between polymorphisms in genes of base excision repair pathway and lung cancer risk. Transl Cancer Res 2020;9(4):2780-2800. doi: 10.21037/tcr.2020.02.44

